FINAL PROGRAMME & ABSTRACTS

17TH

INTERNATIONAL CONFERENCE

ON CACHEXIA, SARCOPENIA & MUSCLE WASTING

6-8 DECEMBER 2024

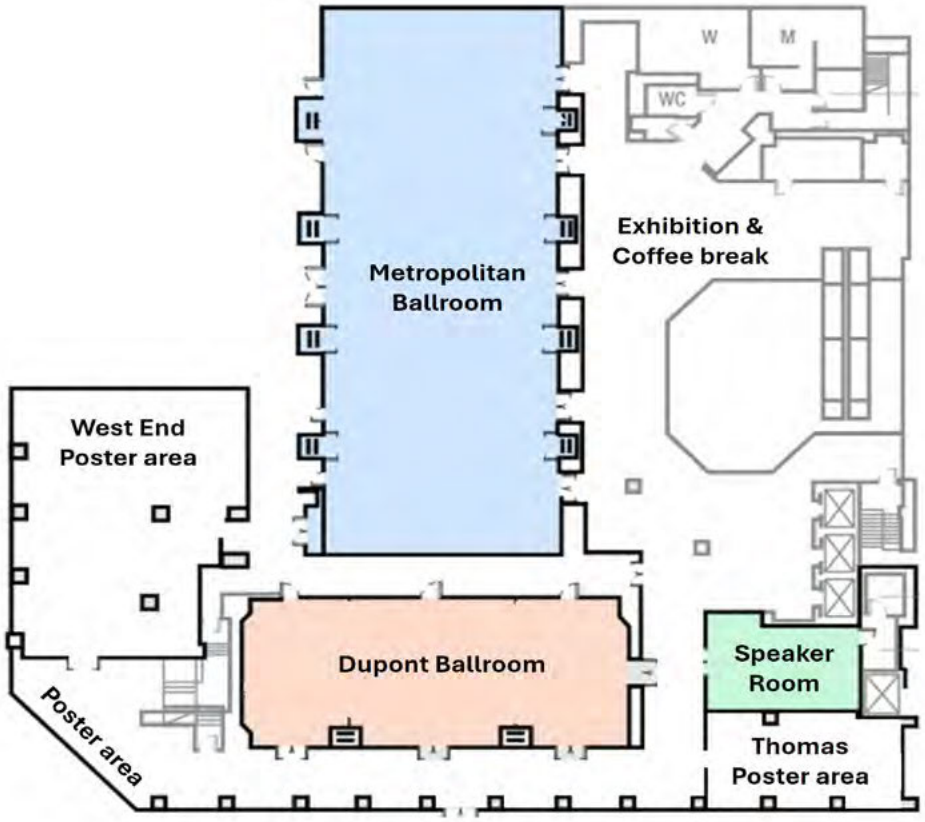
WASHINGTON DC

Follow us on www.cachexia.org

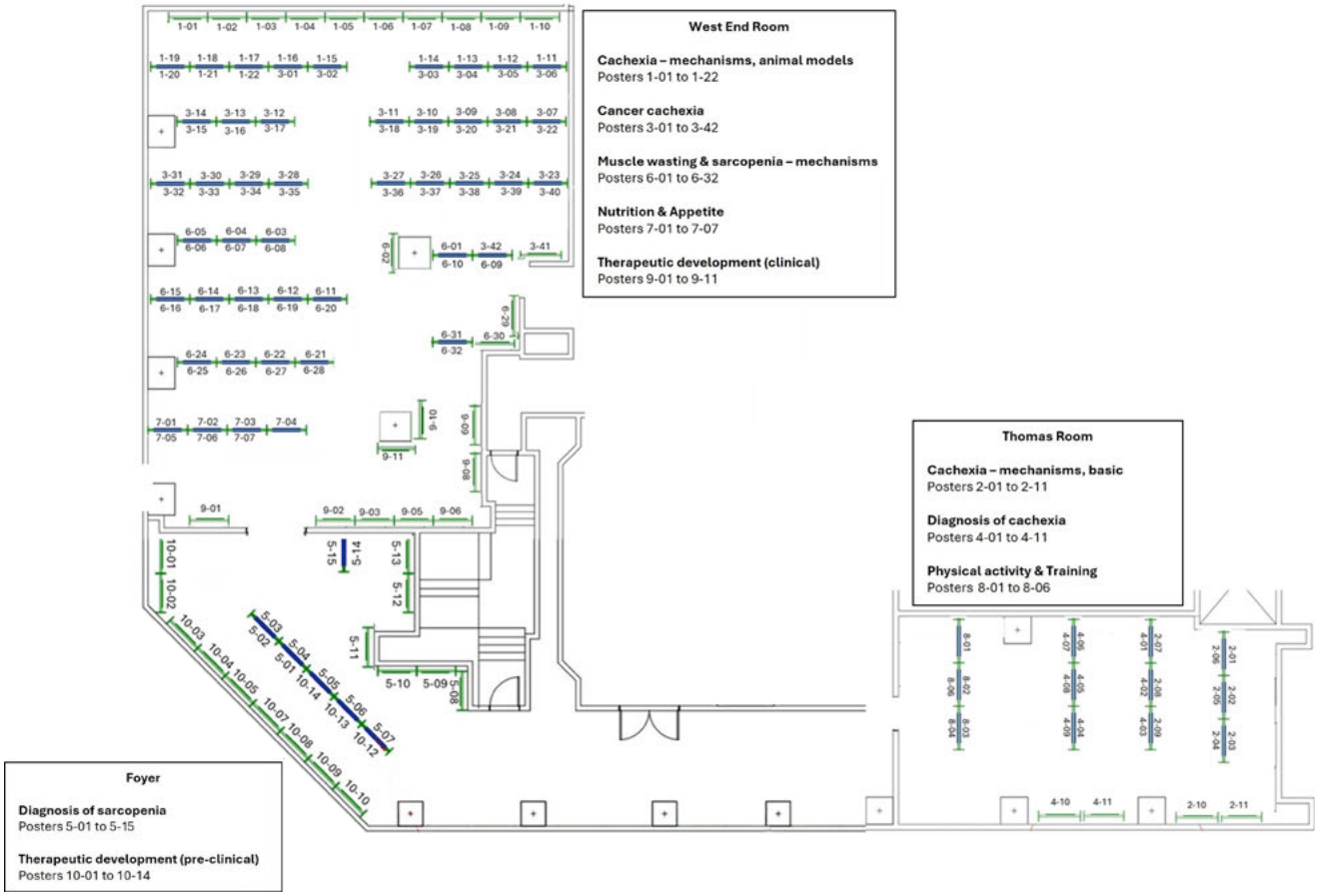
SCWD

SOCIETY ON SARCOPENIA, CACHEXIA & WASTING DISORDERS

OVERVIEW OF THE CONFERENCE VENUE



POSTER AREA



GENERAL INFORMATION

Organization

Society on Sarcopenia, Cachexia and Wasting Disorders (SCWD)
Vers-chez-les-Blanc, route du Jorat 67
c/o Intercomptas fiduciaire Sàrl,
1000 Lausanne 26
Switzerland

Congress Organizer

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75016 Paris, France
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Scientific Office

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Chairmen

Stefan D. Anker, Germany
Jeffrey Crawford, USA

International Scientific Committee

Hidenori Arai, Japan
Vickie E. Baracos, Canada
Andrew Coats, Australia
Wolfram Doehner, Germany
Gustavo Duque, Canada
William J. Evans, USA
David J. Glass, USA
Aminah Jatoi, USA
Kamyar Kalantar-Zadeh, USA
Barry Laird, UK
Reshma Merchant, Singapore
Maurizio Muscaritoli, Italy
Richard Skipworth, UK
Florian Strasser, Switzerland
Stephan von Haehling, Germany
Hidetaka Wakabayashi, Japan

Conference Location

Washington Marriott Georgetown Hotel
1221 22nd St N
Washington, DC 20037
USA

Opening Hours of the On-site Registration Desk

Friday, 6 December 2024
8:00-18:30 hrs
Saturday, 7 December 2024
8:00-18:30 hrs
Sunday, 8 December 2024
8:00-16:00 hrs

Poster Exhibition

Friday,6 December 2024
08:00-19:30 hrs
Saturday, 7 December 2024
8:00-19:30 hrs
Sunday, 8 December 2024
8:00-16:00 hrs

Poster Sessions

Friday, 6 December 2024
15:20-16:10 hrs
Saturday, 7 December 2024
10:20-11:10 hrs
15:05-15:55 hrs
Sunday, 8 December 2024
10:20-11:10 hrs

Coffee Breaks

Friday, 6 December 2024
15:15-16:15 hrs
Saturday, 7 December 2024
10:15-11:15 hrs
15:00-16:00 hrs
Sunday, 8 December 2024
10:15-11:15 hrs

Lunch Breaks

Friday, 6 December 2024
12:00-12:50 hrs
Saturday, 7 December 2024
12:45-13:30 hrs
Sunday, 8 December 2024
12:30-13:30 hrs

A
09:30 – 10:30 **METROPOLITAN BALLROOM**

CANCER CACHEXIA

Abnormal metabolism in cachexia

(each talk: 12 minutes)

Chairs: Tobias Janowitz (USA)
Erin Talbert (USA)

1. 09:30 – 09:42
New insights on the role of purine metabolism in age- and cancer-induced muscle atrophy
Andrea Bonetto (USA)

2. 09:42 – 09:54
Metabolic crosstalk mechanisms in cancer cachexia
Pauline Morigny (Germany)

3. 09:54 – 10:06
cAMP/CREB1-derived mitochondrial dysfunctions in cachexia
Andrea Graziani (Italy)

4. 10:06 – 10:18
Causal mechanisms in the mouse model of cancer cachexia - Lewis Lung Carcinoma
Xavier Clemente-Casares (Canada)

10:18 – 10:30
Discussion

B
10:45 – 11:45 **METROPOLITAN BALLROOM**

GENERAL SARCOPENIA

New findings on muscle wasting

(each talk: 12 minutes)

Chairs: Peggy Cawthon (USA)
Simon Wing (Canada)

1. 10:45 – 10:57
Identifying Mytho as a new regulator of muscle autophagy
Sabbah Hussain (Canada)

2. 10:57 – 11:09
EDA2R-NIK signalling promotes muscle atrophy linked to cancer cachexia
Serkan Kir (Turkey)

3. 11:09 – 11:21
Regulation of muscle sarcomere maintenance and bioenergetics by an unsuspected E3 ligase: a new myopathy gene
Jorge Ruas (USA)

4. 11:21 – 11:33
GLP-2 treatment improves muscle recovery following starvation in rats: a clinical opportunity to reverse muscle wasting?
Didier Attaix (France)

11:33 – 11:45
Discussion

12:00 – 12:50

Break

12:00 – 12:45 **METROPOLITAN BALLROOM**

KEYNOTE INDUSTRY LECTURE:

MRI-based quantification of muscle mass and myosteatosis as biomarkers for clinical trials and sarcopenia assessment

Olof Dahlqvist Leinhard, Sweden

(Supported by AMRA Medical)

C
13:00 – 14:00 **METROPOLITAN BALLROOM**

OPENING SESSION

(Welcome: 5 minutes, talk 2 and 3: 20 minutes + 5 minutes discussion, talk 4: 5 minutes)

Chairs: Stefan Anker (Germany)
Stephan von Haehling (Germany)

1. 13:00 – 13:05
Welcome
Stefan Anker (Germany)

2. 13:05 – 13:25
“Prometheus” basic science key note lecture:
Evolution of cachexia – adaptive to maladaptive
Teresa Zimmers (USA)

3. 13:30 – 13:50
“Hippocrates” clinical science key note lecture:
Integrate the power of preventive nutrition, (p)rehabilitation and positive psychology into cancer cachexia management
Florian Strasser (Switzerland)

4. 13:55 – 14:00
JCSM & SCWD lecture
Stephan von Haehling (Germany)

14:00 – 14:10

tBreak

D
14:10 – 15:15 METROPOLITAN BALLROOM

MECHANISMS, DIAGNOSTICS (BASIC / TRANSLATIONAL)

Advances on the roles of cancer-released extracellular vesicles in cachexia

(each talk: 15 minutes)

Chairs: James Carson (USA)
Denis Guttridge (USA)

1. 14:10 – 14:25
Cancer-cell-secreted extracellular vesicles dysregulate proteolysis and mitochondrial function in skeletal muscle
Shizhen (Emily) Wang (USA)

2. 14:25 – 14:40
The art of war: blocking the secretion of extracellular vesicles from cachexia-inducing tumors
Sai V. Chitti (Australia)

3. 14.40 – 14:55
The role of extracellular vesicles in adipose tissue
Wei Yan (China)

4. 14:55– 15:10
Chemotherapy drugs 5-FU and cisplatin promote cachexia by stimulating extracellular vesicle release from cancer
Yi-Ping Li (USA)

15:10 – 15:15
Discussion

E
14:10– 15:15 DUPONT BALLROOM

CANCER CACHEXIA

Understanding dysregulated metabolic homeostasis in cancer cachexia

(each talk: 15 minutes)

Chairs: Elke Dworatzek (Germany)
Steven Heymsfield (USA)

1. 14:10 – 14:25
Tumor-induced physiological changes in the host in cachexia
Eileen White (USA)

2. 14:25 – 14:40
Identifying metabolic alterations in cancer cachexia: quantitative fluxomics
Sheng Tony Hui (USA)

3. 14:40 – 14:55
Imaging metabolic adaptions in cancer cachexia using positron emission tomography (PET)
David Lewis (UK)

4. 14:55– 15:10
Improving insulin sensitivity to treat cancer cachexia in humans
Justin Brown (USA)

15:10 – 15:15
Discussion

15:15 – 16:15

Coffee Break

15:20 – 16:10 **POSTER AREA**

POSTER VIEWING 1

(each presentation: 2 minutes + 2 minutes discussion)

Poster session 1.1
Cachexia - mechanisms, animal models I (posters 1-01 to 1-09 and 1-12)
Chairs: Denis Guttridge, Sarah Lockie

Poster session 1.2
Cancer cachexia I (posters 3-01 to 3-12)
Chairs: Andrea Bonetto, Tobias Janowitz

Poster session 1.3
Diagnosis of cachexia (posters 4-01 to 4-11)
Chairs: Yi-Ping Li, Ishan Roy

Poster session 1.4
Muscle wasting & sarcopenia I (posters 6-01 to 6-08)
Chairs: Peggy Cawthon, Bill Evans

Poster session 1.5
Nutrition & appetite (posters 7-01 to 7-07)
Chairs: Adrian Slee, Paula Ravasco

Poster session 1.6
Physical activity & training (posters 8-01 to 8-06)
Chairs: Volker Adams, Julian Alcazar

15:20 – 16:10 **METROPOLITAN BALLROOM**

RAPID FIRE ABSTRACTS SESSION 1

(each presentation: 3 minutes + 2 minutes discussion)

Chairs: Mauricio Berriel Diaz (Germany)
Andrea Graziani (Italy)

15:20 – 15:25
Optimization of a mouse model of pancreatic cancer to simulate the human phenotypes of metastasis and cachexia (1-10)
Victoria Spadafora (USA)

15:25 – 15:30
Differential impact of chemotherapy and cachexia in a preclinical colorectal cancer model: a comparative analysis of 5-FU, paclitaxel, and cisplatin by biological sex (1-11)
Regina Cabrera (USA)

15:30 – 15:35
Pilot study of urine titin N-fragment in dogs with naturally-occurring cardiac cachexia (1-22)
Lisa Freeman (USA)

15:35 – 15:40
Novel genetic variants in DRAIC and RFX3 confer risk for weight loss in people with chronic obstructive pulmonary disease (2-01)
Joe W. Chiles (UK)

15:40 – 15:45
Mutual de-differentiation of adipocytes and tumor cells in the macroenvironment of pancreatic cancer cachexia (2-09)
Sephora Jean (USA)

15:45 – 15:50
ASCA101 as innovative multi-target therapeutic drug for cancer cachexia (10-07)
Minhyuk Yun (South Korea)

15:50 – 15:55
Dual targeting of Y5 and ghrelin receptors: a new strategy for treating cancer cachexia (10-10)
Jenna Hunt (Denmark)

15:55 – 16:00
Pharmacological inhibition of USP-19 attenuates cancer cachexia-induced muscle atrophy (10-12)
Vignesh Karthikaisamy (Germany)

16:00 – 16:05
Bimagrumab prevents semaglutide-induced muscle mass loss in diet-induced obese mice (10-13)
Morten Lundh (Denmark)

16:05 – 16:10
Loss of hindlimb muscle mass does not explain the loss of lean mass in semaglutide-treated mice (10-14)
Takuya Karasawa (USA)

F
16:15 – 17:30 DUPONT BALLROOM

NUTRITION

Nutrition and translational cachexia research

(each talk: 15 minutes)

Chairs: Steven Olde Damink (The Netherlands)
Stephan von Haehling (Germany)

1. 16:15 – 16:30
Nutritional treatment options in cancer care
Paula Ravasco (Portugal)

2. 16:30 – 16:45
Microbiota and nutrition in oncology: new player?
Carolina Trabulo (Portugal)

3. 16:45 – 17:00
Balanced nutrition to prevent protein-energy wasting and preserve renal function in chronic kidney disease
Kamyar Kalantar-Zadeh (USA)

4. 17:00 – 17:15
Uncoupling chronic cardiac wasting-associated cardiomyopathy from tumor and skeletal muscle wasting in cancer cachexia
Joseph Metzger (USA)

17:15 – 17:30
Discussion

G
16:15 – 17:30 METROPOLITAN BALLROOM

GENERAL SARCOPENIA

Body composition changes induced by GLP1-RA in obesity therapy

(each talk: 8 minutes)

Chairs: Andrew Coats (Australia)
Jennifer Linge (Sweden)

1. 16:15 – 16:23
The GLP1-RA evidence base for clinical benefits in obesity
Javed Butler (USA), presented by Andrew Coats (Australia)

2. 16:23 – 16:31
How do GLP1-RA cause weight loss?Henning Langer (Germany)

3. 16:31 – 16:39
The use of muscle selective anabolics to make GLP-1 RA weight loss drugs more effective and precise
Mitchell Steiner (USA)

4. 16:39 – 16:47
Body composition changes when giving GLP1-RA
Stefan Anker (Germany)

5. 16:47 – 16:55
Anabolic co-treatment in obesity therapy: rationale and early data
David Glass (USA)

16:55– 17:30
Panel discussion

17:45 – 18:30 **METROPOLITAN BALLROOM**

INNOVATIONS IN CANCER CACHEXIA

Moderators:
Stefan Anker (Germany)
Andrew Coats (Australia)

Cancer cachexia: new pharmacological approaches (10 minutes)
Richard Skipworth (UK)

Are patients reported outcomes meaningful endpoints in cachexia trials? (10 minutes)
Stacie Hudgens (USA)

Innovation in cancer cachexia: S-pindolol a new therapeutic approach (10 minutes)
Andrew Coats (Australia)

Discussion (15 minutes)

(Symposium supported by Actimed Therapeutics)

18:30 – 19:30 **FOYER**

WELCOME RECEPTION

08:00 – 08:50 **FOYER**

Ken Fearon Career Café – Meet the Mentor
(attendance upon application and confirmation)

H
09:00 – 10:15 **METROPOLITAN BALLROOM**

GENERAL CACHEXIA

Multimodal interventions for cachexia

(each talk: 15 minutes)

Chairs: Kamyar Kalantar-Zadeh (USA)
Mitja Lainscak (Slovenia)

1. 09:00 – 09:15
Multimodal interventions in cancer and heart failure cachexia
Masaaki Konishi (Japan)

2. 09:15 – 09:30
Multi-Modal Integrated Exercise, Anti-inflammatory and Dietary counselling (MMIEAD) for kidney cachexia: protocol for a cRCT
Joanne Reid (UK)

3. 09:30 – 09:45
Update on nutrition and exercise interventions in renal cachexia
Adrian Slee (UK)

4. 09:45 – 10:00
Multi-modal therapy in cancer cachexia: what do the ENERGY and other trials tell us
Richard Skipworth (UK)

10:00 – 10:15
Discussion

I
09:00 – 10:15 **DUPONT BALLROOM**

CANCER CACHEXIA

Treatment-induced muscle deficits in cachexia

(each talk: 15 minutes)

Chairs: Andrea Bonetto (USA)
Paola Costelli (Italy)

1. 09:00 – 09:15
Mechanisms of radiation-induced muscle fibrosis
Michael De Lisio (Canada)

2. 09:15 – 09:30
Immune cell signature in chemotherapy-induced cachexia
Brandon VanderVeen (USA)

3. 09:30 – 09:45
Sex dependent effects in chemotherapy-induced cachexia
Nicholas Greene (USA)

4. 09:45 – 10:00
Musculoskeletal consequences of pediatric radiotherapy
Joe Chakkalakal (USA)

10:00 – 10:15
Discussion

10:15 – 11:15

Coffee Break

10:20 – 11:10 **POSTER AREA**

POSTER VIEWING 2

(each presentation: 2 minutes + 2 minutes discussion)

Poster session 2.1
Cachexia – mechanisms, animal models II (posters 1-10 to 1-11 and 1-13 to 1-22)
Chairs: Denis Guttridge, Sarah Lockie

Poster session 2.2
Cancer cachexia II (posters 3-34 to 3-42)
Chairs: Joanne Reid, Florian Strasser

Poster session 2.3
Diagnosis of sarcopenia I (posters 5-05 to 5-12)
Chairs: Richard Skipworth, Faisal Beg

Poster session 2.4
Muscle wasting & sarcopenia II (posters 6-16 to 6-24)
Chairs: Peggy Cawthon, Bill Evans

Poster session 2.5
Therapeutic development (clinical) (posters 9-01 to 9-11)
Chairs: Nicholas Brisson, Tobias Winkler

10:20– 11:10 **METROPOLITAN BALLROOM**

RAPID FIRE ABSTRACTS SESSION 2

(each presentation: 3 minutes + 2 minutes discussion)

Chairs: Elke Dworatzek (Germany)
Wei Yan (China)

10:20 – 10:25
Improved immune response and energy metabolism in the C26 tumor-bearing mice exposed to IL4 (3-03)
Giacomo Rubini (Italy)

10:25 – 10:30
The dynamic role of cardiac-infiltrating neutrophils in pancreatic cancer-induced cardiac dysfunction (3-05)
Aaron Grossberg (USA)

10:30 – 10:35
Impact of the emerging cancer cachexia-biomarker TIMP-1 on the liver (3-18)
Vanessa Brunner (Germany)

10:35 – 10:40
Cancer cachexia epidemiological landscape: lifetime prevalence and severity of cachexia in a population-based longitudinal study (3-21)
Bhumi Bhatt (Canada)

10:40 – 10:45
Adiposity specific micrornas in cancer patients: analysis of plasma levels according to fat distribution assessed by CT-scan (3-25)
Federica Tambaro (Italy)

10:45 – 10:50
Increased nivolumab clearance correlates with elevated GDF15 serum levels in patients with metastatic non-small cell lung cancer (3-29)
Wouter van de Worp (The Netherlands)

10:50 – 10:55
Identifying pretreatment blood metabolic markers associated with weight loss in head and neck cancer patients (3-33)
Ronald Eldridge (USA)

10:55 – 11:00
Practical cancer nutrition, from guidelines to clinical practice: the mypath® project (7-01)
Barry Laird (UK)

11:00 – 11:05
Differences on the prevalence of anorexia and clinical manifestations in patients with solid and hematological tumors who attend a tertiary care hospital from 2023 to 2024 (7-03)
María del Pilar Milke García (Mexico)

11:05 – 11:10
Intermittent hypoxic-hyperoxic training during inpatient rehabilitation improves exercise capacity and functional outcome in patients with long COVID: results of a controlled clinical pilot trial (8-06)
Wolfram Doehner (Germany)

J
11:15 – 12:30 METROPOLITAN BALLROOM

CANCER CACHEXIA

Cancer cachexia – hot topics

(each talk: 15 minutes)

Chairs: Egidio Del Fabbro (USA)
Mitja Lainscak (Slovenia)

1. 11:15 – 11:30
Is Cancer-Reated Fatigue (CRF) in advanced cancer equal to cachexia?
Florian Strasser (Switzerland)

2. 11:30 – 11:45
Effectiveness of self-management in improving hard outcomes in sarcopenia and fatigue cancer research
Ciaran Fairman (USA)

3. 11:45 – 12:00
Potential relevance of blood mitochondrial gene expression in sarcopenia and fatigue
Amber Kleckner (USA)

4. 12:00 – 12:15
Selected abstract talk:
GDF-15 neutralizing antibody visugromab overcomes cancer cachexia
José Medina-Echeverz (Germany)

12:15 – 12:30
Discussion

K
11:15 – 12:30 DUPONT BALLROOM

MECHANISMS, DIAGNOSTICS (BASIC / TRANSLATIONAL)

Novel approaches to the diagnosis of sarcopenia: translating research into practice

(each talk: 15 minutes)

Chairs: Hidenori Arai (Japan)
Bill Evans (USA)

1. 11:15 – 11:30
Sit-to-stand muscle power at the core of sarcopenia assessment
Julian Alcazar (Spain)

2. 11:30 – 11:45
D3Cr muscle mass as a clinically feasible assessment of muscle quantity
Peggy Cawthon (USA)

3. 11:45 – 12:00
Artificial intelligence to diagnose sarcopenia in CT and MRI images
Gustavo Duque (Canada)

4. 12:00 – 12:15
New biomarkers for sarcopenia
Marie-Theres Huemer (Germany)

12:15 – 12:30
Discussion

12:45 – 13:30

Lunch Break

12:45 – 13:30 **METROPOLITAN BALLROOM**

GDF-15 INHIBITION: EVOLVING INSIGHTS

Chairs: Jeffrey Crawford (USA)
Stefan Anker (Germany)

Introductory remarks (5 minutes)
Jeffrey Crawford (USA)
Stefan Anker (Germany)

Biological basis for GDF-15 inhibition (15 minutes)
Danna Breen (USA)

Potential therapeutic approaches to inhibiting GDF-15 in cancer cachexia and heart failure (15 minutes)
John Groarke (USA)

Q&A (10 minutes)
Jeffrey Crawford (USA)
Stefan Anker (Germany)

(Symposium supported by Pfizer)

L
13:45 – 15:00 **METROPOLITAN BALLROOM**

MECHANISMS, DIAGNOSTICS (BASIC / TRANSLATIONAL)

Biomarkers in muscle wasting: the intersect between cachexia, sarcopenia and frailty

(each talk: 15 minutes)

Chairs: John Batsis (USA)
Marie-Theres Huemer (Germany)

1. 13:45 – 14:00
Biomarkers of sarcopenia and cachexia in prostate cancer patients. The ADT Study
Jose Garcia (USA)

2. 14:00 – 14:15
Biomarkers of cachexia in cardiovascular disease
Stephan von Haehling (Germany)

3. 14:15 – 14:30
Biomarkers of frailty
Luigi Ferrucci (USA)

4. 14:30 – 14:45
Functional biomarkers of cancer cachexia
Ishan Roy (USA)

14:45 – 15:00
Discussion

M
13:45 – 15:00 **DUPONT BALLROOM**

GENERAL SARCOPENIA

Muscular disorders in critically and chronically ill patients

(each talk: 15 minutes)

Chairs: Joerg Schefold (Switzerland)
Tobias Winkler (Germany)

1. 13:45 – 14:00
Experimental studies on critical illness myopathy: underlying mechanisms and intervention studies
Lars Larsson (Sweden)

2. 14:00 – 14:15
Critical illness myopathy and critical illness polyneuropathy: pathophysiology
Coen Ottenheijm (The Netherlands)

3. 14:15 – 14:30
Critical illness associated (neuro-) muscular disorders
Joerg Schefold (Switzerland)

4. 14:30 – 14:45
Fasting associated muscle and fat tissue loss – the data, the mechanisms
Faiza Kalam (USA)

14:45 – 15:00
Discussion

15:00-16:00

Coffee Break

15:05–15:55 **POSTER AREA**

POSTER VIEWING 3

(each presentation: 2 minutes + 2 minutes discussion)

Poster session 3.1
Cachexia – mechanisms, basic (posters 2-01 to 2-11)
Chairs: Nicholas Greene, Andrew Judge

Poster session 3.2
Cancer cachexia III (posters 3-13 to 3-23)
Chairs: Joanne Reid, Florian Strasser

Poster session 3.3
Diagnosis of sarcopenia II (posters 5-01 to 5-04 and 5-13 to 5-15)
Chairs: Faisal Beg, Richard Skipworth

Poster session 3.4
Muscle wasting & sarcopenia III (posters 6-25 to 6-32)
Chairs: Wolfram Doehner, Sabbah Hussain

Poster session 3.5
Therapeutic development (pre-clinical) I (posters 10-01 to 10-07)
Chairs: Paola Costelli, Jeffrey Crawford

15:05 – 15:55 **METROPOLITAN BALLROOM**

RAPID FIRE ABSTRACTS SESSION 3

(each presentation: 3 minutes + 2 minutes discussion)

Chairs: Gustavo Duque (Canada)
Reshma Merchant (Singapore)

15:05 – 15:10
Associations of low lean mass by EWGSOP2, FNIH and EASO/ESPEN and MRI muscle composition with all-cause mortality across BMI classes (5-05)
Jennifer Linge (Sweden)

15:10 – 15:15
Comparing predictive ability of sarcopenia definitions using muscle ultrasound for clinical outcomes among older inpatients (5-10)
Nicola Merz (Switzerland)

15:15 – 15:20
Assessing the validity of serological biomarkers in estimating muscle mass: a retrospective cross-sectional NHANES analysis (5-12)
Christian Arias (USA)

15:20 – 15:25
AMPK in skeletal muscle as a therapeutic target for sarcopenic obesity (6-07)
Haiming Kerr (USA)

15:25 – 15:30
The role of hepatokines in MASLD associated muscle wasting (6-13)
Amy Rose Fumo (Germany)

15:30 – 15:35
MyoMed-205 counteracts titin hyper-phosphorylation, muscle dysfunction and atrophy in an animal model of HFpEF (6-14)
Beatrice Vahle (Germany)

15:35 – 15:40
Angiotensin type 2 receptor deficiency exacerbates physical decline and cardiac muscle wasting in aged mice (6-15)
Michael Abadir (USA)

15:40 – 15:45
Radiation reduces fibro/adipogenic progenitor-derived follistatin-like 1 to impair myoblast differentiation (6-16)
Cooper Brabrook (Canada)

15:45 – 15:50
Impact of Ilk1 and Fermt2 AAV-mediated knockdown on sepsis-induced muscle weakness (6-17)
Alexander Pacolet (Belgium)

15:50 – 15:55
Effect of caffeine consumption in patients undergoing immunotherapy for melanoma and lung cancer (7-06)
Paula Ravasco (Portugal)

N
16:00 – 17:15 METROPOLITAN BALLROOM

NUTRITION

Metabolic and nutritional changes in advanced cancer

(each talk: 15 minutes)

Chairs: Wolfram Doehner (Germany)
Tateaki Naito (Japan)

1. 16:00 – 16:15
Body adipose tissue changes in women with advanced breast cancer
Alessio Molfino (Italy)

2. 16:15 – 16:30
Nutritional and symptom considerations in patients with advanced cancer
Egidio Del Fabbro (USA)

3. 16:30 – 16:45
Pancreatic cancer cachexia: is it nutrition-sensitive?
Maurizio Muscaritoli (Italy)

4. 16:45 – 17:00
Selected abstract talk:
Early signatures of cachexia in pancreatic cancer: the importance of fat tissue
Adam Kuchnia (USA)

17:00 – 17:15
Discussion

O
16:00 – 17:15 DUPONT BALLROOM

MUSCLE WASTING

Muscle wasting in critical illness and injury

(each talk: 15 minutes)

Chairs: Joerg Schefold (Switzerland)
Teresa Zimmers (USA)

1. 16:00 – 16:15
The physiological rationale for cachexia: recovery from organ injury
Leonidas Koniaris (USA)

2. 16:15 – 16:30
Burn-induced cachexia
Jeevendra Martyn (USA)

3. 16:30 – 16:45
Persistent Inflammatory / Immunosuppressive Catabolic Syndrome (PICS) after sepsis
Philip Efron (USA)

4. 16:45 – 17:00
Sepsis-induced muscle weakness and dysfunction
Hiroshi Saito (USA)

17:00 – 17:15
Discussion

17:15 – 17:30

Break

P
17:30 – 18:45 METROPOLITAN BALLROOM

GENERAL CACHEXIA

Artificial intelligence for cachexia and sarcopenia

(each talk: 15 minutes)

Chairs: Luigi Ferrucci (USA)
Richard Skipworth (UK)

1. 17:30 – 17:45
Using AI to identify early cachexia; results from national database
Michael Yule (UK)

2. 17:45 – 18:00
Artificial intelligence for body composition and sarcopenia evaluation on computed tomography
Faisal Beg (Canada)

3. 18:00 – 18:15
RNAome guided classification of human skeletal muscle subtypes in cancer cachexia (AI-non-negative matrix factorization method)
Vickie Baracos (Canada)

4. 18:15 – 18:30
Selected abstract talk:
Automatized workflows for assessing the dynamics of muscle wasting
Wouter van de Worp (The Netherlands)

18:30 – 18:45
Discussion

Q
17:30 – 18:45 DUPONT BALLROOM

GENERAL SARCOPENIA

The association of sarcopenia on organ and system dysfunction

(each talk: 15 minutes)

Chairs: Wolfram Doehner (Germany)
Reshma Merchant (Singapore)

1. 17:30 – 17:45
Cardiometabolic effect
Andrew Coats (Australia)

2. 17:45 – 18:00
Osteosarcopenia
Gustavo Duque (Australia)

3. 18:00 – 18:15
Effect on cognition
Miguel Borda (Norway)

4. 18:15 – 18:30
Fat and muscle interactions in the context of obesity
John Batsis (USA)

18:30 – 18:45
Discussion

R
08:00 – 08:50 **METROPOLITAN BALLROOM**

YOUNG INVESTIGATORS AWARD SESSION

(each presentation: 5 minutes + 3 minutes discussion)

Chairs / Judges:
Zaver Bhujwalla (USA)
Samuel Breit (Australia)
Lars Larsson (Sweden)
Florian Strasser (Switzerland)
Eileen White (USA)

08:00 – 08:08
Pancreatic cancer induces population-specific, heterogeneous activation of cachexia genes and reverts differentiation in skeletal muscle myocytes (1-09)
Brittany Counts (USA)

08:08 – 08:16
The LEAP2 response to cancer-related anorexia-cachexia syndrome (2-07)
Salil Varshney (USA)

08:16 – 08:24
KPC pancreatic cancer disrupts the skeletal muscle circadian transcriptome in a FoxP1-dependent manner (2-08)
Jeremy Ducharme (USA)

08:24 – 08:32
An exploration of the GLIM inflammation criteria to predict survival in patients with advanced cancer (4-02)
Chattarin Pumtako (UK)

08:32 – 08:40
Ubiquitous and unseen: cancer cachexia at the end of life (4-09)
Michael Yule (UK)

08:40 – 08:48
Multi-kinase inhibitor Sorafenib triggers cachexia by disrupting the activity of distinct chromatin regulators (2-04)
Bushra Khan (Germany)

S
09:00 – 10:15 METROPOLITAN BALLROOM

GENERAL CACHEXIA

Neural control of cachexia – covering appetite control, neuroinflammation to metabolism

(each talk: 15 minutes)

Chairs: Aaron Grossberg (USA)
Puneeth Iyengar (USA)

1. 09:00 –09:15
Neural control of anorexia
Tobias Janowitz (USA)

2. 09:15 – 09:30
Appetite control and metabolic changes in cancer cachexia
Marcus Goncalves (USA)

3. 09:30 – 09:45
Alterations in brain metabolites in pancreatic cancer cachexia
Zaver Bhujwalla (USA)

4. 09:45 – 10:00
The role of the leptin pathway in amplifying the anorexic effects of GDF15
Samuel Breit (Australia)

10:00 – 10:15
Discussion

T
09:00 – 10:15 DUPONT BALLROOM

GENERAL SARCOPENIA

Advanced biologic and motion therapies for musculoskeletal diseases

(each talk: 15 minutes)

Chairs: Vickie Baracos (Canada)
Steven Heymsfield (USA)

1. 09:00 –09:15
HIPGEN - lessons learned from a Phase III study on allogeneic cell therapy for muscle regeneration in hip fracture patients
Tazio Maleitzke (Denmark)

2. 09:15 – 09:30
Regulatory T-cell targeting biomaterials for skeletal muscle regeneration
Brian Kwee (USA)

3. 09:30 – 09:45
PROTO - digital training therapy for correction of movement after ligament surgery in knee patients
Nicholas Brisson (Canada)

4. 09:45 – 10:00
The Advanced Therapies in Orthopaedics Alliance (ATiO) - an endeavour to create the medicine of the future for musculoskeletal diseases
Tobias Winkler (Germany)

10:00 – 10:15
Discussion

10:15 – 11:15

Coffee Break

10:20 – 11:10 POSTER AREA

POSTER VIEWING 4

(each presentation: 2 minutes + 2 minutes discussion)

Poster session 4.1
Cancer cachexia IV (posters 3-24 to 3-33)
Chairs: Andrea Bonetto, Tobias Janowitz

Poster session 4.2
Muscle wasting & sarcopenia IV (posters 6-09 to 6-15)
Chairs: Wolfram Doehner, Sabbah Hussain

Poster session 4.3
Therapeutic development (pre-clinical) II (posters 10-08 to 10-14)
Chairs: Paola Costelli, Jeffrey Crawford

U

11:15 – 12:30 **METROPOLITAN BALLROOM**

LATE BREAKING SCIENCE

(talk 1-5: 7 minutes + 3 minutes discussion, talk 6 and 7: 10 minutes + 3 minutes discussion)

Chairs: Stefan Anker (Germany)
Andrew Coats (Australia)
Jose Garcia (USA)

1. 11:15 – 11:22
Cachexia in chronic illness – results of a country-wide registry (3-16)
Mitja Lainscak (Slovenia)

2. 11:25 – 11:32
MENAC - a randomised, open-label trial of a multimodal intervention (exercise, nutrition and anti-inflammatory medication) plus standard care versus standard care alone to attenuate cachexia in patients with incurable lung or pancreatic cancer undergoing systemic anti-cancer therapy (9-08)
Barry Laird (UK)

3. 11:35 – 11:42
A synbiotic improves muscle strength, mass and performance in older Australians: preliminary results from a randomized, controlled trial (9-02)
David Barry (Australia)

4. 11:45 – 11:52
BIO101: a drug candidate to reduce GLP1-RA-induced muscle mass or function loss in patients with obesity (9-11)
Rob Van Maanen (France)

5. 11:55 – 12:02
Cancer Appetite Recovery Study (CAReS): Phase 1 dose-ascending, multicenter trial of ART27.13 in patients with cancer anorexia and weight loss
Barry Laird (UK)

6. 12:05 – 12:15
Optimal responders to anamorelin: insights from ROMANA trials (3-28)
Richard Skipworth (UK)

7. 12:18 – 12:28
Efficacy and safety of ponsegromab, a first-in-class, monoclonal antibody inhibitor of growth differentiation factor 15, in patients with cancer cachexia (9-10)
Jeffrey Crawford (USA)

12:30 – 13:30

Lunch Break

12:45 – 13:20 **METROPOLITAN BALLROOM**

DIAGNOSING AND REPORTING CACHEXIA: WHERE ARE WE?

Chairs: Stefan Anker (Germany)
Andrew Coats (Australia)

How to diagnose cachexia in 2025
Stephan von Haehling (Germany)

Cachexia coding: facts, numbers, and challenges
Mitja Lainscak (Slovenia)

How to increase awareness about body wasting and cachexia
Wolfram Doehner (Germany)

(Symposium supported by Splošna bolnišnica Murska Sobota)

V

13:30 – 14:45 **METROPOLITAN BALLROOM**

GENERAL CACHEXIA

Metabolic alterations & damage of certain organs in cachexia

(each talk: 15 minutes)

Chairs: Andrea Bonetto (USA)
Andrew Judge (USA)

1. 13:30 – 13:45
What about the diaphragm in cachexia
Volker Adams (Germany)

2. 13:45 – 14:00
IL-6 induces early cachexia via hepatic STAT-3
Aaron Grossberg (USA)

3. 14:00 – 14:15
Leukemia inhibitory factor impact on hepatic lipid metabolism
Wenwei Hu (USA)

4. 14:15 – 14:30
Transcriptional reprogramming of the liver in cancer cachexia
Mauricio Berriel Diaz (Germany)

14:30 – 14:45
Discussion

W

13:30 – 14:45 **DUPONT BALLROOM**

CANCER CACHEXIA

Ghrelin in cancer cachexia: exploring innovative horizons

(each talk: 15 minutes)

Chairs: Samuel Breit (Australia)
Barry Laird (UK)

1. 13:30 – 13:45
Interrogating the Ghrelin-AgRP system in the KPC mouse model
Sarah Lockie (Australia)

2. 13:45 – 14:00
Macimorelin results from a pilot trial and future directions
Jose Garcia (USA)

3. 14:00 – 14:15
Anamorelin in Japan
Hidetaka Wakabayashi (Japan)

4. 14:15 – 14:30
Biology of PEP-64 – a long-acting stabilized ghrelin analogue
Jenna Hunt (Denmark)

14:30 – 14:45
Discussion

14:45 – 15:45 **METROPOLITAN BALLROOM**

HIGHLIGHTS SESSION

Chairs: Vickie Baracos (Canada)
Jeffrey Crawford (USA)

Basic science
Erin Talbert (USA)

Nutrition
Florian Strasser (Switzerland)

Sarcopenia
Hidenori Arai (Japan)

Cancer cachexia
Aminah Jatoi (USA)

Poster Award
Young Investigator Award
Farewell

ABSTRACTS OF ORAL PRESENTATIONS

A1 *(12 minutes)*

New insights on the role of purine metabolism in age- and cancer-induced muscle atrophy

Chandler S. Callaway[1], Paul A. Roberson[2], Patrick D. Livingston[1], Lila Mouchantat[1], Leah J. Novinger[1,3], Natalia M. Weinzierl[1], Nicholas A. Jamnick[1], Joshua R. Huot[4], Fabrizio Pin[4], **Andrea Bonetto**[1,2]

[1]*Department of Pathology, School of Medicine, University of Colorado Anschutz Medical Campus*
[2]*Division of Endocrinology, Metabolism and Diabetes, University of Colorado Anschutz Medical Campus*
[3]*Comprehensive Cancer Center, University of Colorado Anschutz Medical Campus*
[4]*Department of Anatomy, Cell Biology & Physiology, Indiana University School of Medicine, Indianapolis, IN, USA*

Sarcopenia is the age-related loss of skeletal mass and function that physiologically occurs in older adults, whereas cachexia is a multifactorial syndrome characterized by progressive muscle and fat wasting that frequently associates with the onset of cancer. Both conditions are known to reduce treatment efficacy and negatively impact quality of life and disease outcomes.
To the extent of identifying new pro-cachectic factors and potential targets for intervention, here we found that phosphoribosyl pyrophosphate synthetase 1 (PRPS1)[1], an enzyme that synthesizes purine and pyrimidine nucleotide bases and is rate-limiting for purine metabolism, is highly expressed in skeletal muscle across multiple models of cancer cachexia (C26, HCT116, and ES2)[2, 3]. C2C12 murine myotubes infected with adenoviral constructs to overexpress PRPS1 were smaller at baseline and showed increased xanthine oxidase abundance and activity, coincident with increased pro-catabolic signaling (pSTAT3, pSMAD2, *Trim63,* and *Fbxo32).* Interestingly, elevated PRPS1 did not affect myoblast differentiation and fusion, whereas it was sufficient to disrupt several metabolic pathways and to drive greater atrophy when the myotubes were exposed to conditioned media from cancer cells.
Our data suggests that elevated PRPS1 in skeletal muscle occurs during aging and cachexia. Overexpression of this factor in muscle cells results in PRPS1 superactivity as evidenced by elevated xanthine oxidase levels and activity. This overexpression results in increased pro-catabolic signaling in myofibers without impacting differentiation and worsens cancer-induced myotube atrophy. Overall, our findings demonstrate that PRPS1 contributes to skeletal muscle pathology, thereby supporting further studies aimed at targeting this factor to mitigate skeletal muscle wasting resulting from cancer or aging.

References:

1. de Brouwer APM, Christodoulou J. Phosphoribosylpyrophosphate Synthetase Superactivity. In: Adam MP, Feldman J, Mirzaa GM, Pagon RA, Wallace SE, Bean LJH, Gripp KW, Amemiya A, editors. GeneReviews((R)). Seattle (WA)1993.
2. Huot JR, Novinger LJ, Pin F, Bonetto A. HCT116 colorectal liver metastases exacerbate muscle wasting in a mouse model for the study of colorectal cancer cachexia. Disease models & mechanisms. 2020;13(1). Epub 20200124. doi: 10.1242/dmm.043166. PubMed PMID: 31915140; PMCID: PMC6994937.
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A2 *(12 minutes)*

Metabolic crosstalk mechanisms in cancer cachexia

Pauline Morigny[1], Honglei Ji[1], Alisa Maier[1], Yun Kwon[2], Michaela Vondrackova[3], Radka Trubackova[3], Laura Cussonneau[4], Sabrina Zorzato[4], Fabien Riols[1], Tuna F. Samanci[1], Doris Kaltenecker[1], Tania Krauß[5], Claudine Seeliger[5], Mark Haid[1], Hans Hauner[5], Jerome Gilleron[6], Anja Zeigerer[2], Dominik Lutter[1], Stephan Herzig[1], Bert Blaauw[4], Ondrej Kuda[3], Maria Rohm[1]

[1]Helmholtz Munich, Neuherberg, Germany; [2]Heidelberg University, Mannheim, Germany; [3]Czech Academy of Sciences, Prague, Czech Republic; [4] Veneto Institute of Molecular Medicine, Padova, Italy; [5]Klinikum rechts der Isar, Munich, Germany; [6]Mediterranean Center for Molecular Medicine, Nice, France

Cancer cachexia is still a life-threatening, unresolved disease, which is lacking efficient diagnosis tools and therapy options for its care. Cachexia affects all tissues in the body, ranging from skeletal muscle, adipose tissue, liver, brain, heart, blood cells, among others[1,2]. A key node in cachexia research is the understanding of multi-tissue communication, secretion of pro-cachectic factors and common metabolic alterations. Our research focusses on the study of tissue crosstalk in cachexia with the aim of identifying new metabolic pathways involved in whole-body wasting[3]. Based on metabolomic analysis in various mouse models of cachexia and weight-stable cancer, we identified specific metabolic pathways involved in the alterations of various body compartments. By combining in vitro and in vivo experiments, we confirmed a causal role of these pathways on the mitochondrial capacity to produce energy. Ultimately, we validated our main findings in humanized conditions. Overall, our research identified new metabolic pathways affecting different metabolic tissues and potentially contributing to cachexia development.

References:

[1] Rohm, Schäfer et al. Nat Med, 2016.
[2] Kaltenecker, Al-Maskari, Negwer et al. Nat Methods, 2024.
[3] Morigny, Zuber *et al*. J Cachexia Sarcopenia Muscle, 2020.

A3 *(12 minutes)*

Impaired cAMP/CREB1 signaling drives mitochondrial dysfunction in skeletal muscle during cancer cachexia

Andrea Graziani
University of Turin, Department of Molecular Biotechnology and Health Sciences, Turin, Italy

Skeletal muscle wasting is a hallmark of cachexia, a cancer-associated syndrome that severely affects patients' quality of life. Emerging evidence indicates that at early stages of cachexia a large transcriptional network of genes involved in mitochondrial biogenesis, dynamics, and function is down-regulated in skeletal muscle, thus leading to mitochondrial dysfunction and muscle wasting[1-3]. Here, by exploiting *in vivo* and *in vitro* cachexia models, we report that i) tumor-induced impairment of cAMP/CREB1 signaling in skeletal muscle contributes to the downregulation of the transcriptional network sustaining mitochondrial function; ii) the cAMP-hydrolyzing phosphodiesterase 4D (PDE4D), whose transcript variants are deregulated in cachectic muscle, mediates tumor-induced cAMP signaling impairment *in vitro*; iii) boosting cAMP signaling by targeting PDE4 *in vivo* rescues mitochondrial-related gene expression, mitochondrial dysfunction, and mitigates muscle wasting. Collectively, we identified tumor-induced impairment of cAMP/CREB1 signaling as a driver of skeletal muscle mitochondrial dysfunction occurring during cancer cachexia.

References:
1) Brown, J.L., Rosa-Caldwell, M.E., Lee, D.E., Blackwell, T.A., Brown, L.A., Perry, R.A., Haynie, W.S., Hardee, J.P., Carson, J.A., Wiggs, M.P., et al. (2017). Mitochondrial degeneration precedes the development of muscle atrophy in progression of cancer cachexia in tumour-bearing mice. J. Cachexia Sarcopenia Muscle 8, 926–938.
2) Huot, J.R., Novinger, L.J., Pin, F., Narasimhan, A., Zimmers, T.A., O'Connell, T.M., and Bonetto, A. (2020). Formation of colorectal liver metastases induces musculoskeletal and metabolic abnormalities consistent with exacerbated cachexia. JCI Insight 5. 10.1172/jci.insight.136687
3) Delfinis, L.J., Bellissimo, C.A., Gandhi, S., DiBenedetto, S.N., Garibotti, M.C., Thuhan, A.K., Tsitkanou, S., Rosa-Caldwell, M.E., Rahman, F.A., Cheng, A.J., et al. (2022). Muscle weakness precedes atrophy during cancer cachexia and is linked to muscle-specific mitochondrial stress. JCI Insight 7. 10.1172/jci.insight.155147.

A4 *(12 minutes)*

Causal mechanisms in the mouse model of cancer cachexia - Lewis Lung Carcinoma

Xavier Clemente-Casares
Medical Microbiology and Immunology, University of Alberta, Cancer Research Institute of Northern Alberta, Li Ka Shing Institute of Virology, Canada

In 1951, Margaret R. Lewis isolated the Lewis Lung Carcinoma (LLC) from a spontaneous lung tumour in a C57BL/6 male mouse. LLC is a highly metastatic anaplastic epidermoid carcinoma. After many years of in vivo and in vitro passaging, this cell line has become hypermutated with at least 30 oncogenic mutations, including Kras, Nras, Trp53 and Cdkn2a/b deletions. Since its discovery, LLC has become a staple in cancer research, and cancer cachexia in particular.
Research on the mechanisms of LLC-mediated cachexia has uncovered a complex network of neural, endocrine and immune dysregulation that leads to muscle, fat and liver metabolic alterations. Many studies have probed the role of multitude of cytokines, transcription factors and metabolic pathways in LLC-mediated cachexia. Often, these studies have used systemic targeting or germ-line deficiencies making it difficult to pinpoint their main role in the chain of events that causes cachexia. The development of cell-specific or tissue-specific targeting strategies have provided important understanding in what is happening at end organ level (i.e. adipose tissue, muscle). However, we are just starting to understand upstream events related to the immune system, the CNS or other intermediate metabolic tissues.
Here, I will provide a synthesis of immunological mechanisms in LLC-mediated cachexia and with emphasis in a novel cell-mediated mechanism. LLCs are well-known to induce the expansion of a myeloid immune cell subset with immunosuppressive functions. We call this subset polymorphonuclear (or granulocytic) Myeloid-derived Suppressor Cells (PMN-MDSCs or gMDSCs). We and others have shown that gMDSCs expand and infiltrate a variety of tissues, including adipose tissue, skeletal muscles and the heart where they can cause severe dysfunction. gMDSCs suppress immune responses through a variety of mechanisms with strong effects in metabolism. Many gMDSC-derived effector molecules have been associated with the development of cachexia, including IL-6, IL-1b, TNFa, reactive oxygen species, lipocalin-2 or Activin A.

B1 *(12 minutes)*

Identifying Mytho as a new regulator of muscle autophagy

Sabbah Hussain
McGill University, Canada

Skeletal muscles play key roles in movement, posture, thermogenesis, and whole-body metabolism. Autophagy plays essential roles in the regulation of muscle mass, function and integrity. However, the molecular machinery that regulates autophagy is still incompletely understood. We identified and characterized a novel Forkhead Box O (FoxO)-dependent gene, PHAF1/MYTHO (phagophore assembly factor 1/macro-autophagy and youth optimizer), as a novel autophagy regulator that controls muscle integrity. MYTHO expression is substantially upregulated in multiple conditions leading to muscle atrophy. Short term depletion of MYTHO in mice attenuates muscle atrophy caused by fasting, denervation, cancer cachexia, and sepsis. While MYTHO overexpression is sufficient to induce muscle atrophy, prolonged downregulation of MYTHO causes a severe myopathic phenotype, which is characterized by impaired autophagy, muscle weakness, myofiber degeneration, mammalian target of rapamycin complex 1 (mTORC1) hyperactivation and extensive ultrastructural defects, such as accumulation of proteinaceous and membranous structures and tubular aggregates. This myopathic phenotype is attenuated upon administration of the mTORC1 inhibitor rapamycin. These findings position PHAF1/MYTHO as a novel regulator of skeletal muscle autophagy and tissue integrity.

B2 *(12 minutes)*

EDA2R-NIK signaling promotes muscle atrophy linked to cancer cachexia

Serkan Kir
Department of Molecular Biology and Genetics, Koc University, Istanbul, Turkey

Skeletal muscle atrophy is a hallmark of the cachexia syndrome that is associated with poor survival and reduced quality of life in cancer patients. Muscle atrophy involves excessive protein catabolism and loss of muscle mass and strength. Inflammatory cytokines have been implicated in muscle atrophy, however, available anti-cytokine therapies fail to prevent muscle wasting in cancer patients (1). An effective therapy against muscle wasting is lacking as mechanisms driving the atrophy process remain incompletely understood. Our recent work has revealed the upregulation of Ectodysplasin A2 Receptor (EDA2R) and Oncostatin M Receptor (OSMR) in tumor-bearing mice and cachectic cancer patients. Activation of EDA2R and OSMR signaling pathways promotes skeletal muscle atrophy (2, 3). Stimulation of primary myotubes with EDA2R ligand, EDA-A2, or OSMR ligand, OSM, triggers pronounced cellular atrophy via inducing the expression of muscle atrophy-related genes, such as *Atrogin1* and *MuRF1*. While EDA-A2 drives myotube atrophy via activating NFκB-inducing Kinase (NIK) and the noncanonical NFκB pathway, OSM triggers this process utilizing the JAK/STAT3 pathway. Both EDA-A2 and OSM promote muscle wasting in mice when overexpressed in this tissue. Tumor-bearing mice lacking EDA2R or muscle NIK are resistant to muscle wasting. Tumor-induced OSM upregulates muscle EDA2R expression and muscle-specific depletion of OSMR or neutralization of the circulating OSM preserves muscle mass and function in tumor-bearing mice. Our results demonstrate that EDA2R/NIK signaling mediates cancer-associated muscle atrophy in an OSM/OSMR-dependent manner. Thus, therapeutic targeting of these pathways may be beneficial in preventing muscle loss.

References:
1. Domaniku A, Bilgic SN, Kir S. Muscle wasting: emerging pathways and potential drug targets. Trends Pharmacol Sci. 2023; 44:705-18.
2. Bilgic SN, Domaniku A, Toledo B, Agca S, Weber BZC, Arabaci DH, et al. EDA2R-NIK signalling promotes muscle atrophy linked to cancer cachexia. Nature. 2023; 617:827-34.
3. Domaniku-Waraich A, Agca S, Toledo B, Sucuoglu M, Özen SD, Bilgic SN, et al. Oncostatin M signaling drives cancer-associated skeletal muscle wasting. Cell Rep Med. 2024; 5:101498.

B3 *(12 minutes)*

Regulation of muscle sarcomere maintenance and bioenergetics by an unsuspected E3 ligase: a new myopathy gene

Jorge L. Ruas
University of Michigan Medical School, Department of Pharmacology and Frankel Institute for Heart & Brain Health, Ann Arbor, MI, USA

Myopathies are muscle diseases with diverse phenotypic presentations, which range from severe neonatal manifestations to adult-onset forms. Diagnosis is based on clinical and histological features, often not specific to a particular myopathy form as different etiologies can have overlapping outcomes. Thus, identifying disease-causing mechanisms is fundamental to facilitate diagnosis and tailor therapies. We have compared skeletal muscle transcriptomics data from different forms of dystrophic and non-dystrophic myopathies in mice and humans, to identify common regulatory nodes. Here, we identify an E3 ubiquitin ligase that is necessary for sarcomere maintenance and integrity. Knocking out this gene in mouse skeletal muscle generated a mouse model with progressive molecular and phenotypic signs of combined nemaline and desmin myopathy, with mitochondriopathy. In line with these observations, we identified klhl40 and 41, nebulin, and desmin among the dysregulated proteins, together with other sarcomere thin filament proteins. We have identified two patients diagnosed with an unexplained muscle disease carrying a mutation in this E3 ligase gene, which is absent in the normal population. This work uncovers a novel molecular mechanism and diagnostic gene for myopathy, which encodes a critical component of the sarcomere maintenance machinery.

B4 *(12 minutes)*

GLP-2 treatment improves muscle recovery following starvation in rats: a clinical opportunity to reverse muscle wasting?

Denis Breuillé[1], Martin Lerembour[2], Didier Attaix[3]
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[2]Université Clermont Auvergne, Clermont Auvergne INP, CNRS, ICCF, 63000 Clermont-Ferrand, France.
[3]Université Clermont Auvergne and INRAE, UMR 1019, 63000 Clermont-Ferrand, France.

Muscle wasting prevails in numerous catabolic states associated to major diseases and ultimately resulting in the death of patients. So far, no treatment to preserve muscle protein mass has been approved. In this study, we hypothesized that the intestinal trophic factor Glucagon Like Peptide-2 (GLP-2) may improve skeletal muscle recovery after starvation. Our data show that GLP-2 treatment reduced lysosomal-autophagy intestinal proteolysis and maintained mTOR-S6K1 signaling in skeletal muscle during starvation and refeeding, improving recovery of both tissues. A direct effect of GLP-2 on skeletal muscle was suggested, involving an enhanced expression of the GLP2 receptor, improved muscle amino acid uptake and an effect on some amino acid transporters resulting in accelerated muscle recovery. Increased expression of the muscle GLP2 receptor was also observed in unrelated muscle wasting conditions, i.e. in dexamethasone treated mice and immobilized rats. Our findings show (i) that intestinal proteolysis is mainly lysosomal, (ii) an important interplay between the gut and skeletal muscle protein turnover and (iii) suggests a potential already approved therapeutic strategy by the FDA for intestinal disorders for counteracting muscle wasting in many deleterious diseases. Overall, this strategy may result in reduced health care costs, lengths of hospitalization and morbidity or mortality.

C2 *(20 minutes)*

"Prometheus" basic science key note lecture:

Evolution of Cachexia – Adaptive to Maladaptive

Teresa Zimmers
Department of Cell, Developmental, and Cancer Biology, Knight Cancer Institute, Portland, Oregon Health Science University, Portland, OR, USA

As a research community, we focus on cachexia as a disease. Certainly, tumor-mediated or infection/injury-mediated effects on the central nervous system, sympathetic nervous system, innate immune system and metabolism produce progressive wasting, dysfunction, and mortality. However, cachexia likely arose as an adaptive response to injury or infection. The talk will explore evidence for common mechanisms of cachexia across different conditions, contrasting cancer with organ injury and repair and the possibility of these being evolutionarily linked.

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C3 *(20 minutes)*

"Hippocrates" clinical science key note lecture:

Integrate the power of preventive nutrition, (p)rehabilitation and positive psychology into cancer cachexia management

Florian Strasser
Oncological Palliative Medicine, Clinic Oncology/Hematology, Cantonal Hospital St. Gallen, St. Gallen, Switzerland

Management of patient suffering from cancer cachexia encompasses typically, and as we recommend in guidelines (ESMO, ASCO, ESPEN), assurance of sufficient intake of energy and proteins, the latter with high percentage of animal-based origin. In addition, an as good as possible formal physical activity is recommended. The question is: is this still enough?

There are still too many patients with advanced cancer, who suffer from unrecognized malnutrition, caused by cancer cachexia and anticancer-treatment related toxicities leading to malnutrition. It is of crucial importance to provide adequate recognition and treatment of malnutrition. Also, it remains important to understand and alleviate eating-related distress in advanced cancer and end-of-life.

However, the potentially beneficial effects of cancer (recurrence) preventive nutrition, an evidence-base provided mainly by cohort studies and correlations, may become integrated in cancer cachexia focused nutrition. An anti-inflammatory, plant-based diet may improve tolerability[1], function[2], and anticancer[3] effects of anticancer treatment in advanced cancer. To achieve a dietary provision of all amino acids by plant-based proteins only, knowledge about digestibility of essential amino acid is necessary, and well-designed clinical trials. The dilemma of ultra-processed food elements in often vital oral nutritional supplements poses challenges to nutritional counselling.

Dietary interventions must be combined with physical exercise intervention and psychoeducation. Such trimodal interventions applied in prehabilitation before surgery, show better effects than physical exercise alone[4]. To achieve mid-longterm implementation of health-promoting multimodal interventions as daily routine, additional interventions may be necessary: cognitive behavioural therapy to foster change of habits, integrating practices of mindfulness, sleep hygiene, conscious daily rhythm, nurturing social warmth, and mindset changes supported by positive psychology interventions[5].

Patients demand both malnutrition preventing/resolving and anticancer dietary interventions, are (often) willing to change habits towards more healthy lives, and need the support of clinical and academic professionals in cancer cachexia.

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D1 *(15 minutes)*

Cancer-cell-secreted extracellular vesicles dysregulate proteolysis and mitochondrial function in skeletal muscle

Shizhen Emily Wang
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Our knowledge of short- and long-range intercellular communication experienced an exponential growth in the past decade partially owing to the discovery of the diverse functions of extracellular vesicles (EVs). EVs are a variety of membrane-enclosed nanosized particles that carry and transfer between cells functional cargoes including RNA, DNA, proteins, and lipids. Secretion of EVs is a fundamental and evolutionarily conserved biological process broadly found from bacteria to humans and in all cell types in a higher organism. Due to their bulk loading nature, EVs play a critical and versatile role in the intercellular communication perhaps in all physiological and pathological processes, including the cancer-host crosstalk. Research from our group and others has shown that cancer cell-secreted EVs partake in vascular remodeling, immunomodulation, and formation of pre-metastatic niches. Circulating EV-based biomarkers are being exploited for risk prediction, early diagnosis and prognosis of human diseases such as cancer. Recent studies from my group elucidate how EVs secreted by breast cancer cells influence the skeletal muscle. A decline in skeletal muscle mass and low muscular strength are prognostic factors in advanced human cancers. We find that breast cancer suppressed O-linked N-acetylglucosamine protein modification in muscle through EV-encapsulated miR-122-5p. This results in increased ryanodine receptor 1 and cytosolic calcium which induces calpain protease activation, cleavage of desmin filaments, and reduced skeletal muscle mass and contractility in tumor-bearing mice. We further find that miR-122-5p in cancer-cell-secreted EVs also targets the tumor suppressor TP53 in skeletal muscle to decrease the expression of TP53 target genes involved in mitochondrial regulation, including Tfam, Pgc-1a, Sco2, and 16S rRNA. As such, cancer cell-derived EV miR-122-5p impairs mitochondrial homeostasis and function in skeletal muscle, leading to decreased mitochondrial content and energy production and increased oxidative stress. Our findings thus reveal a critical mechanism of cancer-associated muscle dysregulation mediated by EV miR-122-5p.

D2 *(15 minutes)*

The art of war: blocking the secretion of extracellular vesicles from cachexia-inducing tumors

Sai Vara Prasad Chitti
La Trobe Institute for Molecular Science (LIMS), La Trobe University, Melbourne, VIC, Australia

Introduction: Cachexia, characterized by progressive wasting of muscle and fat, is a major cause of mortality in cancer patients, but clinical options against cachexia remain limited due to the multifactorial nature of the disease. Several seminal studies demonstrated that tumour-cell-released small extracellular vesicles (sEVs) containing key cachexins are necessary and sufficient to induce muscle and fat loss. Furthermore, it is now well known that cancer cells secrete more sEVs compared to non-cancerous cells. Hence, we examined whether decreasing the secretion of sEVs from tumour cells can inhibit cancer-induced cachexia.
Methodology: Cortactin (Cttn) was knocked out (KO) using CRISPR/Cas9 technology in colon cancer cells and sEVs were isolated and quantified. Co-culture and pre-clinical studies were carried out to study the cachectic phenotype. Fluorescence-based high-throughput screening assay was performed to identify the drugs that decreases sEVs secretion.
Results: Loss of Cttn inhibited the release of sEVs. While C26 wild-type (WT) derived sEVs induced atrophy in myotubes and lipolysis in adipocytes, Cttn-KO sEVs did not induce atrophy or lipolysis. Proteomics analysis of sEVs highlighted the enrichment of cachectic proteins in WT sEVs compared to KO sEVs. Follow-up C26 mice pre-clinical studies highlighted that Cttn-KO tumour-bearing mice exhibited stable body weight, reduced tumour burden, and dramatically extended lifespan compared to mice bearing WT tumour. Remarkably, Cttn-KO prevented tumour-induced loss of muscle, fat, and other major organs. To use these findings for therapeutic benefit, we screened the library of FDA-approved drugs and identified several drugs that blocks the release of sEVs. Administration of sEVs inhibitor to the cachexic mice resulted in the abolishment of cancer-associated cachexia and prolonged survival.
Conclusion: Overall, these findings indicate that decreasing sEVs release from tumour might be a promising approach to treat cancer-cachexia, improve quality of life, and extend the lifespan of cancer patients.

D3 *(15 minutes)*

The role of extracellular vesicles in adipose tissue

Wei Yan
College of Life Sciences, Wuhan University, Wuhan, China

Cancer-associated cachexia is a multi-organ weight loss syndrome, especially with a wasting disorder of adipose tissue and skeletal muscle. Our recent study shows breast cancer (BC) cell-secreted exosomal miR-204-5p induces hypoxia-inducible factor 1A (HIF1A) in white adipose tissue (WAT) by targeting von Hippel-Lindau (VHL) gene. Elevated HIF1A protein induces the leptin signalling pathway and thereby enhances lipolysis in WAT. Additionally, exogenous VHL expression blocks the effect of exosomal miR-204-5p on WAT browning. Reduced plasma phosphatidyl ethanolamine level is detected in mice lack of cancer-derived miR-204-5p secretion in vivo. Our study reveals circulating miR-204-5p induces hypoxia-mediated leptin signalling pathway to promote lipolysis and WAT browning, shedding light on both preventive screenings and early intervention for cancer-associated cachexia. Beyond, I will also share some preliemary data for the role of small extracellular vesicles in brown adipose tissue (BAT). We find BC secrets catalase protein through small extracellular vesicles (sEVs) to induce the peroxisome signaling in BAT. Intriguingly, catalase knockout in tumor dysregulates both thermogenesis and mass of BAT. Collectively, our work proves cancer cell-secreted sEVs carrying protein and miRNA cargoes, play vital role in cancer-associated cachexia.

D4 *(15 minutes)*

Chemotherapy drugs fluorouracil and cisplatin promote muscle wasting by stimulating cancer cell release of Hsp70/90-enriched extracellular vesicles

Yi-Ping Li
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Cancer cachexia is a lethal wasting syndrome characterized by muscle wasting. Chemotherapy often promotes cachexia with undefined mechanisms. Here we show that fluorouracil and cisplatin potentiate muscle wasting by stimulating cancer cell release of extracellular vesicles (EVs) enriched with Hsp70 and Hsp90. Therapeutically relevant doses of fluorouracil or cisplatin potentiate muscle wasting in mice bearing KPC pancreatic ductal adenocarcinoma while stimulating KPC cell release of EVs enriched with Hsp70 and Hsp90. In contrast, the same doses of the drugs do not cause muscle wasting in tumor-free mice. Increased EV release by the drugs is caused by Rab27a/b upregulation in response to NF-kB activation induced by the drugs. Mice xenografted with Rab27a/b-deficient KPC cells that do not release EVs are resistant to fluorouracil or cisplatin stimulation of Hsp70/90 release and muscle wasting. On the other hand, the drugs also stimulate release of EVs not enriched with Hsp70/90 from EL4 lymphoma cells that do not cause cachexia. Therefore, fluorouracil and cisplatin promote muscle wasting by stimulating cancer cell release of Hsp70/90-enriched EVs.

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E1 *(15 minutes)*

Metabolic alterations in tumor and host in cancer

Eileen White
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Cancer is a metabolic disease. Oncogenic events alter tumor cell metabolism to produce building blocks and mitigate redox stress while suppressing the high energy consuming functions of normal professional cells. Tumor cells also engage nutrient scavenging pathways (e.g. micropinocytosis for extracellular nutrients and autophagy for recycling of intracellular nutrients) to sustain metabolism. In advanced cancer, factors produced by tumors drive systemic inflammation and the wasting of host tissues, particularly the dedicated nutrient stores of muscle and fat, in a process known as cachexia. Cancer cachexia is responsible for most cancer deaths, but the underlying mechanisms are unclear. Determining who cancer metabolism is altered and how tumors alter the metabolism and function of host tissues can identify new targets for cancer therapy.

E2 *(15 minutes)*

Identifying metabolic alterations in cancer cachexia: quantitative fluxomics

Sheng Tony Hui
Harvard T.H. Chan School of Public Health, Boston, MA, USA

Cancer cachexia is characterized by systemic metabolic changes, targeting which can be a therapeutical strategy. In my talk, I will share our work on using the systematic flux quantification approach, or fluxomics, to identify metabolic alterations in the C26 cancer cachexia model. We focused on energy metabolism and determined the circulatory turnover fluxes for the major energy nutrients and their contribution to the TCA cycle in all major tissues. The flux results showed no change in lipolysis flux and whole-body protein degradation flux in the C26 model, contrary to common beliefs. Instead, the flux results revealed elevated glucose turnover flux, with increased glucose production from glutamine and alanine and increased glucose consumption by the brown adipose tissue, spleen, and small intestine. Thus, a unique feature of energy metabolism in the C26 model is reprogrammed glucose metabolism.

E3 *(15 minutes)*

Imaging metabolic adaptions in cancer cachexia using positron emission tomography (PET)

David Lewis, UK
Cancer Research UK Scotland Institute and University of Glasgow, Glasgow, UK

Cancer cachexia is a debilitating wasting syndrome that systemically disrupts metabolism. Despite its prevalence, the underlying metabolic changes remain poorly understood due to the challenges of obtaining tissue-level data. Advanced total-body PET imaging offers a non-invasive approach to visualize metabolic rewiring across multiple organs. Recent studies have highlighted dysregulated glucose homeostasis as a hallmark of cancer cachexia. To investigate this further, we have utilized [^{18}F]fluorodeoxyglucose ([^{18}F]FDG) PET imaging to map glucose uptake in both patients and genetically engineered mouse models of lung cancer cachexia.
By developing AI-automated pipelines for segmenting and characterizing metabolic activity across various organs, we have identified specific organ-level changes in [^{18}F]FDG uptake in mice. While some changes align with fasting-like metabolic responses, others, particularly in the heart and liver, suggest distinct metabolic alterations associated with cachexia. These findings correlate with alterations in glycolytic intermediates in these organs.
In clinical settings, we observed significant metabolic differences in the brain and heart between cachexic and non-cachexic patients. Machine learning techniques, such as Random Forest and Linear Discriminant Analysis, identified the brain, heart, pancreas, kidney, and muscles as key components of the whole-body metabolic signature of cachexia.
Our research demonstrates the potential of PET imaging to non-invasively identify distinct whole-body features of glucose utilization, providing insights into underlying mechanistic changes. To further elucidate inter-organ rewiring in glucose homeostasis, we are developing a next-generation toolkit for whole-body metabolic imaging of gluconeogenesis in cancer cachexia. This improved understanding holds promise for earlier detection, better classification, and more effective therapy monitoring for cancer cachexia patients.

E4 *(15 minutes)*

Improving insulin sensitivity to treat cancer cachexia in humans

Justin C. Brown
Pennington Biomedical Research Center, Baton Rouge, LA, USA

Insulin regulates various aspects of whole-body metabolism, including metabolic flexibility, muscle protein synthesis, and energy expenditure.[1] Insulin resistance reduces metabolic flexibility, impairs muscle protein synthesis, and increases energy expenditure among individuals without cancer. In cross-sectional studies, patients with cancer often have impaired insulin sensitivity, quantified using the gold standard hyperinsulinemic-euglycemic clamp.
Thiazolidinediones (TZDs) are insulin-sensitizing drugs with two agents, rosiglitazone and pioglitazone, currently approved by the U.S. Food and Drug Administration (FDA) for use in patients with type 2 diabetes. In patients with obesity and type 2 diabetes, TZDs increase hepatic and peripheral (e.g., skeletal muscle) insulin sensitivity. In tumor-bearing rodents, TZDs improve insulin sensitivity, prevent weight loss, preserve skeletal muscle, and improve appetite.[2]
Pioglitazone was approved by the U.S. FDA in 1999 with desirable insulin-sensitizing properties and an established safety profile in patients with type 2 diabetes. The ongoing TRACE-1 trial (https://clinicaltrials.gov/study/NCT05919147) is a randomized phase II study to evaluate the efficacy and safety of pioglitazone as compared with placebo for improving skeletal muscle insulin sensitivity in patients with advanced cancer and cachexia. The TRACE-1 trial will evaluate the hypothesis that sensitizing peripheral tissue to the action of insulin is a means to intercept cachexia to preserve muscle mass. The TRACE-1 trial is sponsored by the Cancer Grand Challenges of Cancer Research UK and the National Cancer Institute.

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F1 *(15 minutes)*

Nutrition options in cancer care

Paula Ravasco
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Muscle wasting and cachexia in cancer, derive from a negative balance of protein and energy caused by various combinations of reduced food intake and metabolic abnormalities. The main features are catabolism and negative protein–energy balance that is difficult to restore. The reversal or prevention of cancer cachexia and muscle wasting represent a major clinical challenge, urging an adequate, early and integrated nutritional intervention throughout the disease course and treatments.

Several studies show that early individualized nutrition support in patients with cancer with increased nutritional risk, reduced mortality and improved functional and quality of life outcomes. Early nutritional support has the potential to reduce the risk for therapy-threatening adverse events and to optimise the likelihood of treatment success and long-term survival. Oral nutrition supplements with dietary counselling are effective in increasing nutritional intake and improving QoL.
Although the optimal nutrient content for "an anti-cachexia diet" is still not defined, ESMO and ESPEN guidelines stress the need for maintaining calorie and protein intake. *Protein*: previously reported anabolic resistance may refer to a higher threshold needed for protein synthesis in response to an anabolic stimulus in patients with cancer. A higher range of protein intake (1.4–1.5-2.0 g/kg/day) seems needed to promote muscle mass balance. Protein source is also a topic of interest for patients and clinicians; although the optimal dietary amino acid composition to support muscle health in cancer is yet to be established, animal-based proteins have a composition that offers superior anabolic potential, compared to plant-derived proteins. Thus, animal-based foods should represent the majority (i.e., ≥65%) of protein intake during active cancer treatments. Ultimately, a dietary amino acid composition that promotes muscle anabolism is optimally obtained through combination of animal- and plant-based protein sources.
*Branched-chain amino acids, l*eucine, isoleucine, and valine have been investigated as target for nutritional therapy; current evidence suggests that BCAAs might help to ameliorate muscle loss in cancer.
β-hydroxy β-methylbutyrate (HMB) is thought to modulate protein turnover, primarily by minimizing protein degradation. Proteolysis is the main mechanism by which muscle is lost in cancer. Currently, HMB supplementation seems beneficial for muscle mass and function. Further research with longer interventions is needed.
Fish oil and eicosapentaenoic acid, *b*ecause of several recent positive clinical trials, a plausible biological rationale, and small side effects, fish oil and EPA could help to improve appetite, food intake, body weight and muscle mass, and modulate inflammation in individuals at risk for body composition alterations.
Glutamine is a non-essential amino acid that has many roles in human metabolism and can become conditionally essential in disease states. To date there is not enough evidence to support the general use of glutamine in patients with cancer.
Carnitine is a di-peptide which can be obtained from food or formed via the conversion from lysine and has traditionally been used in athletic populations as an ergogenic aid. To date there is not enough evidence to recommend carnitine as a potential supplement to prevent or mitigate low muscle mass in cancer.
Creatine is a tripeptide composed of arginine, methionine, and glycine. In older populations, creatine supplementation can improve lean mass and muscle function. Less is known in cancer. Some small studies seem to show a positive effect on body cell mass and function but further research is needed to elucidate the potential efficacy of this supplement for mitigating low muscle mass in cancer.
Vitamins and minerals during the disease trajectory, there is risk of micronutrient deficiency. To date there is insufficient evidence to support the use of vitamin or mineral supplements. Studies have shown that side effects of therapy such as vomiting or diarrhea might deplete micronutrients, i.e. vitamins A and E. Zync supplementation has been studied in the context of dysgeusia with possible positive impact in improving intake. Vitamin D deficiency may be of concern for patients with cancer. Sufficient vitamin D might also be needed for other supplements to be effective. Ensuring adequate levels may be advantageous in the prevention or treatment of low muscle mass.
Immunonutrition in patients who have undergone oncological surgery decreased the levels of inflammatory markers and infectious postoperative complications in almost all localizations. In patients with upper gastrointestinal cancer in the postoperative period, immunonutrition reduced the risk of infectious complications to about 30%.
Fiber and microbiome have been identified as positive to improve immunotherapy efficacy; higher dietary fiber was associated with significantly improved progression-free survival, seeming a low-cost intervention with high clinical impact. In a recent systematic review in colorectal cancer, administration of pre-, pro-, or symbiotic improved surgical outcomes, e.g. incidence of infectious and non-infectious complications, return to normal gut function, hospital length of stay, and antibiotic usage. The supplementation of these microorganisms also alleviated some symptoms from chemotherapy and radiotherapy, mainly diarrhea. More RCTs with larger sample sizes and less heterogeneity are needed to confirm these potential benefits and determine the best strains, dosage, and duration.
Exercise and Nutrition Prehabilitation had a positive effect on Functional Capacity in esophagogastric cancer surgery.

F2 *(15 minutes)*

Microbiota and nutrition in oncology: a new player?

Carolina Trabulo
Faculty of Health Sciences and Nursing, Universidade Católica Portuguesa, Lisbon; Medical Oncology Unit, Unidade de Saúde Local Arco Ribeirinho, Lisbon, Portugal

The gut microbiome is increasingly being recognized for its influence on intestinal and extra-intestinal disorders such as cancer. Recent research highlights the critical interplay between diet, the gut microbiome, and cancer treatment outcomes. Despite the established importance of nutrition, the interaction between malnutrition and the microbiome in cancer therapy remains underexplored.
Current evidence suggests that diet can modify the gut microbiome's composition and diversity, potentially enhancing treatment responses and reducing toxicities associated with cancer therapies. Aiming to consolidate existing knowledge on how dietary intake and microbiota influence cancer treatment, we will explore the theme and pave the way for precision nutrition strategies that could improve cancer outcomes.

F3 *(15 minutes)*

Balanced nutrition to prevent protein-energy wasting and preserve renal function in chronic kidney disease

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Department of Nephrology, The Lundquist Institute for Biomedical Innovation at Harbor-UCLA Medical Center, Torrance, CA, USA

Protein-Energy Wasting (PEW), secondary sarcopenia, and cachexia are common in chronic kidney disease (CKD) and strong predictors of adverse outcomes. The prevalence of PEW in early to moderate CKD is 20-25% and increases as CKD progresses, in part because of activation of proinflammatory cytokines combined with superimposed hypercatabolic states and declines in appetite. This anorexia leads to inadequate protein and energy intake. A decline in body protein mass and energy reserves ensues, including muscle and fat wasting and visceral protein pool contraction. Worsening uremia also renders CKD patients vulnerable to potentially deleterious effects of uncontrolled diets, including higher phosphorus and potassium burden. Uremic metabolites, some of which are anorexigenic and many of which are products of protein metabolism, can exert harmful effects, ranging from oxidative stress to endothelial dysfunction, nitric oxide disarrays, renal interstitial fibrosis, sarcopenia, and worsening proteinuria and kidney function. Given such complex pathways, nutritional interventions in CKD, when applied in concert with non-nutritional pharmaco-therapeutic approaches, encompass an array of strategies aimed at optimizing both patients' biochemical variables and their clinical outcomes. Long-term consumption of high dietary protein intake (DPI) in individuals of older age and/or with CKD may contribute to kidney function deterioration over time. Prescription of a plant-dominant (PLADO) low-protein diet of 0.6-0.8 g/kg/day with >50% protein from plant sources or very low protein diets supplemented with essential amino acids or their keto-analogues may be effective in preserving kidney function in older patients and their younger counterparts, while also monitoring for development of PEW and cachexia. Using tailored precision nutrition approaches in prescribing PLADO diet with low DPI that also maintains adequate energy and nitrogen balance may ameliorate kidney function decline while also preventing development of PEW and sarcopenia in elderly patients or any age with CKD.

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F4 *(15 minutes)*

Uncoupling chronic cardiac wasting-associated cardiomyopathy from tumor and skeletal muscle wasting in cancer cachexia

Joseph Metzger
Department of Integrative Biology & Physiology, Medical School, University of Minnesota, Minneapolis, MN, USA

Cancer cachexia is a multifactorial syndrome of skeletal muscle wasting that affects 50-80% of cancer patients and contributes to poor prognosis, a depreciating quality of life, and high mortality. Notably, cancer cachexia also markedly adversely affects the heart and can lead to heart failure that is responsible for 20-30% of cancer deaths. To date, it has been very challenging to ascertain the disease-causing roles emanating from the tumor, from cardio-toxic anti-tumor drugs, and the debilitating effects of skeletal muscle wasting on cancer-induced heart disease and its long-term evolution. We show here a new reversible cancer cachexia model, featuring tumor-based cachexia induction and remission, that enables long-term post-tumor studies independent of cardio-toxic anti-cancer therapies in mice. Data show that upon tumor cell implantation, severe cachexia developed over a three-week time period at which time the tumor was efficiently ablated via induction of a tumor cell engineered suicide gene program. Notably, upon tumor remission, deficits in body composition and skeletal muscle mass/function, via muscle wasting pathways including MuRF-1 and Atrogin, were all restored to normal. Strikingly, however, data reveal in these post-tumor/post-cachexia animals long-term cardiac muscle wasting-associated cardiomyopathy and progression to fulminant heart failure. Collectively, these findings reveal a cancer-induced chronic hypotrophic cardiomyopathy that persists after tumor regression, independently of the skeletal muscle wasting, and cardio-toxic drugs in cancer survivor mice. These new findings point to factors intrinsic to the heart that underlie the basis of severe atrophic cardiomyopathy post-tumor in cancer remission. Details of the mechanistic underpinnings of these interesting findings will be discussed.

G1 *(8 minutes)*

The GLP1-RA evidence base for clinical benefits in obesity

Javed Butler
Baylor Scott and White Research Institute, Dallas, TX, USA

The presentation will discuss if GLP1RA benefit in weight reduction is clinically meaningful in patients with ASCVD, HF, and CKD and what is the next generation of evidence that is needed.

G2 *(8 minutes)*

How do GLP1-RA cause weight loss?

Henning Tim Langer
Muscle Wasting Laboratory, Department of Geriatrics and Medical Gerontology, Charité-Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt- Universität zu Berlin, Berlin, Germany

According to the World Obesity Federation, the prevalence of patients who are overweight or obese has tripled since the 1970s, currently affecting almost 3 billion people worldwide. After decades of unsuccessful attempts of designing safe and effective anti-obesity medications (AOM), the discovery of incretin-based therapies has revolutionized the battle against obesity. For example, the GLP-1 receptor agonist (GLP-1RA) semaglutide caused 15% weight loss compared to baseline after 68 weeks of treatment in patients without diabetes (1). However, in a subpopulation of this study investigated for changes in body composition, it was found that almost 40% of this weight loss was due to a decrease in lean body mass (LBM) (1). Traditionally, the loss of LBM during physiological interventions such as calorie restriction is estimated to be ~25% (2). With a rapidly increasing number of patients relying on these AOM, this spurred a concern for the effect of incretin-based therapies on muscle mass and function, ultimately impacting the prevalence of sarcopenia and sarcopenic obesity (3). To test whether incretin-based therapies affect skeletal muscle pre-clinically, we performed a 2-week trial in mice with diet-induced-obesity (DIO). Changes in body composition, muscle mass, muscle fiber size, and grip strength were compared between groups that received GLP1-RA, long-acting glucagon receptor agonist (LA-GCGRA), a triple agonist (GLP-1RA/GiPRA/GCGRA), no treatment (vehicle), or calorie reduction. Each of the pharmacological treatments was subdivided into a low and a high dose. We found that, both, pharmacological and physiological interventions caused significant reductions in body weight, fat, and LBM. However, muscle mass and grip strength were barely affected by the loss of LBM. In contrast, we saw robust decreases in liver mass and intra-hepatic fat. To further assess the effect of incretin-based therapies on muscle function, we performed a separate experiment, where we treated DIO mice for 4-weeks with a triple agonist and tested running performance. We found that the mice with the largest loss of body weight and LBM registered the best running performance. Our data in mice is in line with surveys from patients with obesity, who reported improved mobility and physical function despite a decrease in LBM with semaglutide (1). As such, we conclude that incretin-based therapies not just effectively cause weight loss but also appear to favorably affect body composition without disproportionately compromising muscle mass. A decrease in LBM and muscle is offset by an even larger decrease in fat mass, resulting in an improved ratio of muscle mass and function to body weight. Nevertheless, our pre-clinical data needs to be confirmed in patients with obesity. In addition, future research will need to address the effect of repeated weight loss and -regain with AOM and after AOM cessation as well as how this impacts the prevalence of sarcopenia and sarcopenic obesity.

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G3 *(8 minutes)*

The use of muscle selective anabolics to make GLP-1 RA weight loss drugs more effective and precise

Mitchell Steiner, MD
Veru Inc., Miami, FL, USA

Incretin therapy causes significant weight loss by suppressing appetite leading to the nonselective loss of lean and fat mass. Lean mass losses may be up to 50% of the total weight lost by one year. Muscle is important not only for maintaining physical function and preventing falls in obese patients, but also plays a metabolic role to aid weight loss. In a low-calorie state, muscle depletion causes muscle to secrete myokines that signal the hypothalamus to increase appetite, countering the appetite suppression induced by incretins leading to a weight loss plateau. Further, as seen in starvation, removing the energy restriction by stopping incretin therapy, triggers overeating resulting in the rebound, rapid regain of weight which is mostly composed of fat. There is an unmet medical need to develop new drugs that prevent muscle loss to preserve functional and maintain the metabolic role to enhance the quality and quantity of weight loss.

Enobosarm is an oral selective androgen receptor modulator that has demonstrated in preclinical and 5 randomized placebo controlled clinical studies the ability to preserve muscle, decrease fat mass, and improve physical function in older healthy patients and in patients with a cancer induced loss of appetite and muscle wasting. Enobosarm has a large safety database of 27 clinical trials (1581 men and women) and was generally well tolerated with no increases in gastrointestinal side effects. This is important as there are already significant and frequent gastrointestinal side effects with a GLP-1 RA treatment alone.

A Phase 2b placebo-controlled, randomized, dose-finding clinical trial is being conducted to evaluate enobosarm 3mg, enobosarm 6mg, or placebo as a treatment to preserve muscle and augment fat loss in 168 elderly patients (>60 years of age) patients receiving semaglutide (Wegovy®). The primary endpoint is total lean mass, and the key secondary endpoints are total body fat mass at 16 weeks. The expectation is that enobosarm combined with a GLP-1 RA would augment fat loss while preserving lean mass. Patients will then continue in a blinded extension clinical trial where GLP-1 RA treatment will be stopped. The Phase 2b extension clinical trial will evaluate whether enobosarm can maintain lean mass and prevent the fat and weight gain that occurs after discontinuing a GLP-1 RA.

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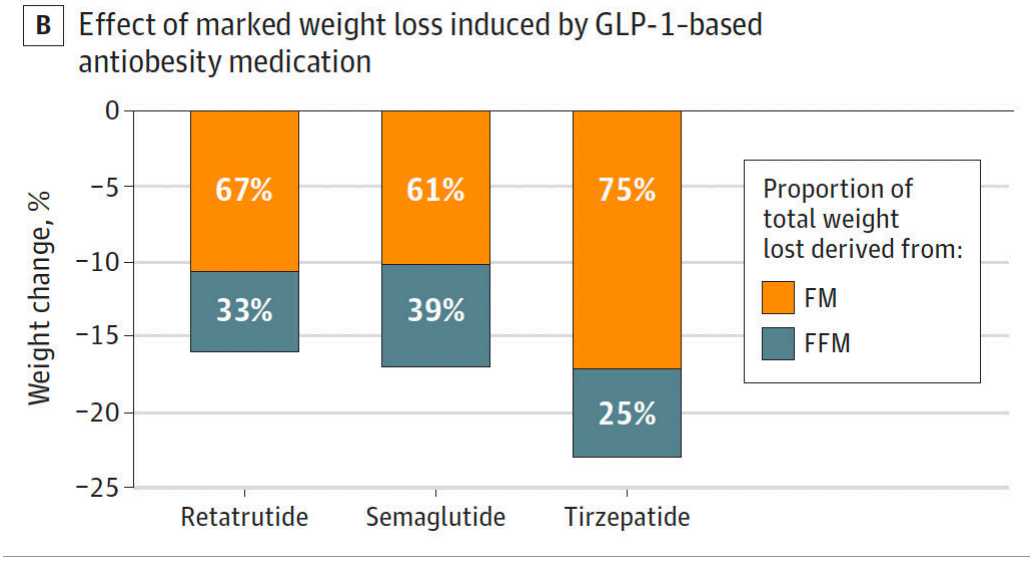
G4 *(8 minutes)*

Body composition changes when giving GLP1-RA

Stefan D. Anker
Charité - Universitätsmedizin Berlin, Department of Cardiology (Virchow Klinikum), Division of Cardiology and Metabolism - Heart Failure, Cachexia & Sarcopenia, Berlin, Germany

Recent publications suggest that there is not only loss of fat tissue when people treated with incretins lose weight, but also loss of fat tissue (see figure attached).
Less is known about body composition changes for tripple agonist drugs and for the time after GLP1-RA is ended. This data will be discussed with its possible clinical consequences.



Reference for Figure:
Is Weight Loss–Induced Muscle Mass Loss Clinically Relevant?
Conte C, Hall KD, Klein S. JAMA 2024

G5 (8 minutes)

Anabolic co-treatment in obesity therapy: rationale and early data

David Glass
Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA

Obesity is one of the greatest challenges to Western societies - especially the United States. Currently, a large component of the obese population is on GLP1 agonists to induce weight loss. One potential issue with this therapy is that along with fat, skeletal muscle is lost - which can be a special challenge to aged populations. In aged animals and humans, there is a decline in skeletal muscle mass and function, known as "sarcopenia". Sarcopenia is part of the frailty syndrome observed in humans. In order to discover treatments for sarcopenia, it is necessary to determine appropriate preclinical models and the genes and signaling pathways that change with age in these models - to see if these might also be correlated and perhaps causative of human sarcopenia.

To understand the changes in gene expression that occur as a result of aging in skeletal muscles, we generated a multi-time-point gene expression signature throughout the lifespan of mice and rats, as these are the most commonly used species in preclinical research and intervention testing. Gastrocnemius, tibialis anterior, soleus, and diaphragm muscles from male and female C57Bl/6J mice and male Sprague Dawley rats were analyzed at ages 6, 12, 18, 21, 24, and 27 months, plus an additional 9-month group was used for rats. More age-related genes were identified in rat skeletal muscles compared with mice; this was consistent with the finding that rat muscles undergo more robust age-related decline in mass. The specific pathways perturbed coincident with sarcopenia will be discussed, as well as potential consequences of these changes.

Further, changes in the motor neuron and thus potentially the neuromuscular junction will be discussed. Finally, potential therapies to counter-act the loss of skeletal muscle, especially in the setting of GLP1 agonists, will be discussed.

H1 *(15 minutes)*

Multimodal intervention for cardiac cachexia

Masaaki Konishi
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Cancer is a disease that is more prevalent in the elderly; however, in developed countries, heart failure (HF) consists of even older patients. Therefore, it has long been emphasized that the care for HF should not only focus on cardiac function but also require multimodal approaches, which may also be effective for cardiac cachexia. Our report indicated that 36% of older patients hospitalized for HF met the Evans criteria for cachexia, and their prognosis was poor[1]. The Evans criteria are based on a combination of multiple factors among which our study found that low muscle strength and low fat-free mass were independent prognostic factors. Thus, exercise and nutritional therapy are considered key points for intervention. While exercise therapy is generally recommended for all patients with HF as part of cardiac rehabilitation, there is limited evidence and recommendations for nutritional therapy. Although intervention by oral nutritional supplements (ONS) for malnutrition reduced mortality in hospitalized patients with HF[2], the effects of ONS on chronic HF remain unclear. We are currently undergoing a prospective study of ONS in chronic HF[3]. Although anorexia did not emerge as an independent prognostic factor in our study[1], a recent study has shown that a monoclonal antibody targeting GDF-15, which is closely related to appetite loss, is effective for cancer cachexia, and research on the effects of this drug in HF is ongoing. Furthermore, social[4] and psychological[5] factors were also associated with the prognosis of HF in our studies, and future intervention studies are anticipated. However, when cachexia is advanced, the effectiveness of interventions is limited. We have established the Asian Working Group for Cachexia (AWGC) and proposed criteria for diagnosing cachexia earlier (more lenient cut-off for weight loss) and more easily (only 3 phenotypic criteria) than the Evans criteria[6]. Several studies evaluating the prognosis of cachexia patients diagnosed by these criteria are currently underway, and early diagnosis and treatment in the future may bring significant benefits to patients.

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H2 *(15 minutes)*

Multi-Modal Integrated intervention combining Exercise, Anti-inflammatory & Dietary counselling (MMIEAD) for renal cachexia: a mixed-methods feasibility cluster randomised controlled trial and process evaluation

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Background: Renal cachexia is a major contributor to higher morbidity, mortality, increased healthcare costs and reduced quality of life (1). Patients with or at risk of cachexia, would benefit from support to maintain body weight, improve strength, enhance functionality, stabilise abnormal biochemistry and prolong survival. Research has determined that unimodal therapy has limited success in cachectic populations, given the multifactorial pathogenesis associated with cachexia (2). This study will explore the potential use of a Multi-Modal, Integrated, Exercise, Anti-inflammatory and Dietary counselling (MMIEAD) intervention for renal cachexia.
Aims: To determine the feasibility and acceptability of the MMIEAD intervention.
Design: The MMIEAD study will deliver a 12-week multimodal intervention using a feasibility cluster randomised controlled trial (cRCT) design with a process evaluation. A 12-week intervention has been deemed adequate considering the findings of our critical review (3) and other established multimodal trials in cachexia. A multi-professional international expert reference group including patient public representatives have guided the development of this study (4) and will continue to direct the implementation of MMIEAD across the duration of the trial.
This presentation will cover the programme of work leading up to this trial and the methodology of the feasibility cRCT.
Funding: This study is funded by Northern Ireland Kidney Research Fund.

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H3 *(15 minutes)*

Update on nutrition and exercise for renal cachexia

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Cachexia in chronic kidney disease is an understudied and underappreciated condition associated with muscle wasting and poor clinical outcomes, and there is significant overlap with conditions such as malnutrition, protein energy wasting and sarcopenia (1). A literature review was undertaken to investigate the impact of recent nutrition and/or exercise intervention trials in dialysis patients (2). Key areas discussed included use of resistance training (RT) at having potential for improving muscle strength, with some evidence on positive changes in muscle mass and physical function. Additionally, combined RT and aerobic exercise may improve overall functionality capacity. Modality of preference comparing inter/intra-dialytic versus home-based programmes were also discussed with no superiority found between them. Oral nutrition supplements have been found to have some benefits to improving nutritional status. Omega-3 fatty acids have also been shown to have anti-inflammatory effects in dialysis patients and may have potential for improving muscle mass and strength.
In response to previous and current research a specific multimodal treatment plan for renal cachexia has been developed and details discussed in recent work (3). This novel clinical trial project 'MMIEAD' (multimodal, integrative, exercise, anti-inflammatory and dietary counselling) will include key components such as dietary counselling with an aim to improve and maintain recommendations for energy and protein intake, exercise, e.g. RT and omega-3 fatty acid supplementation. A patient exercise co-design workshop was recently undertaken to develop a feasible RT strengthening exercise protocol that may be best aligned with patient preferences and considerations. The MMIEAD project is due to begin in 2025.
In addition, a new novel project ('Project Muscle') led by a clinical group in Diaverum, Saudi Arabia have been trialling out an enhanced assessment of malnutrition, sarcopenia and cachexia protocol in dialysis patients in combination with a multimodal nutrition and exercise treatment plan as routine standard of care. This was developed through preceding work (4) and by adopting and adapting different protocols. Data from this work will be available in coming months/years.
(1,950 characters – no spaces)

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H4 *(15 minutes)*

Multi-modal therapy in cancer cachexia: what do the ENERGY and other trials tell us

Richard Skipworth
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I1 *(15 minutes)*

Mechanisms of radiation-induced muscle fibrosis

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Radiation-induced muscle pathology, characterized by muscle atrophy and fibro/fatty tissue accumulation, is the most common debilitating late effect of cancer therapy in childhood cancer survivors. Consequently, childhood cancer survivors experience muscle weakness and impaired mobility, ultimately resulting in increased morbidity and disability. Fibro/adipogenic progenitors (FAPs) are skeletal muscle-resident fibroblast and adipocyte precursor cells that contribute to fibro/fatty tissue accumulation in muscle pathology. In healthy muscle, FAPs are required for muscle maintenance and regeneration. However, the role of FAPs in radiation induced muscle pathology is not well-understood. Thus, the overall objective of this work was to examine the extent to which FAP dysfunction underlies persistent muscle degeneration following radiation exposure. Our results indicate that radiation therapy depletes FAPs while fibro/fatty tissue accumulates which was related to changes in FAP bioenergetics[1]. Single cell RNA-sequencing of irradiated mouse muscle identified that radiation specifically depletes the population of deep-quiescent satellite cells and enriches pro-fibrotic signaling in FAPs through TGFβR2[2]. We have further identified alterations to the irradiated FAP secretome that reduced satellite cell differentiation and contributes to long-term muscle atrophy[1]. Excitedly, a murine model of combined resistance and endurance exercise training reversed several of the pathological consequences of juvenile radiation exposure[2]. Together, these results suggest that radiation induces FAP dysfunction characterized by enhanced fibrosis and anti-myogenic changes to the secretome that may underlie the characteristic pathological alterations in skeletal muscle. Resistance/endurance exercise training reverses several of the radiation-induced pathological changes in skeletal muscle, in part, by restoring FAP populations. These results offer new therapeutic opportunities, such as exercise training, that target FAP fate and function to improve skeletal muscle health in juvenile cancer survivors.

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I2 *(15 minutes)*

Immune cell signature in chemotherapy-induced cachexia

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Immune cell-driven pathways are linked to cancer cachexia. Tumor presence is associated with immune cell infiltration whereas cytotoxic chemotherapies reduce immune cell counts. Despite these paradoxical effects, both cancer and chemotherapy can cause cachexia; however, our understanding of immune responses in the cachectic condition with cancer and chemotherapy is largely unknown. Fluorouracil (5FU) alone decreases skeletal muscle immune cells and blocks the infiltration of immune cells following injury. This impaired infiltration disrupted the immune microenvironment resulting in impaired remodeling shown by increased collagen production and a reduction in centralized nuclei and myofibrillar cross-sectional area compared to controls. Interestingly, there were differences in the skeletal muscle and adipose tissue immune cell populations in untreated tumor-bearing and 5FU treated tumor-bearing mice. These distinct immune cell signatures reveal differences in the immune microenvironment within wasting tissues with and without chemotherapy. Despite chemotherapy suppressing tumor growth, cachexia persisted along with decreases in skeletal muscle and adipose tissue inflammatory immune cells suggesting that these inflammatory cells are not required for wasting. However, profibrotic cells and muscle inflammatory/atrophic signaling appeared consistent. Chemotherapeutic, 5FU impairs skeletal muscle immune cell infiltration sufficient to perturb repair and remodeling. Additionally, tumor presence and chemotherapy have contrasting effects on certain immune cells lending to complexity in unraveling the role of the immune system with cachexia's progression.

I3 *(15 minutes)*

Sex dependent effects in chemotherapy-induced cachexia

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Cancer related cachexia exhibits significant heterogeneity in the outcomes and mechanisms depending on several variables. Our laboratory has taken a strong interest in recent years in exploring this heterogeneity in preclinical models. We notably have observed significant divergence in the phenotype and likely mechanisms of cancer-induced cachexia between sexes[1-4], we further recently noted differential responses to mitochondria-targeted therapeutics between sexes[5]. Further still, we recently performed a secondary analysis of transcriptomic responses observing large heterogeneity between sexes and cancer types[6]. Overall, these prior works point to significant heterogeneity in the presentation and mechanisms of cancer-induced cachexia but the overwhelming majority of prior data in preclinical research focus exclusively on the tumor bearing state and does not well consider the interaction with anti-cancer treatments. A growing body of evidence suggests many common chemotherapeutics may induce cachexia themselves[7-10], free of cancer, and that like cancer these impacts may exhibit divergences by biological sex[11]. To better examine the interaction of cancer and chemotherapeutics on cachexia outcomes and how these outcomes may differ by biological sex we recently completed a study utilizing an array of chemotherapeutics in the established C26 preclinical model of colorectal cancer across sexes. Our current data suggest there may be differential effects of varying chemotherapeutic agents on muscle mass outcomes between sexes. Overall, it appears likely sex differences in the cancer/chemotherapy interaction impact cachexia outcomes and mechanisms.

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I4 *15 minutes)*

Musculoskeletal consequences of pediatric radiotherapy

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One of the great achievements in medical sciences is the improved survival rate among children diagnosed with cancer. Although estimates indicate the 5-year survival rate of children diagnosed with a malignancy is near 80%, most of these individuals prior to the age of 40 demonstrate indices of physical limitation normally associated with the elderly population. Among the treatments received by pediatric cancer patients is multimodal fractionated x-ray irradiation and chemotherapy. Both induce genotoxic stress that eliminates proliferative cancer cells; however, direct and indirect effects of radiation and chemotherapy can negatively impact normal tissue growth and maintenance especially in actively growing populations. Phenotypes observed earlier in pediatric cancer survivors is the accelerated onset of frailty indices such as neuromuscular decline. In a murine model, we find weeks after image guided pediatric fractionated x-ray irradiation of hindlimbs reduced skeletal muscle fiber size, impaired neuromuscular function, extracellular matrix (ECM) modification, and activation of stress related gene expression. Single cell RNA sequencing (scRNASeq) analysis revealed radiation induced stress related gene expression to be prominent in non-myogenic cells. In our murine model of multimodal pediatric cancer treatment and survivorship, we find deficits in body weight gain and exacerbation of neuromuscular related phenotypes observed with fractionated radiation alone[1,2]. Therefore, our long-term goal is to rigorously characterize the mechanisms whereby treatment related genotoxic stress from non-myogenic cells impacts neuromuscular related phenotypes in our murine model of multimodal pediatric cancer therapy and survivorship. Ideally, such insight would be used to uncover interventions to attenuate pediatric cancer treatment related neuromuscular decline that increases morbidity and burdens survivors.

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J1 *(15 minutes))*

Is Cancer-Reated Fatigue (CRF) in advanced cancer equal to cachexia?

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The current, old Cancer-related Fatigue definition covers both post-curative cancer survivors (years after anticancer treatment without active cancer) and patients with advanced, incurable cancer disease even close to end-of-life. Mixed groups of patients may obscure data, as a recent systematic review of physical activity in lung cancer patients suggest[1]
Currently the MASCC working group fatigue pursues a consensual project to define and distinguish cancer-treatment related fatigue, cancer-disease related fatigue and co-factors (such as metabolic, inflammatory, nutritive, psychiatric, infectious comorbidities). Characterizations encompass patient disease trajectories, severity and impact, domains, screening and assessment and multimodal treatment.
Active cancer disease can cause specific local complications and symptoms (e.g. bowel obstruction, pulmonary atelectasis), but also systemic effects. The understanding how cancer develops can be summarised under the hallmarks of cancer[2,3]. But the question how active cancer causes symptoms, syndromes and associated functional deficits is less understood. Current symptom cluster research tackling fatigue report in advanced cancer patients fatigue clusters with lack of energy, drowsiness, lack of appetite, depression, functional status[4] and a fatigue/anorexia-cachexia/depression cluster explaining 63% of total variance of fatigue in advanced cancer patients[5]. The cancer cachexia community still struggles to define pre-cachexia and to distinguish starvation in advanced cancer from cachexia.
Merging clinical and research activities tackling CRF and Cachexia is suggested.

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J2 *(15 minutes)*

Effectiveness of self-management in improving hard outcomes in sarcopenia and fatigue cancer research

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Physical deconditioning and fatigue are some of the most common and debilitating impairments that impact individuals treated for cancer. Cancer treatments are well documented to accelerate physical decline, decreasing the ability to perform activities of daily living and accelerating the trajectory towards disability and mortality. Thus, individuals treated for cancer endure long and lingering impacts on physical function, health status, and quality of life that accompany chemotherapy as a “trade-off” for more effective cancer control. This presentation will give an overview of the evidence of self-management interventions in improving outcomes in individuals with sarcopenia and fatigue. Specifically, the presentation will use the lens of physical activity and exercise, and address current knowledge and research gaps in this area.

J3 *(15 minutes)*

Potential relevance of blood mitochondrial gene expression in sarcopenia and fatigue

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Cancer cachexia is associated with increased proteolysis and ATP demands, which are associated with a reduction in the efficiency of mitochondrial energy production. Impaired oxidative phosphorylation results in oxidative stress, fatigue, and a host of downstream consequences. There has been an acceleration in the understanding of mitochondrial features, activities, and functions in the last decade,[1] including in the context of cachexia,[2] and mitochondria-targeted treatments are beginning to emerge as effective interventions to mitigate the progression of cachexia. The majority of the work to understand mitochondrial dysfunction as a cause or consequence of cachexia has been done in animal models because the collection of metabolically active tissues, for example liver and skeletal muscle, are unethical or painful to collect. Therefore, there is a demand for tools to study mitochondrial function among humans with cancer from blood or non-invasively in order to elucidate underlying mechanisms of cachexia as well as develop biomarkers to predict, early diagnose, and monitor the progression of cachexia.
Herein, we present the results of two studies that probe mitochondrial function in human participants. In Study 1, we recruited participants with curable cancer undergoing chemotherapy (n=30). We freshly isolated T cells and assessed oxygen consumption rate under conditions of various metabolic inhibitors. We saw lower basal respiration (p=0.044), lower maximal respiration (p=0.021), and lower spare capacity (p=0.029) was associated with higher patient-reported fatigue.[3] In Study 2, we recruited women with curable cancer undergoing chemotherapy (n=29) and performed unbiased bulk RNA-Seq on whole blood. After controlling for lymphocyte and neutrophil concentrations, pathway analysis revealed perturbed biological processes in mitochondrial function, chiefly cellular/aerobic respiration, electron transport chain, generation of precursor metabolites and energy, and fatty acid oxidation. These pathways tended to be down-regulated among participants with more fatigue (unpublished). These results suggest that novel interventions that target mitochondrial energy production may be promising to prevent and treat cancer-related fatigue and, ultimately, cancer cachexia.

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J4 *(15 minutes)*

GDF-15 neutralizing antibody visugromab overcomes cancer cachexia

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Introduction: Growth and differentiation factor 15 (GDF-15), a divergent member of the TGF-β superfamily, is overexpressed in cancer cells and leads to serum elevation in cancer patients. GDF-15 has been shown to induce cachexia in patients via the brainstem-restricted receptor GFRAL. Visugromab is a GDF-15 blocking antibody currently under evaluation in patients with advanced cancers r/r to aPD -(L)1 therapy (GDFATHER; NCT04725474) in combination with nivolumab.
Methods: Visugromab-based neutralization of GDF-15 binding to and activation of GFRAL was assessed by enzyme-linked immunosorbent assay (ELISA) and homogeneous time resolved fluorescence (HTRF) cell line system-based functional assays *in vitro*. *In vivo* visugromab-mediated neutralization of cancer-induced cachexia was assessed in SK-MEL-5, SK-MEL-5 GDF-15KO and MKN45 tumor-bearing xenograft models. Visugromabs anti-cachexia properties were further evaluated in a subgroup of non-small cell squamous lung cancer (NSCLC), urothelial cancer (UC) and hepatocellular carcinoma (HCC) patients with elevated GDF-15 serum levels as part of an ongoing combined ph1/2a trial (GDFATHER; NCT04725474).
Results: Visugromab binds specifically to GDF-15 in a dose-dependent manner and blocks GDF-15-induced GFRAL/Erk1/2 phosphorylation. SK-MEL-5 and MKN45 bearing xenografts showed alleviation of cachexia parameters as body weight and food consumption upon treatment with visugromab. In the ph1/2a trial visugromab treatment (in combination with nivolumab) increased body weight significantly in patients with cachexia-inducing GDF-15 serum levels (GDF-15 >1.5ng/mL at baseline) at week 10.
Conclusions: Visugromab effectively neutralizes GDF-15, preventing GFRAL signaling-induced cachexia. In preclinical models, visugromab can block cancer-induced cachexia associated symptoms. Visugromab-induced GDF-15 blockade resembled body weight maintenance as in GDF-15KO tumor bearers, reflecting the key role of GDF-15 in cancer induced cachexia. Clinical data from a ph1/2a trial of visugromab+nivolumab show a significant body weight gain already at week 10 in patients with advanced cancer and elevated serum GDF-15 concentrations. Collectively, this provides compelling evidence for visugromab as anti-cachexia treatment option in cancer patients.

K1 *(15 minutes)*

Sit-to-stand muscle power at the core of sarcopenia assessment

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Rapid progress in research over the last years has provided novel measurement tools and technologies that may outperform traditional tools to assess sarcopenia in terms of feasibility, reliability, cost, effectiveness, and clinical relevance. For example, the use of wearables may not only facilitate widespread assessment of sarcopenia during clinic visits, but also provide relevant information on the patient's status remotely. Muscle power is defined as the rate at which mechanical work (e.g. human movement) is performed. Muscle power increases progressively during the childhood and remain at peak levels during the early adulthood. However, age-related decreases in muscle power are already evident in middle-aged adults and are progressively accentuated in older adults. Of note, muscle power has been shown to decline with age at a faster rate and to be more strongly related with mobility limitations than muscle mass and strength (1). However, its relative complexity and lack of cut-off points has prevented its assessment in the clinical setting in the past. Fortunately, the use of smartphones and wearables provides us with the opportunity to access measurements that previously could only be taken in a laboratory. The sit-to-stand (STS) muscle power test has demonstrated to be a valid, feasible, reliable, and inexpensive method to assess older people's muscle power in the clinical setting (2). Importantly, low STS muscle power has been associated to a higher risk of mobility limitations, frailty, disability, hospitalization, and all-cause mortality. Normative data, cut-off points and an operational algorithm to diagnose low STS muscle power in older people has been provided in the literature (3). Thus, the present lecture will provide new insights into the use of the STS muscle power test in the clinical setting, and the inclusion of the STS muscle power test in the operational algorithm for the assessment of sarcopenia. In addition, this presentation will share novel findings on the application of effective countermeasures to revert the loss of muscle power with aging.

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K2 *(15 minutes)*

D_3Cr muscle mass as a clinically feasible assessment of muscle quantity

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Many proxy and direct measures have been used to approximate muscle mass or volume, including those derived by bioimpedance analysis (BIA) or dual-energy x-ray absorptiometry (DXA) for lean mass; computed tomography (CT) and magnetic resonance imaging (MRI) for cross-sectional area or volume at a given anatomical site; and more recently, deuterated creatine (D_3Cr) dilution for total body skeletal muscle mass. D_3Cr muscle mass is measured using a standard protocol in which patients take a 30 mg of D_3Cr dose and subsequently and provide a fasting, morning urine sample 72–144 hours later. From the urine sample, D_3Cr enrichment, unlabeled creatinine, and creatine are measured using high-performance liquid chromatography–tandem mass spectroscopy; these measures were then included in a modified algorithm to determine total body creatine pool size and thus skeletal muscle mass. While the urine sample requires fasting, no other medication or dietary control is required for valid assay results. Older men and women with low D_3Cr muscle mass have worse strength, power, physical performance, fitness (VO_2peak) and self-reported function than those with higher values. Similarly, in longitudinal studies, those with low D_3Cr muscle mass have a higher risk of disability, fractures and mortality than those with greater amounts. Declines in D_3Cr muscle mass over time mirror declines in strength. Akin to other measures of body composition (e.g., fat, bone), associations between D_3Cr muscle mass and various strength and functional measures may vary by sex. In summary, the D_3Cr method is clinically feasible and identifies individuals who are at risk of functional and physical decline.

K3 *(15 minutes)*

Artificial intelligence to diagnose sarcopenia in CT and MRI images

Gustavo Duque
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Artificial intelligence (AI) can be an effective tool for diagnosing sarcopenia using CT (Computed Tomography) and MRI (Magnetic Resonance Imaging) images. AI models, particularly convolutional neural networks (CNNs), are used to segment muscles in CT and MRI images. These models can automatically identify and extract regions of interest (ROIs), such as muscle groups, and differentiate them from fat tissue or other structures. AI algorithms can accurately measure muscle cross-sectional area, volume, and fat infiltration in the segmented muscle regions. This helps in estimating muscle mass, which is a key factor in diagnosing sarcopenia. AI can also assess muscle quality by quantifying fat infiltration within muscle tissues. Fat infiltration, or myosteatosis, is often seen in sarcopenia and can be a more sensitive indicator of muscle deterioration than just mass loss alone. We can use AI models to automatically extract key features like muscle density, fat-to-muscle ratio, and specific tissue characteristics, which are important for diagnosing sarcopenia. This reduces the need for manual analysis and speeds up the process. In addition, these machine-learning models can be trained on large datasets of labeled CT and MRI scans to predict sarcopenia. These models can combine image features with clinical data to provide a more accurate and comprehensive diagnosis. In this session, we will discuss the characteristics of the optimal use of AI to diagnose sarcopenia. Our own experience using the TissueCompass model to diagnose sarcopenia in older persons living with dementia will be discussed. In summary, AI is transforming the way sarcopenia is diagnosed by providing more efficient, accurate, and scalable solutions, particularly in analyzing CT and MRI images. This can aid early detection and personalized treatment strategies for patients, especially in aging populations.

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K4 *(15 minutes)*

New biomarkers for sarcopenia

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The search for biochemical markers suitable for sarcopenia has accelerated over the last years and has been fueled by recent technological advances. Appropriate biomarkers are needed for various applications in sarcopenia covering diagnosis, staging of severity, prognosis, personalized treatment, detection of drug targets, and treatment monitoring. A recent milestone in biomarker research constitutes a consensus paper that proposed several biochemical markers to be assessed in Phase II and Phase III clinical trials of drugs for the treatment of sarcopenia (1). In addition, several further biomarkers have been proposed and will be discussed in this talk, including muscle-specific markers such as myostatin, myoglobin, and the ratio of serum creatinine to cystatin C. In line with the concept of “inflammaging” (2), several inflammatory markers such as C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor alpha (TNF-α) have been investigated in relation to sarcopenia and its treatment, but with conflicting results. Hormonal changes particularly in anabolic hormones such as testosterone, insulin-like growth factor 1 (IGF-1), and growth hormone (GH) may indicate imbalances in muscle protein turnover. More recently, alterations in microRNA expression have been observed in sarcopenia as well as after exercise and have been discussed in the context of assessing inflammaging. Beyond the search for individual biomarkers - since sarcopenia has a multifactorial pathophysiology - combining multiple biomarkers into panels or scores may enhance the predictive accuracy. The applications of omics technologies such as proteomics and genomics have demonstrated to facilitate the detection of potential new biomarkers, while applications of epigenomics are advancing as the epigenetic clock has been applied to human skeletal muscle and DNA methylation changes have been observed in the context of sarcopenia and exercise. Finally, the talk will cover considerations for the study design when investigating biomarkers for sarcopenia and will depict an outlook on the next steps and crucial future research.

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L1 *(15 minutes)*

Biomarkers of sarcopenia and cachexia in prostate cancer patients. The ADT Study

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Biomarkers are defined as outcomes that can predict clinical benefit but are not a direct measurement of it. They are considered surrogate endpoints and may include laboratory measurements, radiographic images or physical signs. Biomarkers can serve different purposes in clinical trials and drug development including diagnostic, monitoring, predictive, prognostic and safety. They may also help studies avoid a ceiling effect.
Prostate cancer (PCa) negatively impacts muscle mass, physical function, and patient reported outcomes (PROs).[1] Androgen deprivation therapy (ADT), a widely used treatment for PCa, exacerbates these effects.[2] This recently completed study characterized the relationship between body weight, body weight history, muscle mass, strength, endurance, PROs, mitochondrial function[3] and other biomarkers suitable for muscle wasting before and during ADT in PCa patients.
Prior to ADT, higher mitochondrial function and endurance, but not HGS, was associated with better quality of life (QOL), physical functioning (PF), and less fatigue. Higher appendicular lean mass (ALM) correlated with worse PROs. Greater baseline VO_2 peak and mitochondrial function predicted smaller declines in ALM, muscle function, and PROs after six months of ADT. Maintenance of ALM during ADT was related to preservation of muscle function and PROs.
VO_2 peak and mitochondrial function may serve as predictive biomarkers for muscle mass, function, and PRO changes upon ADT. This data may help select patients and outcomes for clinical trials. Future studies should independently validate these results and test if mitochondria may be a suitable target for improving physical function and PROs in PCa.

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L2 *(15 minutes)*

Biomarkers of cachexia in cardiovascular disease

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Cachexia is a multifactorial syndrome associated with cardiovascular disease, most prominently with heart failure. It is characterized by significant body weight reduction, muscle wasting, and loss of fat and bone mass. Blood-based biomarkers play a crucial role in elucidating the pathophysiological mechanisms, enabling early diagnosis, monitoring, and prognostication. For muscle wasting, the C-terminal agrin fragment (CAF) reflects neuromuscular degradation and correlates with atrophy severity, while myostatin serves as a pivotal negative regulator of muscle growth, exacerbating catabolic pathways. Recent discoveries highlight the relevance of growth differentiation factor 15 (GDF-15) and activin A in driving muscle loss and systemic metabolic disturbances. Fat loss biomarkers include adiponectin and fibroblast growth factor 21 (FGF21), which accelerate lipolysis, with leptin levels also showing significant, though complex, alterations that warrant further study. Bone depletion, a less explored but critical aspect of cachexia, is indicated by reduced osteocalcin levels and heightened markers of resorption like C-terminal telopeptide of type I collagen (CTX-I), reflecting disturbed bone turnover and increased fragility. Prognostic biomarkers such as interleukin-6 (IL-6) and C-reactive protein (CRP) are robustly linked to adverse outcomes and mortality risk. Furthermore, circulating microRNAs have emerged as reflective of muscle and metabolic dysfunction, adding a new layer of insight into disease progression. Collectively, this biomarker landscape enhances our understanding of cachexia's complexity and guides the pursuit of targeted therapeutic interventions.

L3 *(15 minutes)*

Biomarkers of frailty

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Aging adults experience increased health vulnerability and compromised abilities to cope with stressors, which may evolve into severe frailty. Proposed biomarkers to detect frailty and pre-frailty in the clinical setting are often not reproducible across cohorts. We performed analyses to identify proteomic and metabolomic biomarkers of frailty in the InCHIANTI study (N=1453), a longitudinal study performed in a representative cohort of men and women living in the Chianti area of Tuscany, Italy. Several circulating proteins were associated with frailty both cross-sectionally and longitudinally. Enrichment analysis identified several pathways associated with frailty, including inflammation, processing of the intercellular matrix, and down-regulation of oxidative metabolism. Metabolomic analyses performed in the same population highlighted a dysregulation of triglycerides and phospholipids metabolism. To better understand these findings, we developed a predictive model incorporating biological and clinical frailty measures to identify robust biomarkers across two datasets: the InCHIANTI Study and the Atherosclerosis Risk in Communities Study (n = 6508) from four U.S. communities. A complex systems approach to biomarker selection with a tree-boosting machine learning (ML) technique for supervised learning analysis was used. Unique biomarker features identified in the InCHIANTI study allowed us to predict frailty with a model accuracy of 0.72 (95% confidence interval (CI) 0.66–0.80). Replication models in ARIC maintained a model accuracy of 0.64 (95% CI 0.66–0.72). Interestingly, both biomarkers and clinical parameters contributed independently to the model fit. During the presentations, I will propose several concrete next steps to further improve the detection of frailty with biomarker-based methods.

L4 *(15 minutes)*

Functional biomarkers of cancer cachexia

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Background: Decline in functional independence is a defining event of cancer cachexia[1] and attempts at creating cachexia-specific therapies have largely failed due to the inability to identify treatments that improve functional capacity[2]. One explanation is that currently used measures are not sensitive enough to detect functional recovery[3]. Grip strength is a frequently used outcome measure in cachexia clinical studies, though, the use of gait-based measures is now emerging[4]. These two outcome measures have never been directly compared in cachexia, and we hypothesize that gait-based measures more comprehensively act as a proxy measure for functional independence.
Methods: In a retrospective study of 485 cancer patients who required inpatient rehabilitation, we assessed six-minute walk test (6MWT) and hand grip strength (hGS). Functional capacity was defined as mobility and activities of daily living (ADLs), quantified by measures of functional independence (Total Motor Score). Cachexia patients were identified using the Fearon *et al.* consensus criteria, Weight Loss Grading Scale (WLGS), Prognostic Nutritional Index (PNI), and Neutrophil-to-Lymphocyte Ratio (NLR). Primary outcomes were change in Total Motor Score, discharge destination (e.g. homebound status or need for care facility), and 6-month survival.
Results: The presence of cachexia was 63% based on the Fearon criteria. Mean age was 63±0.63 (SEM) years. Multivariate linear regression demonstrated that change in 6MWT ($p<0.0001$) but not hGS ($p>0.08$) correlated with Total Motor Score gain after controlling for age, disease burden, cancer type, previous cancer treatment, and baseline function. Area under the curve analysis revealed that change in 6MWT ($p<0.0001$, AUC=0.77) was a stronger predictor of Total Motor Score gain than hGS ($p<0.01$, AUC=0.59). In multivariate logistic regression, discharge to home with independence was predicted by change in 6MWT ($p<0.001$) but not hGS ($p>0.80$). Finally, six-month survival was predicted by change in 6MWT ($p<0.05$) but not hGS ($p>0.80$) in a Cox proportional hazards model.
Conclusions: Multiple analytical approaches to our data set demonstrate that changes in 6MWT are better associated with cachexia-related outcomes and should be included in future cachexia studies.

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M1 *(15 minutes))*

Experimental studies on critical illness myopathy: underlying mechanisms and intervention studies

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Intensive care units (ICUs) have undergone significant development resulting in improved survival rates due to improved medical technologies, progress in therapies, and the introduction of evidence-based medicine resulting in removal of harmful interventions. However, lifesaving ICU interventions are also associated with complications reflective of acquired myopathies resulting in delayed weaning from ventilator and prolonged ICU and post-ICU rehabilitation with staggering negative consequences for patient quality of life, morbidity mortality. Critical Illness Myopathy (CIM) is the dominating cause underling the compromised muscle function and reducing the negative consequences of CIM has the potential to transform ICU survival rates, and patients' lives post-ICU. To achieve this goal requires research focused on developing mechanism-based countermeasures for CIM.
Sepsis, corticosteroids and neuromuscular blockade have been forwarded as the factors triggering CIM. However, CIM is observed in the absence of these triggers in both clinical and experimental studies, although they have additive negative effects. The only two factors all patients with CIM have in common are long-term mechanical ventilation and complete mechanical silencing (absence of weightbearing and activation of contractile proteins). These factors are hypothesized to be the primary factors triggering the complex CIM pathophysiology involving organ-to-organ and muscle-to-muscle communication. Due to the heterogeneity among ICU patients, it is important to have an experimental model mimicking the ICU condition and allowing long-term survival in parallel with clinical studies in ICU patients with CIM. For this purpose we have used an experimental ICU (ExICU) model allowing long-term (weeks) studies in rats exposed to mechanical silencing and mechanical ventilation. Furthermore, muscle wasting and old age are the two factors most strongly associated with ICU mortality/morbidity and these two factors probably act synergistically.
Our current research is therefore focused on mechanosignaling and the lung injury caused by mechanical ventilation and interventions targeting these triggering factors and how they are affected by old age.

M2 *(15 minutes)*

Critical illness myopathy and critical illness polyneuropathy: pathophysiology

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Patients receiving mechanical ventilation in the intensive care unit (ICU) frequently develop contractile weakness of the diaphragm. Consequently, they may experience difficulty weaning from mechanical ventilation, which increases mortality and poses a high economic burden. Because of a lack of knowledge regarding the molecular changes in the diaphragm, no treatment is currently available to improve diaphragm contractility. We found that in myofibers isolated from the diaphragm of ventilated ICU patients, myosin is trapped in an energy-sparing, super-relaxed state, which impairs the binding of myosin to actin during diaphragm contraction. Exposing slow- and fast-twitch myofibers isolated from the diaphragm biopsies to small-molecule compounds activating troponin restored contractile force.

M3 *(15 minutes)*

Critical illness associated (neuro-) muscular disorders

Joerg C. Schefold
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In the traditional understanding, critical-illness associated (neuro-) muscular disorders mainly embrace ICU-acquired weakness (ICUAW), a condition observed in patients with e.g. increased disease severity and prolonged ICU length of stay. However, recent research indicates that a number of additional (neuro-) muscular disorders may present much more often in ICU populations. Additional (neuro-) muscular disorders in ICU populations include swallowing dysfunction (dysphagia: about 20% of adult ICU patients admitted to mixed medical-surgical ICUs for emergency reasons) and ventilator-induced diaphragmatic dysfunction (VIDD). From a clinical perspective, it appears that respective (neuro-) muscular disorders may partially overlap, should be systematically screened for on all ICUs in all patients post extubation (dysphagia), and understood as distinct entities (ICUAW, VIDD, Dysphagia). The current presentation will highlight the clinical consequences of swallowing disorders in the critical ill and focus on potential future therapies. The talk will further expand the views on (neuro-) muscular dysfunctions observed on the ICU, and the effects of respective conditions on patient outcomes.

M4 *(15 minutes)*

Fasting associated muscle and fat tissue loss – the data, the mechanisms

Faiza Kalam
USA

N1 *(15 minutes)*

Body adipose tissue changes in women with advanced breast cancer

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A large amount of evidence reported that adipose tissue changes are crucial in the development of cachexia in different types of cancer. In particular, patients with breast cancer may differ in terms of clinical characteristics from those affected by other types of cancer (e.g, gastrointestinal, lung, etc.).
In fact, the diagnosis of cachexia in breast cancer is less frequent and is often associated with the advanced stages of the disease. A large meta-analysis including 213,075 breast cancer survivors showed that obesity was associated with reduced overall and breast cancer survival (1). Considering body composition analysis, the presence of high adiposity and low muscularity was associated with poor prognosis in patients with non-metastatic breast cancer. However, in advanced stages of the disease, data on changes in body composition and their effects on clinical outcomes (e.g. survival, anticancer treatments toxicities and quality of life) are still scanty.
Interestingly, different studies analyzed the impact of changes in body composition in metastatic breast cancer patients treated with novel treatments, including alpelisib (2), CDK4/6 inhibitors, and trastuzumab (3), showing not univocal role for adiposity (high vs low, and/or its distribution) in affecting the outcomes. Clarifying the role of body composition changes in this setting may be crucial to improve nutritional status and and therapeutic strategies, including physical exercise to ameliorate quality-of-life and survival.
For this reason, we recently collected data on two cohorts of patients with metastatic breast cancer treated with trastuzumab deruxtecan and CDK4/6 inhibitors, and we observed significant changes overtime of adiposity (visceral and subcutaneous) after treatment initiation and a correlation with the presence of treatment toxicities was confirmed.
In this light, in the setting of metastatic breast cancer, it appears clinically useful to measure body composition parameters overtime to stratify the risk of developing complications, including treatment-related toxicities.

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N2 *(15 minutes)*

Nutritional and symptom considerations in patients with advanced cancer

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Patients with advanced cancer and weight loss often consume insufficient calories and protein. A retrospective study of 320 patients found the majority consumed diets insufficient to maintain weight even in healthy individuals. Target intakes of between 25 to 30 kcal/kg/day and 1 g/kg/day to 1.5 g/kg/day of protein are recommended for patients with cancer.

High symptom burden may impact nutrition intake and exacerbate weight loss, muscle wasting and poor physical performance. A preliminary working definition of Nutrition Impact symptoms (NIS) has been proposed: 'NISs are symptoms that compromise patients' desire or ability to eat, interfering with their nutritional needs and increasing the risk for malnutrition, loss of lean body mass, and impaired Quality of Life'. S Nutrition impact symptoms (NIS) limit an individual's ability to consume food because of symptoms such as chronic nausea, depression, and pain either due to the cancer or anti-neoplastic treatment side-effects. NIS are common, with a median of three symptoms, and ≥ 5 in 15% of cachectic ambulatory patients. Increased number of NIS is associated with poor quality of life, increased risk of malnutrition and decreased survival.

Non –pharmacologic interventions such as nutritional counseling combined with inexpensive and readily available medications for NIS, may improve oral intake, quality of life and stabilize weight loss. The choice of specific medications for NIS should be guided by evidence for efficacy and risk of side-effects e.g. Pro-kinetic agent such as metoclopramide for chronic nausea secondary to gastroparesis. Psychosocial interventions can mitigate eating related distress and may be particularly important for patients with advanced cancer.

Furthermore, addressing NIS and decreasing symptom burden may benefit sarcopenia related outcomes given the association between symptoms and physical function. For example, in 359 older oncology patients from two tertiary medical centers, each unit increase in a composite symptom score was associated with greater instrumental activity of daily living (IADL) impairment, falls, and SPPB ≤9 ($P<0.05$)

In summary, a multimodal interdisciplinary approach in patients with advanced cancer should include management of NIS with relatively inexpensive pharmacologic and non-pharmacologic therapies. Preliminary studies of NIS showing associations with adverse outcomes such as weight loss, poor QoL and decreased survival may also have implications for clinical trial design.

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N3 *(15 minutes)*

Pancreatic cancer cachexia: is it nutrition-sensitive?

Maurizio Muscaritoli
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N4 *(15 minutes)*

Early signatures of cachexia in pancreatic cancer: the importance of fat tissue

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Introduction: Opportunistic analysis of routine CT scans has high potential benefit to patient care outcomes. This study sought to investigate the prognostic utility of CT-based muscle, fat, and other organ parameters in a cohort of adults with pancreatic cancer.
Methods: This retrospective study applied a validated, automated body composition segmentation algorithm to contrast-enhanced abdominal CT staging exams in patients with newly diagnosed with pancreatic cancer. At the L3 axial level, area and density was evaluated for muscle, visceral adipose tissue (VAT), subcutaneous adipose tissue (SAT), liver, spleen, and kidney. Time-to-event analyses for mortality were conducted to generate univariate hazard ratios (HR) comparing lowest quartile to the highest three quartiles, multivariate HR by median values, and Kaplan-Meier curves.
Results: A total of 456 patients (mean age 65.6±11.0, 45% female) were included, of which 235 died upon follow-up. Risk of death decreased for every one standard deviation increase in muscle, VAT, and SAT area (HR = 0.79, 0.80, and 0.83, respectively, $p<0.05$). Conversely, risk of death increased for every one standard deviation increase in VAT and SAT median density (HR = 1.23 and 1.26, respectively, $p<0.001$). Risk of death was increased ($p<0.05$) in patients in the lowest quartile for liver density (HR = 1.39) and highest quartile for VAT median density (HR = 1.48) and SAT median density (HR = 1.46). The combination of low muscle density and high VAT density yielded the greatest increase risk of death (HR = 1.88, $p<0.001$).
Conclusion: There is value in assessing opportunistic CT scans using fully automated segmentation and body composition algorithms as it provides timely and relevant prognostic information for patients with pancreatic cancer. The results from this work identify fat density alone or in combination with muscle density as early prognostic signatures of wasting unique to pancreatic cancer.

O1 *(15 minutes)*

The physiological rationale for cachexia: recovery from organ injury

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Post injury or infection the body undergoes repair through a catabolic mechanism involving changes in the metabolic state. This systemic catabolism occurs with loss of muscle and fat that is proportional to the required anabolic reparative response. The liver is an essential mediator of this process through activation of the Yap1 signaling pathway. Hepatic gene expression analysis demonstrates the reparative process is indistinguishable from liver gene expression changes seen in cancer cachexia. Thus, the liver is a mediator of cachexia which is also a normal physiologic response.

O2 *(15 minutes)*

Burn-induced cachexia

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Despite major advances in critical care of burn injury (BI), the muscle wasting (MW), which has short- and long-term morbid sequelae, remains unresolved. Correction of aberrant catabolic signaling in muscle, use of enhanced nutritional supplements and/or even early mobilization techniques have not rectified the MW. Correction of MW of BI, therefore, warrants a paradigm shift with novel approaches and new therapeutic strategies.
The anterograde electrical impulses and nutritional cargo transport from motor neuron to muscle via the synapse or the neuromuscular junction (NMJ) are pivotal to the stability of the NMJ, muscle function and mass/contraction. In inflammatory CNS pathologies (e.g., amyotrophic lateral sclerosis, encephalitis), the associated microglia-mediated neuroinflammation causes dysregulated motor neuron function together with synaptic denervation and MW. During systemic inflammation, there is often concomitant neuroinflammation, evidenced as inflammatory cytotoxic cytokine release by innate immune microglia.[1] BI is associated with systemic inflammation and there is evidence for microglia activation.[2] Thus, the usually protective microglia can become hyperreactive and induce neuroinflammation leading to dystrophic neuron-immune interactions including neurodegeneration, with deleterious anterograde effects on the synapse and muscle. We posited that the neuroinflammation of BI has inimical effects on the motor neuron and is the major driver of the synaptic change and MW.
We found that major body BI was associated with microglia activation, evidence of motor neuron morphological changes, apoptosis and decreased neuron numbers in the ventral horn, together with synaptic denervation-like changes and MW.[3] The spinal cytokine levels were also increased. Preliminary data indicated that exploitation of the anti-inflammatory properties exhibited by the alpha7 acetylcholine receptors expressed in microglia by pharmacological stimulation decreased the spinal cytokine release, improved synaptic denervation and MW. Motor neuron apoptosis was also mitigated but not completely reversed. These data suggest an important central role in the MW of BI and needs for evaluation.

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O3 *(15 minutes)*

Persistent Inflammatory / Immunosuppressive Catabolic Syndrome (PICS) after sepsis

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With improvements in the early detection and rapid clinical treatment of septic patients, more individuals survive their acute hospital course. This has led to the creation of two cohorts of sepsis survivors: rapid recovery and chronic critical illness. The latter group often enter the Persistent Inflammation Immunosuppression Catabolism Syndrome (PICS), which is associated with increased morbidity and mortality. This presentation will define PICS, as well as delineate its epidemiology and highlight the need for future research in this patient population. In addition, this presentation will discuss specific mechanisms of pathology in PICS, including but not limited to myeloid-derived suppressor cells as well the need for precision medicine (e.g. sexual dimorphism) in addressing therapeutics for this syndrome. Finally, data specifically regarding sepsis-induced myopathy will be reviewed.

O4 *(15 minutes)*

Sepsis-induced muscle weakness and dysfunction

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Background: Although a majority of sepsis survivors suffer from chronic skeletal muscle weakness, particularly individuals middle-aged and older, the precise mechanisms of this condition remain unclear. We previously reported that skeletal muscle undergoes dynamic changes in muscle mass, inflammation, and mitochondrial function during and after sepsis (*eLIFE* 8: e49920). This study aimed to identify a causal factor(s) responsible for post-sepsis muscle weakness.
Experiments: Late middle-aged C57BL/6 mice (16 months old, equivalent to early 50s in humans) were subjected to experimental abdominal sepsis by cecal slurry injection followed by repeated antibiotic/fluid treatment starting at 12h for 5 days (*Shock* 47:726-734). Before (day -1), during (day 4, acute phase), and after sepsis (days 14 and 70, chronic phase), mice were anesthetized and subjected to measurement of plantar flexion function. Histological analyses and RNA sequencing were performed on muscle tissues collected from another cohort of mice euthanized at the same timepoints. We also compared sepsis-induced muscle weakness in transgenic mice overexpressing the mitochondrial antioxidant enzyme MnSOD versus litter mate wild-type control mice. Finally, we administered a small mitochondria-protecting tetrapeptide SS-31 to examine whether this pharmacological treatment could protect mice from sepsis-induced mitochondrial abnormalities and subsequent muscle weakness.
Results: Muscle weakness develops progressively from pre-sepsis to sepsis day 4 and further worsened by day 14 and remained by day 70. The body weight significantly decreased on day 4 and 14, but recovered by day 70. Cross sectional area analysis on muscle tissue revealed significant muscle wasting on day 4, which is resolved by day 14. Gene expression analyses found significant upregulation of acute inflammatory genes which were mostly resolved by day 14. Mitochondrially encoded genes were significantly downregulated on both days 4 and 14, and expression patterns of additional mitochondria-related genes were altered only on day 14. This progressive mitochondrial dysfunction from acute sepsis to the chronic phase is further confirmed by *in situ* histological staining of mitochondrial enzymes and also by electron microscopy. Mice overexpressing MnSOD were protected from sepsis-induced mitochondria and muscle dysfunction. Pharmacological protection of mitochondria after sepsis also prevented chronic muscle weakness, further indicating that mitochondrial abnormalities are critical causal factors in sepsis-induced skeletal muscle weakness.
Conclusions: Sepsis-induced skeletal muscle weakness develops progressively and is persistently present even after atrophy is resolved. Muscle weakness during acute sepsis is likely caused by a combination of wasting and mitochondrial abnormalities, while long-term muscle dysfunction is mainly caused by mitochondrial aberrations.

P1 *(15 minutes)*

Using AI to identify cachexia: results from national database

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Cachexia is characterised by weight loss, muscle wasting and metabolic disturbance. Early symptoms of cachexia can overlap with other chronic conditions such as chronic obstructive pulmonary disease (COPD) (1). These shared symptoms can obscure precise identification and mask underlying disease processes, which are critical for timely intervention. One solution is to use machine learning models to examine electronic patient records to identify patients at scale with both conditions and where they overlap (2). Previous work has already tested this model in cancer cachexia on a publicly available ICU dataset of 46,520 patients using the Fearon 2011 consensus definition of cachexia. Natural Language Processing (NLP) models diagnosed 315% more patients then ICD coding. The model works with both structured data (e.g., height, weight, BMI) and unstructured data (free text patient notes). For patient notes the NLP tools take medical terms and their synonyms such as 'hypertension', 'HTN', and '150/95' and combines them into a single term – standardised with human phenotype ontology and SNOMED-CT dictionaries. These terms are then aggregated from various sources (structured and unstructured data, different patient letters) to give a complete patient profile. This technology was then applied to a dataset of 23,000 ICU patients and identified 4,471 patients with COPD and 643 patients with cachexia, with 264 patients having both conditions. These data were compared with ICD codes in a larger dataset to evaluate concordance. Prospective evaluation of cachexia is the gold standard but is slow, and retrospective review of notes is time consuming and open to human error. However, this AI-driven approach expedites data processing, enabling rapid identification of patients of interest for further study. Within this presentation an overview of this work will be presented with potential implications for further research in this area discussed.

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P2 *(15 minutes)*

Artificial intelligence for body composition and sarcopenia evaluation on computed tomography

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The DAFS vision of body composition is to go beyond the manual assessment of single-slice axial CT images for muscle and fat, and automate the difficult and tedious task of segmenting and quantifying muscle, fat, bone, internal organs (the heart, lungs, liver, pancreas, spleen, kidneys, prostate, intestines, arteries), lesions in these organs, blood vessels and lymph nodes, tissue edema, ascites and pleural fluid etc. to enable a rich and comprehensive characterization of body habitus of the individual patient. This rich characterization is in our view necessary to stage body composition for assessment of sarcopenia, cachexia, and the monitoring of organ and tissue health over time as a function of disease course and interventions. Accurate and automated segmentation is necessary to enable this vision, to the point that failures in segmentation are extremely rare. In this talk, I will showcase our DAFS platform, currently in use in ~200 research labs in 25+ countries, the challenges in building an automated AI platform for body composition and sarcopenia evaluation that is robust to the imaging in the real-world, and the workflow engineering needed for delivering such a platform for research and clinical workflows. I will also review some of the recent publications using DAFS for developing personalized predictive models.

References:
[1] https://jamanetwork.com/journals/jamasurgery/fullarticle/2817238: This paper used DAFS to analyze CT images from 48,444 patients to build models for predicting surgical outcomes finding that assessment of muscle quantity and quality via CT can provide an objective measure of patient frailty that may identify patients at high risk of mortality or readmission.
[2] https://www.nature.com/articles/s41591-023-02232-8: This paper used DAFS to assess body composition in the lung-cancer cachexia TracerX trial finding individuals in the bottom 20th percentile of the distribution of skeletal muscle or adipose tissue area at the time of lung cancer diagnosis, had significantly shorter lung cancer-specific survival and overall survival.
[3] https://www.journal-of-cardiology.com/article/S0914-5087(24)00192-8/abstract This paper used DAFS for body composition assessment, finding that subcutaneous adiposity in chest CT scans (vs adipopenia) is associated with higher 6-month cardiac resynchronization therapy (CRT) response and improved long-term outcomes, while intramuscular adiposity correlates with greater frailty.
[4] https://academic.oup.com/bjs/article/111/4/znae098/7642778 This paper used DAFS for body composition assessment, finding that low cachexia index (CXI) is associated with increased disease progression during neoadjuvant chemotherapy, higher rates of inoperability, worsened postoperative mortality, and reduced overall survival in patients with locally advanced oesophagogastric cancer, highlighting CXI's potential for prognostication and decision-making.

P3 *(15 minutes)*

RNAome guided classification of human skeletal muscle subtypes in cancer cachexia (AI-non-negative matrix factorization method)

Vickie Baracos
University of Alberta, Canada

Multiomics (multiple omics) provides an integrated approach to power discovery across multiple levels of biology and may include genomics, epigenomics, transcriptomics, proteomics, lipidomics, metabolomics, radiomics and /or microbiomics. Integrated 'omic research is increasing exponentially in clinical and experimental research in the study of diverse conditions ranging from cardiomyopathy (PMID: 35980883), cancer (PMID: 36434961) to Alzheimer's disease (PMID: 38619646). Cachexia research is just beginning to see the advent of multi-omic data sets e.g. simultaneous mRNA, proteome and lipidome (PMID: 38659807). Statistical approaches used in this context can uncover the co-varying features across 'omic data sets and identify molecular subtypes. In this presentation we introduce integrative analysis of muscle RNA (mRNA, lncRNA, miRNA, and small non-coding RNA) in patients with cancer. and discuss integrative non-negative matrix factorization (intNMF), an approach providing robustness of sample clustering, data dimensionality reduction, and decomposition of non-negative expression datasets.

P4 *(15 minutes)*

Automatized workflows for assessing the dynamics of muscle wasting

Lars H.B.A. Daenen[1,2], Wouter R.P.H. van de Worp[3], Behzad Rezaeifar[1], Joël de Bruijn[4], Peiyu Qiu[3], Justine M. Webster[3], Dirk De Ruysscher[1], Ramon C.J. Langen[3], Cecile J.A. Wolfs[1*], Frank Verhaegen[1,4*]
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**These authors contributed equally*

Introduction: Cachexia affects more than half of stage III non-small cell lung cancer (NSCLC) patients, diminishing cancer treatment effects and increasing mortality. Cone-beam computed tomography (CBCT) images, routinely acquired during radiotherapy treatment, might contain valuable anatomical information for monitoring cachexia. For this purpose, we propose an automatic artificial intelligence (AI)-based workflow, consisting of CBCT to synthetic (sCT) conversion, followed by segmentation of the pectoralis muscles for longitudinal follow-up of muscle mass changes.
Methods: Data from 140 stage III NSCLC patients was used. Two deep learning models, CycleGAN and contrastive unpaired translation (CUT), were used for image-to-image translation, to generate sCT images from CBCT images. The no-new U-Net (nnU-Net) model was used for automatic pectoralis muscle segmentation. To evaluate tissue segmentation performance in the absence of ground truth labels, an uncertainty metric (UM) based on Monte Carlo dropout was developed and validated. The contribution of change in pectoralis muscle area (PMA) to overall survival (OS) was analysed by Kaplan-Meier and Cox regression analysis.
Results: Both CycleGAN and CUT restored the Hounsfield unit fidelity of the CBCT images and visually reduced streaking artefacts. The nnU-Net achieved a Dice Similarity Coefficient (DSC) of 0.94 for the sCT images, respectively, on an independent test set. The UM showed a high correlation with DSC with a correlation coefficient of -0.89 for the sCT dataset. PMA loss of more than 3% during radiotherapy was observed in 48% of the patients, which had a negative impact on OS (HR 1.74 [95%CI 0.95-3.19], P=0.072).
Conclusion: This work demonstrates a proof-of-concept for automatic AI-based monitoring of the pectoralis muscle area during radiotherapy treatment based on CBCT images, presenting an unprecedented time resolution of muscle wasting associated with cachexia progression. Ultimately, the proposed workflow could provide valuable information for early intervention of cachexia, ideally resulting in improved cancer treatment outcome.

Q1 *(15 minutes)*

Cardiometabolic effect

Andrew Coats
Heart Research Institute, Sydney, New South Wales, Australia

Sarcopenia can be associated with cardio metabolic abnormalities either because of a common aetiology and pathophysiology or because cardiometabolic abnormalities can occur in response to skeletal muscle wasting. It is known that a reduction in skeletal muscle mass will lead to an increase in insulin resistance which can precipitate or worsen type 2 diabetes. By the well-known muscle syndrome of chronic wasting disorders it is also known that skeletal muscle wasting and metabolic dysfunction is associated with exaggerated muscle ergo-reflex responses which produce sympathetic hyperactivation and can contribute to neurohormonal overactivity. These responses can further worsen cardiometabolic complications. In some chronic disease states associated with this syndrome, exercise training can partially ameliorate these cardiometabolic abnormalities whilst also improving exercise tolerance and reducing symptoms and on occasion preventing disease progression or complications. Evidence of the benefits of muscle training have been seen chronic heart failure-related skeletal myopathy as well as in cancer, chronic kidney disease and chronic obstructive pulmonary disease related skeletal muscle wasting. In the treatment of age related sarcopenia the training maybe most effective when there is a strength and resistance training element.

Q2 *(15 minutes)*

Osteosarcopenia

Gustavo Duque
Dr. Joseph Kaufmann Chair in Geriatric Medicine, Faculty of Medicine and Health Sciences, McGill University; Principal Investigator - Bone, Muscle, and Geroscience Group - Research Institute of the McGill University Health Centre, Director - The Simone Edouard Schouela RUISSS McGill Centre of Excellence for Sustainable Health of Seniors (Schouela CEDurable), Canada

Sarcopenic muscle can contribute to dysfunctional bone through several interconnected mechanisms involving mechanical, biochemical, inflammatory and endocrine pathways. Sarcopenia is often linked with osteoporosis or osteopenia, leading to a condition known as osteosarcopenia, where both muscle and bone deteriorate. The interconnected nature of muscle and bone health means that interventions targeting sarcopenia can also benefit bone health, potentially preventing osteosarcopenia. In this session, the mechanisms of osteosarcopenia will be discussed from a biological and therapeutic perspective.

Q3 *(15 minutes)*

Muscle health and neurodegeneration: exploring the link between sarcopenia and cognitive decline

Miguel Borda
Centre for Age-Related Medicine (SESAM), Stavanger University Hospital, Stavanger, Norway

The relationship between muscle health and neurodegenerative conditions, particularly Alzheimer's disease and dementia, reveals a complex interplay that impacts cognitive outcomes as people age. Sarcopenia, is increasingly recognized as a significant contributor to cognitive impairment and dementia risk. Factors like physical inactivity, suboptimal nutrition, and chronic inflammation contribute to both sarcopenia and neurodegeneration, suggesting overlapping pathways that may be modifiable.
Mechanisms linking muscle and brain health include the action of myokines that play vital roles in supporting neuronal function and protecting against cognitive decline. Evidence shows that physical interventions, benefit both muscle strength and cognitive performance in older adults. Additionally, nutritional strategies, such as protein supplementation and adherence to a Mediterranean diet, have demonstrated efficacy in supporting both muscle integrity and cognitive resilience.
Early intervention in sarcopenia presents a promising avenue to delay cognitive decline, with ongoing research exploring therapies that target the muscle-brain axis to address both muscle atrophy and neurodegenerative processes. This evolving understanding of muscle's role in brain health highlights the potential for integrative approaches to support cognitive and physical well-being throughout aging.

Q4 *(15 minutes)*

Fat and muscle interactions in the context of obesity

John A. Batsis
Division of Geriatric Medicine, University of North Carolina at Chapel Hill School of Medicine, Chapel Hill, NC, USA

Sarcopenic obesity results from complex interactions between age-related changes in lifestyle, body composition, hormonal imbalance, inflammation, oxidative stress, altered metabolism, and muscle satellite cell activity. In older adults, chronic conditions further exacerbate these factors, leading to a cycle of ectopic fat deposition and loss of muscle mass and strength, which contributes to functional decline and disability. This presentation will provide an overview of the physiological changes in muscle and fat with aging, focusing on how these shifts drive inflammation, glucose dysregulation, and hormonal effects on physical function. We will begin by discussing age-related body composition changes, including the progressive loss of muscle mass and strength, as well as increased fat deposition in both visceral and ectopic areas. We will explore the role of myosteatosis and its impact on biological mechanisms and physical function, discussing changes in inflammation, mitochondrial dysfunction, and altered glucose metabolism. The talk will also address the shared risk factors and mechanisms underlying both sarcopenia and obesity, examining how diet and exercise influence these processes and the relevance of myostatin and mTOR pathways in the syndrome's pathophysiology. Finally, we'll highlight gaps in the biological understanding of sarcopenic obesity that contribute to its variability, suggesting possible targets for future interventions.

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S1 *(15 minutes)*

Neural control of anorexia

Tobias Janowitz
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Patients with cachexia experience extreme fatigue, apathy, and clinical depression. In the C26 mouse model, cachexia induced apathy-like symptoms through a cytokine-sensing brainstem-to-basal ganglia circuit. This neural circuit detects elevated interleukin-6 (IL-6) at cachexia onset in the area postrema, translating inflammatory signals via the parabrachial nucleus into decreased mesolimbic dopamine, thereby increasing effort-sensitivity. We alleviated these apathy-like symptoms by targeting key nodes of the circuit: administering an anti-IL-6 antibody treatment, ablating cytokine sensing in the brainstem, and boosting mesolimbic dopamine. Our findings uncover a central neural circuit that senses inflammation and orchestrates behavioral changes. Beyond cancer cachexia, we provide mechanistic insights into the connection between chronic inflammation and depressive symptoms.

S2 *(15 minutes)*

Appetite control and metabolic changes in cancer cachexia

Marcus Goncalves
NYU Langone Health, New York, NY, USA

Cancer cachexia is a complex syndrome defined by involuntary weight loss, muscle wasting, and systemic inflammation, leading to significant patient morbidity and mortality. A critical yet underexplored contributor to this syndrome is reduced feeding, driven by disrupted central appetite regulation. This presentation will examine the impact of decreased food intake on cachexia progression, highlighting the role of impaired leptin signaling in the hypothalamus, which exacerbates anorexia and muscle catabolism. The dysregulated leptin pathway not only contributes to appetite suppression but also perpetuates systemic inflammation through downstream JAK/STAT activation. Recent data suggest that JAK inhibition may restore feeding behavior and attenuate metabolic wasting by normalizing leptin signaling. We will present evidence from preclinical and clinical studies illustrating the potential of JAK inhibitors to target this pathway, offering a promising therapeutic avenue to alleviate anorexia, mitigate muscle loss, and improve clinical outcomes in cachexia patients.

S3 *(15 minutes)*

Alterations in brain metabolites in pancreatic cancer cachexia

Saleem Yousf, Raj Kumar Sharma, Balaji Krishnamachary, Paul Winnard, James D. Barnett, Yelena Mironchik, Marie-France Penet, Michael G. Goggins, Zaver M. Bhujwalla
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Over the past decade we have applied molecular and functional imaging to understand cachexia with a focus on pancreatic cancer induced cachexia [1, 2]. During the course of our studies we have identified significant alterations in brain metabolism in the Pa04C patient-derived model of pancreatic ductal adenocarcinoma (PDAC) [2]. We observed a significant depletion of choline, as well as significant increases of glutamine and formate, relative to normal controls and non-cachectic tumor-bearing mice [2]. The metabolic alterations were accompanied by brain weight loss. We further investigated changes in brain volume and vascular oxygenation with optoacoustic imaging that confirmed a reduction of brain volume and significant changes in vascular hemodynamics with an oxygen breathing challenge. Our ongoing studies are evaluating mechanisms underlying these changes in brain metabolism and oxygenation, and the effects of glutamine targeting of cancer cells in modifying cachexia and brain metabolism. These results highlight the metabolic and functional impact of cachexia on the brain, and identify potential targets to reverse these changes.

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S4 *(15 minutes)*

Possible modifiers of the anorexic/cachectic actions of GDF15

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GDF15, a member of the glial-derived neurotrophic factor receptor (GDNF) family within the TGFb superfamily, is a major aetiological factor in anorexia/cachexia syndromes linked to disorders like cancers, chronic heart and renal failure (1). Cell stress induced GDF15 elevation in serum levels acts on its highly hindbrain region localised receptor glial-derived neurotrophic factor receptor alpha like (GFRAL), triggers anorexic and aversive behaviours. Progressive loss of lean and fat mass and eventually the anorexia/cachexia syndrome results. Antibodies to GDF15 or its receptor, are currently being trialled by several companies as therapeutics for patients with anorexia cachexia syndromes and the favourable results of a phase II study in cancer cachexia have recently been reported.

In all likelihood there are other metabolic mediators that modify the action of GDF15 and if of sufficient significance, may also serve as therapeutic targets for anorexia/cachexia syndromes and we have explore the actions of one of these, Leptin (2). We provide evidence based on in vivo experiments in mice, for i) the additive effects of Leptin and GDF15 ii) for the interconnections between leptin and GDF15 neurons and iii) the impact of interruption of the hindbrain leptin pathway on mouse body weight

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T1 *(15 minutes)*

HIPGEN - Lessons learned from a Phase III study on allogeneic cell therapy for muscle regeneration in hip fracture patients

Tazio Maleitzke, Denmark

T2 *(15 minutes)*

Regulatory T-cell targeting biomaterials for skeletal muscle regeneration

Brian Kwee
University of Delaware, Ammon Pinizzotto Biopharmaceutical Innovation Center, Newark, DE, USA

Regulatory T-cells (Tregs) are potent anti-inflammatory immune cells that broadly suppress pro-inflammatory responses during tissue injury. Tissue-specific Tregs, a subset of Tregs that are recruited to injuries in an antigen-specific manner, also secrete factors that drive muscle stem cell differentiation, innervation, and angiogenesis.[1] In particular, muscle-specific regulatory T-cells are recruited to sites of acute muscle injury and sarcopenia to enhance functional muscle repair and reduce fibrosis.[2, 3] However, Tregs are recruited to severe muscle injuries at low frequencies, resulting in degenerating pro-inflammatory microenvironments and fibrosis. We engineered injectable, oxidized, calcium-crosslinked alginate hydrogels to provide spatiotemporal release of factors that regulate the recruitment, proliferation, and activation of Tregs at sites of ischemic muscle injury. We specifically tested these hydrogels in a model of hindlimb ischemia in BALB/c mice, which exhibit long term muscle mass loss, denervation, and loss of blood perfusion. We designed our hydrogels to provide sustained release of IL-33, to recruit tissue-specific Tregs, as well as the IL-2/anti-IL-2 complex, which specifically drives the proliferation of Tregs. Incorporation of charged laponite nanodiscs into the hydrogel enhanced both the burst release and long-term rate of release of IL-33 and IL-2/anti-IL-2 from the hydrogel by modulating electrostatic interactions between the drugs and hydrogel. Delivery of IL-33 from our hydrogel in the model of hindlimb ischemia demonstrated a trend of increasing blood perfusion recovery relative to delivery of a blank hydrogel. We also designed our hydrogel to release amphiregulin (AREG), a potent activator of Tregs, with near zero-order kinetics after moderate burst release. Delivery of AREG from our hydrogel to the model of hindlimb ischemia reduced tissue necrosis and enhanced the walking gait of the mice relative to delivery of a blank hydrogel. Our preliminary work in designing Treg targeting biomaterials demonstrate that 1) we can rationally design the rate of release of cytokines from our alginate hydrogels to modulate Treg function and 2) hydrogels that modulate the number and activity of Tregs at sites of ischemic muscle injury may enhance limb function and regeneration.

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T3 *(15 minutes)*

Digital training therapy for correction of movement after ligament surgery in knee patients

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Following knee ligament injuries, patients often develop maladaptive gait patterns, which can significantly increase the risk of post-traumatic osteoarthritis (PTOA) due to altered joint mechanics and excessive joint loading [1]. The PROTO project addresses this risk with an innovative, sensor-based physical training intervention designed to correct pathological gait patterns and restore physiological joint biomechanics. At the core of this project is the *re.flex* system, which provides real-time feedback through wearable sensors and a mobile app, guiding patients through a structured, 12-week program focused on neuromuscular training, strength building, and gait retraining.

This intervention targets the critical post-injury "window of opportunity," a period where early correction of gait abnormalities may help prevent the onset of irreversible joint degeneration [2,3]. In addition to clinical assessments, the study employs advanced magnetic resonance imaging and biomarker analyses to evaluate whether digital rehabilitation can foster sustainable improvements in movement quality and joint health. By enabling unsupervised, sensor-based training, PROTO offers consistent and accessible rehabilitation beyond traditional clinical settings, encouraging broader patient engagement and adherence.

This project exemplifies the potential of digital health innovations to prevent PTOA by addressing maladaptive movement patterns early in recovery. PROTO underscores the importance of personalized, targeted interventions to protect long-term joint health in at-risk populations.

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T4 *(15 minutes)*

The Advanced Therapies in Orthopaedics Alliance (ATiO) - creating the medicine of the future for musculoskeletal diseases

Tobias Winkler
BIH Center for Regenerative Therapies & Julius Wolff Institute; Center for Musculoskeletal Surgery; Berlin Institute of Health @ Charité – Universitätsmedizin Berlin, Germany

The burden of musculoskeletal diseases continues to rise globally, affecting over 1.7 billion people and imposing significant disability and economic costs, projected to reach $2.8 trillion annually by 2040. Despite these staggering figures, musculoskeletal conditions remain an area of substantial unmet need in healthcare.[1]
The Advanced Therapies in Orthopaedics Alliance (ATiO) was established to address this challenge by creating a collaborative ecosystem that accelerates the development and application of cutting-edge therapies in orthopaedics.
ATiO serves as a nexus for scientists, clinicians, industry leaders, finance and regulatory experts, united by the goal of transforming pioneering research into clinically viable solutions. To date, knowledge and ressources are heavily compartmentalized within these different entities and the ATiO strives to bring them together. By fostering international partnerships and setting standards, ATiO aims to streamline the path from innovation to implementation, ensuring that breakthrough therapies can reach patients more swiftly and safely.
In this presentation, we will discuss ATiO's role in reshaping the future of musculoskeletal medicine through initiatives that bridge the gap between research and real-world application. Our work encompasses facilitating early-stage project development, curating an exclusive online platform for professional networking and knowledge-sharing, and hosting an annual, invitation-only summit that brings together key opinion leaders to drive collaborative advancements.
Through ATiO's multi-disciplinary approach, we are building the foundations for a new era in treatment of diseases of our motion apparatus — one that holds the promise of personalized, regenerative, and advanced therapeutic solutions for patients worldwide.

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U1 *(7 minutes)*

Cachexia in chronic illness – results of a country-wide registry

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Background: Cachexia remains frequent in patients with chronic diseases and is associated poor performance and outcome. The International Classification of Diseases (ICD) has codes for cachexia but information about use in clinical practice as well as association with outcome is scarce. In this study, we aimed to investigate prevalence of cachexia coding in hospitalized patients with chronic diseases and their outcome.
Methods: This was a retrospective analysis of the National Hospital Health Care Statistics Database using the 10th revision of the ICD codes. In timeframe 2004 – 2019, cachexia codes (R64, C80.9 and B22.2) were linked with codes of cancer, chronic heart failure, chronic obstructive pulmonary disease and chronic kidney disease. The primary endpoint the discharge code of cachexia; secondary endpoints were length of hospital stay, in-hospital and post discharge all-cause mortality.
Results: Over 16 years, 5.484.103 hospitalisations were screened; cachexia was coded 19,348 times (0.35%) in 14089 patients (67±13 yo, 42% women). From 2004 to 2019, prevalence of cachexia increased steadily from 1.2% to 1.9%, which was most prominent for cancer and COPD. At one year post discharge, 49% patients with cachexia were dead as compared to 26% in patients without cachexia. In Cox multivariate analysis, cachexia predicted post-discharge death in any of chronic diseases (hazard ratio of 1.28 in heart failure to 1.47 in chronic kidney disease).
Conclusions: In our report from a national hospitalisation database we found that ICD-10 coded cachexia at discharge was rare in patients with chronic disease. When diagnosed, it was associated with higher hazard of post discharge mortality.

U2 *(7 minutes)*

MENAC - a randomised, open-label trial of a multimodal intervention (exercise, nutrition and anti-inflammatory medication) plus standard care versus standard care alone to attenuate cachexia in patients with incurable lung or pancreatic cancer undergoing systemic anti-cancer therapy

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Introduction: Combining interventions for cancer cachexia is proposed as an effective strategy. Building on a promising pilot study, we conducted the MENAC (Multimodal Exercise Nutrition Anti-inflammatory Cachexia) trial to comprehensively evaluate this.
Methods: MENAC was a multicentre, randomised phase 3 trial in 4 countries. Patients with stage III or IV lung or pancreatic cancer receiving SACT with non-curative intent were randomly assigned (1: 1) to a multimodal intervention consisting of nutritional counselling plus fish oil containing oral nutritional supplements, physical exercise (endurance and strength) and non-steroidal anti-inflammatory drugs (NSAIDs) versus standard care. Randomisation was stratified by country, cancer type and stage.
Our primary objective was to body weight. Secondary Objectives assessed muscle mass (measured by CT L3 technique) and physical activity (assessed through step count using ActivPAL activity meter) between arms. Exploratory endpoints included treatment response (RECIST), survival, and Quality of Life. Assessments were conducted at base line (pre-randomisation), at endpoint (after 6 weeks) and follow -up (12 weeks).
Results: From May 2015 to February 2022, 212 patients were enrolled (105 to multimodal treatment, 107 standard care). Over 6 weeks, weight stabilised in patients assigned to multimodal treatment compared with those assigned to standard care (mean weight change [SD] 0.05 kg [3.8] *vs* – 0.99 kg [3.2], respectively) with a mean difference in weight change of -1.04, 95 % CI -2.02 to -0.06, p = 0.04. There was no difference in muscle mass (mean change [SD] -6.5cm^2 [10.1] *vs* -6.3cm^2 [11.9], p = 0.93) or in step count (mean change [SD] -377.7 [2075] *vs* -458 [1858], p = 0.89). There were 28 and 24 reported SAEs in the intervention and control arm respectively, no SUSARs were reported. Data on exploratory endpoints and 12 week follow up will be presented.
Conclusion: A multimodal cachexia intervention stabilised weight compared to standard care at six weeks. There was no difference in physical activity or muscle mass between trial arms.

clinicaltrials.gov id: nct02330926

U3 *(7 minutes)*

A synbiotic improves muscle strength, mass and performance in older Australians: preliminary results from a randomized, controlled trial (9-02)

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Introduction: The etiology of sarcopenia is complex and multifactorial yet recent evidence suggests one contributing factor may be age-related alterations in gut microbiota. Synbiotic administration appears effective in modifying gut microbial composition, however it remains unclear if these changes translate into functional improvements. We examined the effects of synbiotic (SYN) supplementation compared with placebo (PLA) on muscle strength, lean body mass and physical performance in older adults.
Methods: A randomized, double-blinded controlled trial was performed among 70 community-dwelling, older (60-85 years) adults. Participants were randomly allocated (1:1) to receive either SYN or PLA daily for 16 weeks. Outcomes including handgrip strength (HGS), Short Physical Performance Battery (SPPB), timed up and go (TUG) and body composition (dual-energy X-ray absorptiometry) were assessed at baseline and after 16 weeks.
Results: Sixty-four participants (72.7 ± 5.6 years; 61% female) completed the trial. Compared with PLA, SYN supplementation for 16 weeks resulted in significantly increased HGS (p = .024) and total SPPB score (p = .006), and significantly improved times for gait speed (p < .001) and TUG (p = .001). No significant between-group changes in body composition were observed (p > .05). Absolute and relative fat mass decreased in the SYN group (Δ -0.24 kg and Δ -0.26%, respectively) and increased in the PLA group (Δ 0.03 kg and Δ 0.09%, respectively), however, these were not significant (p > .05). A larger increase in lean body mass was observed in the SYN vs. PLA group (Δ 0.14 kg vs. Δ 0.04 kg, p = .697).
Conclusions: Sixteen weeks of synbiotic supplementation improved muscle strength and physical performance in community-dwelling older adults compared with placebo. These improvements were not accompanied by significant changes in body composition.

U4 *(7 minutes)*

BIO101: a drug candidate to reduce GLP1-RA-induced muscle mass or function loss in patients with obesity (9-11)

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Introduction: GLP-1 receptor agonists (GLP-1RAs), also named incretins, effectively reduce body weight, however up to 40% of the total lost weight is lean body mass, which includes loss of skeletal muscle mass. Similar levels of weight loss with bariatric surgery are associated with clinically significant reductions in muscle mass and strength. Combining skeletal muscle-targeted drug candidates with GLP-1RAs may preserve skeletal muscle mass and function. BIO101 (20-hydroxyecdysone; 20E), an oral MAS receptor activator, could be a promising treatment to prevent the loss of muscle mass or strength in patients with obesity or overweight treated with GLP-1RAs.
Methods: Preclinical studies of 20E-treated myoblasts and high fat diet (HFD) obese mice were completed to characterize the metabolic, muscular and weight loss properties of 20E. In addition, a 12-week double-blind placebo-controlled study (6-week hypocaloric intervention phase followed by 6-week weight loss maintenance phase) with 37.5mg 20E was conducted in 58 participants with overweight or obesity (BMI ≥ 27 kg/m² and ≤ 38 kg/m²) aged 20-65 years.
Results: Preclinically, 20E has pro-differentiating effects *in vitro* in murine and human myocytes, increasing myotube diameter. *In vivo*, 20E improved muscle function and physical capacity. In HFD mice, 20E significantly prevented increase in adipose tissue by limiting adipocyte size, adipokines and inflammatory markers (leptin, MCP-1), insulin resistance (osteopontin) and decreased genes involved in lipid storage (lipoprotein lipase).
In patients with overweight or obesity, 37.5mg 20E significantly decreased android fat mass (p=0.039). From biopsies, a statistically significant reduction in adipocyte diameter was also observed over the entire trial period. Compared to placebo, a trend for improvement in handgrip strength occurred in the subpopulation who lost more than 5% of their initial weight during the weight loss phase.
Conclusions: Supported by these data, a phase 2 Proof-of-Concept study combining BIO101 treatment with a GLP-1 RA will be shortly initiated.

U5 *(7 minutes)*

Cancer Appetite Recovery Study (CAReS): Phase 1 dose-ascending, multicenter trial of ART27.13 in patients with cancer anorexia and weight loss

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Background: Cannabinoids have shown potential as therapeutic agents for Cancer Anorexia-Cachexia Syndrome (CACS) by modulating the cannabinoid 1 (CB_1) receptor, which plays a key role in appetite regulation and body weight maintenance. ART27.13, an investigational, peripherally selective CB_1/CB_2 receptor agonist being developed by Artelo Biosciences, has demonstrated the ability to increase body weight in healthy volunteers as well as protect against myotube degeneration in a pre-clinical model simulating cancer cachexia conditions[4]. A phase 1 trial has been completed examining ART27.13 in patients with CACS. The aims of this phase 1 trial were to assess safety, dosing, and potential efficacy in a cancer population.

Methods: A single arm, open-label phase 1 dose ascending trial was conducted in multiple cancer centers. Eligible patients met the following criteria: adult cancer patients; anorexia (self-reported); unintentional weight loss <5% (preceding 6 months); not on anti-cancer therapy with some specified exceptions; Karnofsky Performance Score >50. Following baseline assessments, participants were treated with daily doses of ART27.13 and in groups of 6 were assigned to escalating dose cohorts of 150, 250, 400, and 650 µg for 12 weeks.

Primary outcomes were: Safety (Adverse Events); Assessment of Dose-Limiting Toxicity; Assessment of most effective safe starting dose for a phase 2 trial. Secondary outcomes were: changes in weight; lean mass; appetite (by Visual Analog Scale); Quality of Life (e.g. FAACT and EORTC QLQ-C15 PAL). Outcomes were assessed at 28 days. An evaluable patient was one who received at least 21/28 doses in the first, 4 week-cycle. Each of the 4 dose cohorts (150, 250, 400, and 650 µg) had at least 6 evaluable patients. Descriptive analyses were undertaken.

Results: Twenty-seven patients received at least one dose of ART27.13 and there were 22 patients with a recorded weight at the end of Cycle 1. There were no events considered as dose limiting toxicities (DLTs) and no fatal AEs related to trial treatment. The most common (> 1 patient) AEs related to trial drug were somnolence (11%) and dry mouth (11%). No dose response for AEs was noted. Based on the positive safety profile and the response pattern observed, a dose of 650 micrograms was selected as the most effective, safe, starting dose for the placebo-controlled phase 2 trial. In 14/22 (64%) of patients, there was weight stabilisation or weight gain observed at day 28. Changes in lean mass, appetite, and quality of life were variable.

Discussion: The results of the Phase 1 trial for ART27.13 were promising. The compound demonstrated a robust safety profile, with no dose-limiting toxicities observed across all study cohorts. Moreover, the observed effects on weight were encouraging, supporting the potential efficacy of ART27.13. Based on these positive findings, a starting dose for the Phase 2 randomized, placebo-controlled, double-blind trial was established at 650 µg/day. This trial, currently recruiting at sites in the UK, Ireland, and Norway, aims to further evaluate the efficacy and safety of ART27.13 in a larger patient population. The data from the Phase 1 trial provide a strong foundation for investigating the potential clinical benefits of ART27.13 in the treatment of cancer anorexia.

Trial registration: EudraCT NUMBER:2020-000464-27

Research Ethics Committee reference: 20/NE/0198.

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U6 *(10 minutes)*

Anamorelin Efficacy in Non-Small Cell Lung Cancer Patients with Cachexia: Insights from ROMANA 1 and ROMANA 2 (3-28)

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Background: Cancer cachexia presents a significant challenge, but the ghrelin agonist anamorelin shows promise as a potential treatment. This study examined whether the baseline systemic inflammatory response (SIR) (measured by the modified Glasgow Prognostic Score [mGPS]), low BMI or greater weight loss, was associated with a differential treatment effect of anamorelin in people with cachexia and non-small cell lung cancer (NSCLC).
Methods: ROMANA 1 and ROMANA 2 were double-blind, placebo-controlled, randomised phase 3 trials that enrolled people with inoperable stage III/IV NSCLC with cachexia (≥5% weight loss within 6 months or body mass index [BMI] <20 kg/m^2). Patients were randomised 2:1 to anamorelin 100 mg once daily or placebo, for 12 weeks. This is a post-hoc analysis of efficacy endpoints (body weight, body composition (Lean body mass [LBM], Fat Mass [FM]), stratified by baseline mGPS, BMI and weight loss and measured in the modified intent-to-treat pooled population.
Results: 795 patients had available data. Anamorelin improved body weight ($p<0.001$) and body composition parameters (LBM, FM, $p<0.01$) in all mGPS groups. In patients with mGPS=2, anamorelin increased weight >5% and improved hand grip strength (HGS) and the Functional Assessment of Anorexia Cachexia Therapy Anorexia/Cachexia Subscale (FAACT A/CS). In patients with BMI <20 kg/m^2 at baseline or weight loss ≥10% in the prior 6 months, anamorelin led to significant increases in body weight from baseline ($p<0.001$) versus placebo. Patients with weight loss ≥10% in the prior 6 months showed the highest improvements in LBM ($p<0.001$). Patients with BMI <20kg/m^2 at baseline showed the highest improvements in FM ($p<0.001$).
Conclusion: Anamorelin improved body composition parameters in all patients, as well as physical function and symptom burden, particularly in patients with systemic inflammation, BMI<20kg/m^2 and weight loss≥10%. These results highlight the anabolic mechanisms of anamorelin irrespective of weight loss or systemic inflammation (high risk groups).

NCT Identifiers: ROMANA 1: NCT01387269; ROMANA 2: NCT01387282

U7 *(10 minutes)*

Efficacy and safety of ponsegromab, a first-in-class, monoclonal antibody inhibitor of growth differentiation factor 15, in patients with cancer cachexia: a randomized, placebo-controlled, phase 2 study

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Introduction: Cancer cachexia can lead to weight loss, muscle wasting, and reduced quality of life. Ponsegromab is a humanized monoclonal antibody targeting growth differentiation factor 15 (GDF-15), a circulating cytokine implicated in cachexia. Here, we report the results of a phase 2, randomized, double-blind trial of ponsegromab vs placebo in patients with cancer cachexia.
Methods: Patients with cancer cachexia and elevated serum GDF-15 (≥1500 pg/mL) were randomized 1:1:1:1 to subcutaneous ponsegromab (100, 200, 400 mg) or matching placebo every 4 weeks for 12 weeks. The primary endpoint was a change in weight from baseline to 12 weeks. Other endpoints included change in appetite and cachexia symptoms (Functional Assessment of Anorexia/Cachexia Treatment [FAACT] Anorexia Cachexia Subscale [FAACT-ACS] and 5-item Anorexia Symptom Scale [FAACT-5IASS]), non-sedentary physical activity, and lumbar skeletal muscle index (LSMI).
Results: Overall, 187 patients (39.6% non-small cell lung, 31.6% pancreatic, and 28.9% colorectal cancer; 73.3% stage 4) were randomized. Ponsegromab resulted in significant dose-responsive increases in weight, with placebo-adjusted modeled median (95% credible interval) increases of 1.22 kg (0.37, 2.25) [100 mg], 1.92 kg (0.92, 2.97) [200 mg] and 2.81 kg (1.55, 4.08) [400 mg] at 12 weeks. Placebo-adjusted weight gain was observed at week 8 in all ponsegromab groups. In the 400 mg ponsegromab group, placebo-adjusted modeled median (95% credible interval) improvements in FAACT-ACS (4.50 [1.29 to 7.77]); FAACT-5IASS, (2.39 [0.61 to 4.15]); non-sedentary physical activity (71.70 [37.01 to 107.21] minutes), and LSMI (2.04 [0.27 to 3.83] cm^2/m^2) were also observed compared with placebo. All-causality and treatment-related adverse events occurred in 70.4% and 7.7% of ponsegromab-treated patients and 80.0% and 8.9% of placebo-treated patients, respectively.
Conclusion: Ponsegromab improved weight, symptoms, overall activity, and skeletal muscle mass in patients with cancer cachexia and elevated GDF-15, confirming GDF-15 as a primary driver of cancer cachexia.

Adapted from Annals of Oncology, Volume 35, Crawford, J. et al. LBA82 Efficacy and safety of ponsegromab, a first-in-class, monoclonal antibody inhibitor of growth differentiation factor 15, in patients with cancer cachexia: A randomized, placebo-controlled, phase II study. S1269.

V1 *(15 minutes)*

What about the diaphragm in cachexia

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The diaphragm is both among the largest muscles in humans and the main respiratory muscle responsible for normal ventilatory behaviors. Loss of muscle mass and muscle dysfunction in the diaphragm is often observed in patients exhibiting cachexia due to heart failure, cancer or after mechanical ventilation. Initial descriptions of inspiratory muscle involvement in heart failure with reduced ejection fraction (HFrEF) date back to the 1990s with a small study showing that patients with HFrEF had lower Pi_{max} compared with healthy controls. With regard to morbidity and mortality, different studies documented that diaphragm weakness and its degree of reduction is an independent predictor of mortality.
With respect to molecular mechanisms it seems that elevated mitochondrial stress is an important trigger for muscle dysfunction and fiber atrophy in cancer and heart failure models. Based on this observation several studies will be discussed during the presentation aiming to target mitochondrial function and reactive oxygen production to prevent diaphragm dysfunction in cancer and heart failure models. Besides mitochondrial dysfunction also the activation of the specific ubiquitin E3-ligase Murf-1 was observed in models of heart failure, and the treatment with a small molecule interfering with interaction of MuRF1 and titin attenuated muscle atrophy and dysfunction. Last but not least we will discuss the impact of exercise precondition on ventilation-induced diaphragm dysfunction and some molecular mechanism involved.
Taken together, diaphragm dysfunction is often observed in cachectic situations like cancer, heart failure and mechanical ventilation and based on the molecular understanding several therapeutic strategies have been developed.

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V2 *(15 minutes)*

IL-6 induces early cachexia via hepatic STAT-3

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Patients with pancreatic ductal adenocarcinoma (PDAC) often suffer from cachexia, a wasting syndrome that significantly reduces both quality of life and survival. Although advanced cachexia is associated with inflammatory signaling and elevated muscle catabolism, the early events driving wasting are poorly defined. To understand early drivers of muscle wasting, we developed an orthotopic mouse model of early PDAC cachexia in 12-week old C57BL/6J mice and utilized nutritional deprivation interventions to test the capacity for metabolic adaptation. We measured anthropometrics, physical activity, and energy expenditure longitudinally. Wasting was measured by muscle mass, gene expression, and cross-sectional area, whereas adaptive metabolism was evaluated by circulating hormone and metabolite levels, hepatic lipid content, and ketogenic response to fasting or medium-chain fatty acid bolus at termination. Pre-cachectic PDAC mice were unable to preserve gastrocnemius muscle mass in the context of calorie restriction and displayed impaired fatty acid oxidation, resulting in a hypoketotic state. These findings were mirrored among patients with PDAC. Prior work linked IL-6 to cachexia[1] and impaired ketogenesis[2] in PDAC. We found that global deletion of IL-6 or hepatocyte-specific deletion of STAT3 reversed both this susceptibility to muscle wasting and the deficiencies in hepatic fatty acid oxidation and ketogenesis. Provision of a carbohydrate-free ketogenic diet can overcome the IL-6-mediated loss of fatty acid oxidation in the liver. We conclude that, during the pre-cachectic state, muscle vulnerability to wasting is dependent on inflammation-driven metabolic reprogramming in the liver. Dietary and anti-inflammatory interventions that restore hepatic lipid oxidation may be a viable preventative approach for pre-cachectic patients with pancreatic cancer.

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V3 *(15 minutes)*

The impact of Leukemia inhibitory factor on hepatic lipid metabolism

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Cancer cachexia is a systemic metabolic syndrome characterized by involuntary weight loss, and muscle and adipose tissue wasting. Cachexia occurs frequently in advanced cancer patients with many progressing to death. Mechanisms underlying cachexia remain poorly understood. Cancer cachexia can be in part driven by the competition between tumor and host cells for nutrients. Importantly, there are metabolic and signaling crosstalk between organs, including the brain, liver, gut, muscle, and adipose tissues, which contribute to the cachectic state.
Leukemia inhibitory factor (LIF), a multi-functional cytokine, has been suggested as a cachexia-inducing factor. We established a transgenic mouse model with conditional LIF expression to demonstrate that systemic elevation of LIF induces cachexia. We found that LIF overexpression disrupts lipid homeostasis in the liver. Liver-specific LIF receptor knockout attenuates LIF-induced cachexia, suggesting that LIF-induced functional and metabolic changes in the liver contribute to cachexia. Mechanistically, LIF overexpression activates STAT3 to downregulate PPARα, a master regulator of lipid metabolism, leading to the downregulation of a group of PPARα target genes involved in lipid metabolism in the liver. Activating PPARα by fenofibrate, a PPARα agonist, restores lipid homeostasis in the liver and inhibits LIF-induced cachexia. These results provide insights into cachexia, which may help develop strategies to treat cancer cachexia.

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V4 *(15 minutes)*

Transcriptional reprogramming of the liver in cancer cachexia

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Cancer cachexia is a multifaceted syndrome characterized by unintended weight loss and poor survival rates[1]. Despite extensive research into muscle and adipose tissue deterioration as key indicators of cancer cachexia, the contribution of the liver to cachexia progression remains incompletely understood.

To explore how cancer cachexia affects the gene expression and chromatin structure of hepatocytes, we conducted genomic profiling using livers from different mouse models of weight-stable cancer and cancer cachexia. Through an integrative multilevel analysis approach[2], we identified transcriptional regulators that drive the cachexia-associated gene program and highlighted the circadian clock as a key modulator of hepatic transcriptional reprogramming in cancer cachexia. Additionally, we discovered hepatocyte-secreted factors that were upregulated under wasting conditions.

Intriguingly, genetic reconstitution of the cachexia-repressed circadian clock regulator REV-ERBα ameliorated peripheral tissue wasting and was associated with reduced circulating levels of specific liver-secreted factors. Moreover, we found that these REV-ERBα-regulated hepatokines could induce catabolic processes in various cell types *in vitro*, suggesting a contribution to systemic wasting. In addition, these factors were elevated in the plasma of cachectic gastrointestinal cancer patients, indicating that our findings from modeling cancer cachexia in mice are also relevant cancer cachexia in humans.

Together, we provide novel insights into the liver's role in contributing to disease progression in cancer cachexia through mechanisms of tissue crosstalk.

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W1 *(15 minutes)*

Interrogating the Ghrelin-AgRP system in the KPC mouse model

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Introduction: Ghrelin is a peptide hormone which rises in response to fasting, drives eating behaviour, decreased energy expenditure and growth hormone release. The ghrelin analogue anamorelin is a potential candidate for treating cachexia. The primary target neurons of ghrelin are the Agouti related peptide/neuropeptide Y-containing neurons in the arcuate nucleus of the hypothalamus (AgRP neurons).
Methods/Results: We used the syngeneic KPC mouse model of pancreatic ductal adenocarcinoma (PDAC) in male mice to assess ghrelin action in vivo. After the onset of PDAC-induced anorexia, PDAC-carrying mice ate significantly less than control mice in response to injected ghrelin, indicating ghrelin loss of ghrelin sensitivity in cancer cachexia even before noticeable wasting has occurred. Mice did not show gross dysregulation of the endogenous ghrelin system, a finding supported by others (1)
To circumvent the observed ghrelin resistance, we used targeted chemogenetics (DREADDs) to chronically artificially activate AgRP neurons during cancer cachexia in PDAC-bearing mice (2). AgRP neuronal activation rescued both fat and skeletal muscle mass loss in male mice. We measured circulating levels of the pro-cachexia factors, activin A and B. PDAC-bearing mice with or without AgRP neuronal activation showed a similar, significant elevation in activin A and B levels, compared to non-PDAC bearing mice. Importantly, AgRP neuronal activation protected mice from the wasting effects of elevated activins, as the levels seen in this model are sufficient to drive significant wasting. Detailed analysis of feeding behaviour using BioDAQ feeding cages revealed PDAC-bearing mice with activated AgRP neurons ate significantly more during the light phase, indicating these differences are primarily driven by increased food intake, an observation supported by pair-feeding studies.
Conclusions: The observed perturbations in ghrelin signalling indicate that ghrelin-based therapy may be of limited utility in cancer cachexia. However, we demonstrate that direct activation of AgRP neurons can correct negative energy balance in cachexia, which is driven by increased feeding during the light phase. This suggests that therapies that target central (3), rather than peripheral, energy balance homeostasis mechanisms may be more effective therapeutic targets.

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W2 *(15 minutes)*

Macimorelin results from a pilot trial and future directions

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Cancer cachexia is associated with reduced body weight, appetite, and quality of life (QOL) with no approved treatments. Growth hormone secretagogues like macimorelin have potential to mitigate these effects.
This pilot study assessed the safety and efficacy of macimorelin for one week. Efficacy was defined a priori as one-week change in body weight (≥0.8 kg), plasma insulin-like growth factor (IGF)-1 (≥50 ng/mL), or QOL (≥15%). Secondary outcomes included food intake, appetite, functional performance, energy expenditure, and safety laboratory parameters. Patients with cancer cachexia were randomized to 0.5 or 1.0 mg/kg macimorelin or placebo; outcomes were assessed non-parametrically.
Participants receiving at least one of either macimorelin dose were combined (N=10; 100% male; median age = 65.50 +/- 2.12) and compared to placebo (N=5; 80% male; median age = 68.00 +/- 6.19). Efficacy criteria achieved: body weight (macimorelin N=2; placebo N=0; p=0.92); IGF-1 (macimorelin N=0; placebo N=0); QOL by Anderson Symptom Assessment Scale (macimorelin N=4; placebo N=1; p=1.00) or Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F; macimorelin N=3; placebo N=0; p=0.50). No related serious or non-serious adverse events were reported. In macimorelin recipients, change in FACIT-F was directly associated with change in body weight (r=0.92, p=0.001), IGF-1 (r=0.80, p=0.01), and caloric intake (r=0.83, p=0.005), and inversely associated with change in energy expenditure (r=-0.67, p=0.05).
Daily oral macimorelin for one week was safe and numerically improved body weight and QOL in patients with cancer cachexia compared to placebo. Longer-term administration should be evaluated for mitigation of cancer-induced reductions in body weight, appetite, and QOL in larger studies. These results and future directions will be discussed during this presentation.

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Herodes M, Anderson LJ, Shober S, Schur EA, Graf SA, Ammer N, Salas R, Marcelli M, Garcia JM. Pilot clinical trial of macimorelin to assess safety and efficacy in patients with cancer cachexia. J Cachexia Sarcopenia Muscle. 2023 Apr;14(2):835-846. doi: 10.1002/jcsm.13191. Epub 2023 Mar 1. PubMed PMID: 36860137; PubMed Central PMCID: PMC10067502.

W3 *(15 minutes)*

Anamorelin in Japan

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Anamorelin was approved for manufacturing and marketing in Japan on January 22, 2021 for the treatment of cancer cachexia in non-small cell lung cancer, gastric cancer, pancreatic cancer, and colorectal cancer[1]. Japanese clinical practice guidelines for pancreatic cancer and lung cancer recommend anamorelin for cancer cachexia. Post-marketing surveillance showed that the increase in body weight from baseline to weeks 3, 12, 24, and 52 was 0.64 kg, 1.19 kg, 1.40 kg, and 1.42 kg, respectively[2]. Mean changes in the Functional Assessment of Anorexia/Cachexia Treatment (FAACT) 5-item Anorexia Symptom Scale total score from baseline to weeks 3, 12, 24, and 52 were 3.2, 4.8, 5.2, and 5.3, respectively[2]. The incidences of hyperglycemia, hepatic impairment, conduction disturbances, and related adverse events were 4.8%, 1.2%, and 1.1%, respectively[2]. Fatal arrhythmias should be closely monitored, even with the first dose.
A recent study showed that a combination of anamorelin and rehabilitation improved not only body weight, skeletal muscle mass, and FAACT score, but also non-dominant handgrip strength after 12 weeks in patients with cancer cachexia. So, anamorelin combined with diet, physical activity, and exercise may be more useful than anamorelin alone in the treatment of cancer cachexia.
In Japan, anamorelin is often not used in patients with cancer cachexia because they are not diagnosed with cachexia. The idea that the terminal stage of cancer equals cachexia is still strong in Japan. Therefore, the Asian Working Group for Cachexia (AWGC) developed a consensus paper on the definition, diagnostic criteria, and outcomes of cachexia in 2023. In 2024, we changed the name of the former association to the Japanese Association for Cachexia and Sarcopenia (JACS) to establish concepts, diagnostic criteria, and treatment strategies for cachexia and sarcopenia in Japan and Asia. Anamorelin should be used appropriately in patients with cancer cachexia for whom it is indicated in Japan.
Reference
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W4 *(15 minutes)*

Biology of PEP-64 – a long-acting stabilized ghrelin analogue

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The endogenous peptide ghrelin has emerged as a therapeutic target for cancer cachexia primarily due to its influence on energy balance. This is manifested by increased growth hormone secretion[1], elevated appetite[1,2], and enhanced lipogenesis[3]. Encouragingly, clinical trials involving cancer patients treated with native human ghrelin have shown promising improvements in both food intake and overall quality of life. However, the pharmacological utility of ghrelin is limited by its short half-life. This limitation underscores the necessity of ghrelin analogues with improved pharmacokinetics.

Here, we demonstrate the feasibility and superiority of an extended half-life peptide approach[4] for treating cancer cachexia by presenting the novel long-acting ghrelin analogue PEP-064. We show PEP-064 to be efficacious in increasing both body weight and food intake in mice; demonstrate PEP-064's ability to regulate hypothalamic neuronal activity and influence peripheral growth hormone (GH) secretion; and show sub-chronic treatment with the PEP-064 had a superior effect on ameliorating cancer cachexia in the Lewis Lung Carcinoma (LLC) mouse model of cancer cachexia compared to the therapeutic candidate anamorelin.

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2. Chen SR, Chen H, Zhou JJ, Pradhan G, Sun Y, Pan HL *et al. J Neurochem* 2017;**142**:512–520.
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4. Fosgerau K, Hoffmann T. *Drug Discov Today* 2015;**20**:122–8.

POSTER SESSIONS

Poster Session 1.1 **Cachexia – mechanisms, animal models I (posters 1-01 to 1-09 and 1-12)**
Chairs: Denis Guttridge, Sarah Lockie

1-01
RNA-sequencing and global proteomics of diaphragm weakness in female rats after myocardial infarction
***Dryden R. Baumfalk*[1], Jose C. Martinez[2], Brian McDonagh[2], Leonardo F. Ferreira[1]**
[1]Department of Orthopaedic Surgery, Cardiovascular Research Center, Duke University School of Medicine; [2]Department of Physiology, National University of Ireland, Galway

1-02
Untargeted metabolomic profiling of dogs with heart failure shows metabolic differences associated with cardiac cachexia
Lisa M. Freeman, John E. Rush, Emily T. Karlin
Cummings School of Veterinary Medicine, Tufts University, North Grafton, MA, USA

1-03
Effects of dietary linoleic acid on insulin resistance and skeletal muscle atrophy in a mouse model of cancer cachexia
***Avonti Basak Tukun*[1]; Dakota Dustin[1]; Kate Marris[1]; Ali Kalhori[1]; Rachel M Cole[1]; Martha A. Belury[1]**
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1-04
The effects of cardiac cachexia on the myogenic capacity of satellite cells
Jack Campbell, Ben Witmer, Julio Cisneros, Risha Gupta, Stephanie Tobin
Trent University, Toronto, Canada

1-05
Biomarkers and Mechanisms Related to Cancer-Induced Cardiac Cachexia
***Lisa Bagnall*[1], Oliver Grundmann[2], Marilyn G. Teolis[3], Saun-Joo L. Yoon[4]**
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1-06
Sex-dependent effects of monocrotaline on cachexia
Jack Cambell*[1,2], Abbey Politeski[1], Alex Rico[1], Julio G Cisneros Medrano[1], Ben Witmer[1], Risha Gupta[1], Aaron Shafer[2], Holly E. Bates[1,2], Kirk Hillsley[1,2], *Stephanie W. Tobin*[1,2]
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1-07
Lung cancer has sex dependent effects on the musculoskeletal system
Cecilia H.A. Gouveia*[1], Anika Shimonty,[2] Joshua R Huot[2,3,4,5], Gang Peng[2], Lynda F Bonewald[2,3,5], Fabrizio Pin[2,3,5]
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1-08

The IL-8/CXCR2 pathway as a potential therapeutic target in pancreatic cancer cachexia and related muscle wasting

***Yu-Chun Lin*[1], Ya-Chin Hou[1, 2], Hao-Chen Wang[1, 3, 4], Hao-Yun Chen[1], and Yan-Shen, Shan[1, 2, 4]**

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1-09

Pancreatic Cancer Induces Population-Specific, Heterogeneous Activation of Cachexia Genes and Reverts Differentiation in Skeletal Muscle Myocytes

***Brittany R. Counts*[*1], Sephora Jean[1], Omnia Gaafer[1], Sara Ota[1], Sha Cao[2], Hyun C. Roh[3], Iishaan Inabathini[1], Michael C. Ostrowski[4], Denis C. Guttridge[5], Leonidas G. Koniaris[6], Teresa A. Zimmers[1,7]**

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1-12

Liver metastases accelerate muscle wasting in lung cancer cachexia

***Anna M. Miller*[1,2], Fabrizio Pin[2,3,4], *Joshua R. Huot*[2,3,4,5]**

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Poster session 1.2 **Cancer Cachexia I** (posters 3-01 to 3-12)
Chairs: Andrea Bonetto, Tobias Jannowitz

3-01

The art of war: blocking the secretion of pro-cachectic factors from cachexia inducing cancer cells

Sai V. Chitti, Akbar L Marzan, Suresh Mathivanan

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3-02

Reassessing the role of progenitor cells in tumor-associated muscle wasting

***Spencer G. Miller*[1], Benjamin R. Pryce[1], David J. Wang[1], Denis C. Guttridge[1,2]**

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3-03

Improved immune response and energy metabolism in the C26 tumor-bearing mice exposed to IL4

***Giacomo Rubini*[1], Laia Carballo-Botinas[1], Simona Rolla[1], Simone Reano[2], Nicoletta Filigheddu[2], Andrea Bonetto[3], Fabio Penna[1], Paola Costelli[1]**

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3-04

Temporal examination identifies features in cachexia etiology with sex-based heterogeneity

Chris Karagiannis, Rachel E Thomson, Craig A Goodman, Paul Gregorevic

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3-05

The dynamic role of cardiac-infiltrating neutrophils in pancreatic cancer-induced cardiac dysfunction

Parham Diba[1], Abigail C. Buenafe[2], Peter R. Levasseur[3], Paige Arneson-Wissink[3], Xinxia Zhu[3], Heike Mendez[3], Daniel L. Marks[4], Aaron J. Grossberg[3,5,6]

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3-06

Myofiber-specific FoxP1 deletion protects against pancreatic cancer-induced muscle atrophy and weakness

Martin M. Schonk[1,2], Daria Neyroud[1,2], Sarah M. Judge[1,2], Andrew R. Judge[1,2]

UF Myology Institute[1] and Department of Physical Therapy[2], University of Florida, Gainesville, FL, USA

3-07

A dual target PERPetrator in pancreatic cancer and cachexia

Aneesha Dasgupta[1,2], Rebecca E. Schmitt[1], Mark I. Zoberi[1,2], Martin Fernandez-Zapico[3], Gina L. Razidlo[3], Jason D. Doles[1,2]

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3-08

Interleukin 6 induces complex and dose-dependent response to pancreatic cancer

Paige C. Arneson-Wissink[1], Alexandra Q. Bartlett[2], Heike Mendez[1], Xinxia Zhu[1], Abigail O'Niel[3], Jessica Dickie[1], Peter R. Levasseur[1], Matthew McWhorter[2], Alexandra Pederson[3], Parham Diba[1], Gregory D. Scott[4], Jacob Raber[3,5,6], Robert Eil[2], Aaron J. Grossberg[1,5,7]

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3-09

Tumor-derived CTGF drives PDAC-induced cancer cachexia

Brittney Poole[1], Chandler S Callaway[1], Andrew C D'Lugos[1], Orlando Laitano[2], Miles E Cameron[1], Jianmin Zuo[3], Kim Williams[3], David Olsen[3], Kenneth E Lipson[3], Andrew R Judge[1], Sarah M Judge[1]*

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3-10

Therapeutic targeting of mitochondrial permeability transition in a mouse model of pancreatic cancer cachexia

Maya Semel, Cole Lukasiewicz, Abbey Mannings, Rashad Austin, Russell T. Hepple

University of Florida, USA

3-11
Flux studies of energy metabolism in cancer cachexia
Young-Yon Kwon, Yanshan Liang, Guangru Jiang, Juliya Hsiang, and Sheng Hui
Department of Molecular Metabolism, Harvard T.H. Chan School of Public Health, Boston, MA, USA

3-12
Hsp70/90-carrying EVs potentiate muscle wasting during chemotherapy-induced cancer cachexia
Edson Alves de Lima Junior[1], Hongyu Wu[1], Song Gao[1], Omar Yousif[2], Zicheng Zhang[1], Guohua Zhang[1], Rene Flores[1], George Gerald Rodney Jr[2], Yi-Ping Li[1]
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Poster session 1.3 **Diagnosis of Cachexia** (posters 4-01 to 4-11)
Chairs: Yi-Ping Li, Ishan Roy

4-01
A Comparison of Established Diagnostic Criteria for Cachexia and Their Impact on Prognostication in Patients with Oesophagogastric Cancer
Leo R. Brown [1], Maria Soupashi [1], Michael S. Yule[1,2,3], Cathleen M. Grossart [1], Donald C. McMillan [4], Barry J.A. Laird [2,3], Stephen J. Wigmore[1], Richard J.E. Skipworth[1]
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4-02
An exploration of the GLIM inflammation criteria to predict survival in patients with advanced cancer
Chattarin Pumtako[1] *, Ross D Dolan[1], Marie Fallon[2], Louise E Daly[3], Claribel Pl Simmons[3], Aoife M Ryan[3], Josh McGovern[1], Derek G Power[3], Barry J Laird[2], Donald C McMillan[1]
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4-03
Prevalence and prognostic value of GLIM phenotypic cachexia criteria in patients with cancer: Systematic review and meta-analysis
Chattarin Pumtako, Ross D Dolan, Donald C McMillan
Academic Unit of Surgery, School of Medicine, College of Medical Veterinary & Life Sciences, University of Glasgow, Glasgow, UK

4-04
Prevalence and Prognostic Value of the Global Leadership Initiative on Malnutrition (GLIM) Etiologic Cachexia Criteria in Patients with Cancer: Systematic Review and Meta-Analysis.
Chattarin Pumtako, Ross D Dolan, Joshua Thompson, Donald C McMillan
Academic Unit of Surgery, School of Medicine, College of Medical Veterinary & Life Sciences, University of Glasgow, Glasgow, UK

4-05
Impact of Modified GLIM Criteria on Mortality Outcomes in Cancer Patients Receiving Palliative Care
Naoharu Mori[* 1, 2], Keisuke Maeda[3], Tatsuma Sakaguchi[2]
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4-06

Cross-Cultural Adaptation and Application of the miniCASCO Tool for Detecting Muscle Weakness in Cancer Patients

***Orellana López, Cristian*[1], *Manríquez, Claudia*[2], *Ortega, Francisco*[3], *Busquets, Silvia*[4], *Argiles, Josep M*[4], *Oyarzún Opazo, Henry*[5], *Águila Vera, Javier*[5], *Valladares, Moira*[5]**

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4-07

Prevalence and prognosis of cachexia in patients with non-sarcopenic dysphagia: a retrospective cohort study

Hidetaka Wakabayashi

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4-08

Towards a fully automatic workflow for resolving the dynamics of muscle wasting associated with lung cancer cachexia using cone beam computed tomography

***Lars H.B.A. Daenen*[1,2], *Wouter R.P.H. van de Worp*[3], *Behzad Rezaeifar*[1], *Joël de Bruijn*[4], *Peiyu Qiu*[3], *Justine M. Webster*[3], *Dirk De Ruysscher*[1], *Ramon C.J. Langen*[3], *Cecile J.A. Wolfs*[1*], *Frank Verhaegen*[1,4*]**

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4-09

Ubiquitous and Unseen: Cancer Cachexia at the End of Life

***Michael S. Yule*[1,2], *Flora Flinn*[3], *Iain J. Gallagher*[4], *Elizabeth Mitchell*[3], *Jonathan Grey*[5], *Leo R. Brown*[6], *Ratish Balagangatharan*[2], *Duncan Brown*[1], *Barry J. A. Laird*[1,2] & *Richard J. E. Skipworth*[6]**

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4-10

Fully automated CT-segmented fat density may better identify early signatures of wasting in pancreatic cancer.

***Adam J. Kuchnia*[1], *Jevin Lortie*[1], *Rachel Fenske*[1], *Ryan Zea*[2], *John Garrett*[2,3], *Perry J. Pickhardt*[2]**

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4-11

Characterization of muscle in patients with head and neck cancer cachexia

***Leah J. Novinger*[1], *Patrick Livingston*[1], *Alexander J. Jones*[2], *Fabrizio Pin*[3], *Michael G. Moore*[3] , *Andrea Bonetto*[1]**

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Poster session 1.4 **Muscle Wasting & Sarcopenia I** (posters 6-01 to 6-08)
Chairs: Peggy Cawthon, Bill Evans

6-01
chemR23 as a new therapeutic target for uraemic sarcopenia?
Luke Baker[1], Thomas Wilkinson[2], Matthew Graham-Brown[3], Daniel March[3], James Burton[3], Robert Ashford[4], Joao Viana[5], Alice Smith[6], Emma Watson[3]
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6-02
Astaxanthin Mtigates Doxorubicin-Induced Muscle Atrophy by Inhibiting NF-κB-Mediated TRPC6 Upregulation
Ji-Hee Kim[1], Seon-Ho Eom[2], SangMok Jung [3], Chul-Hyun Kim[2]
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6-03
Ferroptosis in facioscapulohumeral muscular dystrophy
Yi-Wen Chen[1,2], Lulya Okubamariam[1], Adam J Bittel[1]
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6-04
The effects of glucagon-like peptide-1 receptor agonists on skeletal muscle mitochondrial function: a systematic review
Victoria J Old[1], Melanie J Davies[2], Dimitris Papamargaritis[2], Pratik Choudhary[2], Emma Watson[1]
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6-05
Mitochondrial permeability transition causes skeletal muscle alterations common in Sarcopenia Cachexia and Wastind Disorders
Russell T. Hepple, Sarah Skinner, Michael Cohen, Dennis Wolan, Maya Semel, Cole Lukasiewicz
University of Florida, USA

6-06
Effects of iron deficiency on bone health in patients with chronic heart failure:
Results from the Studies Investigating Co-morbidities Aggravating Heart Failure (SICA-HF)
Ryosuke Sato[1], Tania Garfias-Veitl[1,2], Mirela Vatic[1,2], Guglielmo Fibbi[1,2], Wolfram Doehner[3,4,5], Stefan D. Anker[3,5,6], Stephan von Haehling[1,2]
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6-07

AMPK in skeletal muscle as a therapeutic target for sarcopenic obesity

Haiming L. Kerr, Kora Krumm, Nornubari Bagia, Ross Burnside, Artur Rybachok, Siyi Jiang, Amanda Chen, Elizabeth Dacek, Lucas Caeiro, Jessica Li, Morgan Sydor, Jose M. Garcia

Geriatric Research, Education and Clinical Center, Veterans Affairs Puget Sound Health Care System, Seattle, USA; Gerontology and Geriatric Medicine, University of Washington Department of Medicine, Seattle, USA

6-08

Endurance exercise accelerates disease progression in desminopathy

Henning T. Langer[1,3], Alec M. Avey[2], Hermann Zbinden-Foncea[4], Keith Baar[2,3], Agata A. Mossakowski[1,2]

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Poster session 1.5 **Nutrition & Appetite** (posters 7-01 to 7-07)
Chairs: Adrian Slee, Paula Ravasco

7-01

Practical cancer nutrition, from guidelines to clinical practice: the mypath® project

Barry Laird[1,2,3], Lisa Heide Koteng[1], Amaia Urrizola[1], Kristin Solheim Hustad[1], Judith de Vos-Geelen[4], Stein Kaasa[1]

On behalf of the MyPath consortium: Jann Arends[5], Sandra Beijer[6], Asta Bye[7], Augusto Caraceni[8], Olav Dajani[1], Luc Deliens[9], Marie Fallon [1,2], Marianne Jensen Hjermstad[1], Maxime Kohlen[6], Geana Kurita[10], Tonje Lundeby[1], Nicoleta Mitrea[11], Cathy Payne[12], Susana Roselló-Keränen[13], Galina Velikova[14], Nicole Warmbrodt[15]

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7-02

Edentulism as a Risk Factor for Sarcopenia in Older Chileans. A Longitudinal Study

Cecilia Albala, Rodrigo Saguez, Carlos Marquez, Gerardo Fasce, Felipe Salech, Moises Sandoval

Institute of Nutrition and Food Technology, Universidad de Chile, Chile

7-03

Differences on the prevalence of anorexia and clinical manifestations in patients with solid and hematological tumors who attend a tertiary care hospital from 2023 to 2024

Osorio Ramírez Arantza Andrea, Milke García María del Pilar, Razcón Echeagaray Andrea, Castañeda Moreno Astrid Jazmín, Bastida Pineda Mayra Judith

Department of Hemato Oncology. National Institute of Medical Sciences and Nutrition Salvador Zubirán, Mexico City, Mexico

7-04
Food acceptance in hospitalized cancer patients
Natalia Rodríguez Díaz, Mariana P Milke García, Andrea Hernández Vaillard, Cristina de Silva Vázquez, Fatima Reynoso Castro, Andrea Arantza Osorio Ramírez, Laura Sofia Juárez García, Carlos Nava Muñóz, Paola Barrios Trejo
Department of Hemato Oncology. National Institute of Medical Sciences and Nutrition Salvador Zubiran (INCMNSZ), Mexico City, Mexico

7-05
Dietary assessment of hospitalized cancer patients
Andrea Hernández Vaillard, Mariana Milke García, Natalia Rodríguez Díaz, Cristina de Silva Vázquez, Fatima Reynoso Castro, Arantza Andrea Osorio Ramírez, Laura Sofia Juárez García , Carlos Nava Muñoz
Department of Hemato Oncology, National Institute of Medical Sciences and Nutrition Salvador Zubirán, Mexico City, Mexico

7-06
Effect of caffeine consumption in patients undergoing immunotherapy for melanoma and lung cancer
Alice Fonseca Marques[1], Edgar Pratas[1], Tiago M Alfaro[2], Paula Ravasco[3]
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7-07
Malnutrition assessment in palliative cancer patients
Danara Krug, Luisa V. Ramer, Jan Porthun, Markus S. Anker
Deutsches Herzzentrum Charité, Campus Benjamin Franklin, Berlin, Germany

Poster session 1.6 **Physical Activity & Training** (posters 8-01 to 8-06)
Chairs: Volker Adams, Julian Alcazar

8-01
Co-designing the implementation process of an exercise intervention as part of a multimodal intervention for patients with renal cachexia
Carolyn Blair*[1], Clare McKeaveney[1], Adrian Slee[2], Ian Swaine[3], Joanne Reid[1]
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8-02
Endurance training did not mitigate transcriptional changes in muscle apelin induced by systemic inflammation in rats with cardiac cachexia
Daniela Sayuri Inoue[1], Quinten Pigg[1], Dillon Harris[1], & Mariana Janini Gomes[1]
[1]Department of Kinesiology and Sport Management, Texas A&M University, College Station, USA

8-03
Impact of aerobic training on inflammatory and autophagic markers in rats with heart failure
Dillon Harris, Quinten Pigg, Daniela Sayuri Inoue, Mariana Janini Gomes[1]
Department of Kinesiology and Sport Management, Texas A&M University, College Station, TX, USA

8-04

Effects of wearable electrical muscle stimulation on lower muscles during walking-workout

***Seon-Ho Eom*[1], *Kiwan Kim*[2], *Young Koo Lee*[3], *Young-jin Jo*[1], *Youngil Lee*[4], *Chul-Hyun Kim*[1]¶**

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8-06

Intermittent hypoxic-hyperoxic training during inpatient rehabilitation improves exercise capacity and functional outcome in patients with long COVID: Results of a controlled clinical pilot trial

***Wolfram Doehner*[1,2,3], *Azadeh Shafieesabet*[3], *Banafsheh Alimi*[4], *Jasmin Muhar*[4], *Antje Meyer*[1,3], *Jochen Springer*[1], *Christop Altmann*[5], *Per Otto Schueller*[4]**

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Poster session 2.1 **Cachexia – mechanisms, animal models II**
(posters 1-10 to 1-11 and 1-13 to 1-22)
Chairs: Denis Guttridge, Sarah Lockie

1-10
Optimization of a mouse model of pancreatic cancer to simulate the human phenotypes of metastasis and cachexia
Victoria Spadafora[1], Benjamin R. Pryce[1], Alexander Oles[1], Erin E. Talbert[2], Martin Romeo[3], Silvia Vaena[3], Stefano Berto[3,4], Michael C. Ostrowski[3,5], David J. Wang[1], and Denis C. Guttridge[1,3]
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1-11
Differential impact of chemotherapy and cachexia in a preclinical colorectal cancer model: a comparative analysis of 5-FU, paclitaxel, and cisplatin by biological sex
Ana Regina Cabrera[1], Eleanor Schrems[2], Ruqaiza Muhyudin[1], Francielly Morena da Silva[1], Stavroula Tsitkanou[1], Ronald Jones III[3], Kaitlyn Parker[1], Morghan Relich[1], Tyrone A. Washington[2], Nicholas P. Greene[1]
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1-13
Cachectic tumours promote gut alterations through JAK/STAT pathway in *Drosophila* larvae
Jennifer Falconi, Miriam Rodríguez-Vázquez, Charles Géminard, Alexandre Djiane
Institut de Recherche en Cancérologie de Montpellier, Inserm, Univ Montpellier, ICM, Montpellier, France

1-14
The role of glucocorticoid receptors in regulating skeletal muscle regeneration in cancer cachexia
Shaden Alharbi[1,3], Rashida Rajgara[2], Alex Brown [1], Nadine Wiper Bergeron[2]
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1-15
Effect of age on cancer cachexia pathogenesis in male and female mice
Rebecca Rodriguez, Allen Dao, Jaden M. Wells, Marc Magana, Carla M.C. Nascimento, Cory M. Dungan, Michael P. Wiggs, Michelle L. Law
Robbins College of Health and Human Sciences, Baylor University, Waco, Texas, USA

1-16
Restoring neuromuscular function in murine cancer survivors
Debra Smith[1], Fabrizio Pin[1,2,3], Joshua R. Huot[1,2,3,4]
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1-17
Melusin modulation of AKT-GSK3β signalling mitigates cachexia-induced muscle atrophy
Davide Acquarone, Matteo Sorge, Elisabth Wyart, Paolo E. Porporato, Mara Brancaccio
Department of Molecular Biotechnology and Health Science, Univ. of Turin, Italy

1-18
Development of home-cage and machine learning based physical function measure for pre-clinical cachexia modeling
Adolphus Adams[1], Ruohui Chen[2], Ioanna Karras[1] , Amber Willbanks[1], Addison Barber[1], Ishan Roy[1]
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1-19
Altered autophagy and oxidative metabolism in rats with heart failure-associated skeletal muscle atrophy
Quinten Pigg, Dillon Harris, Daniela Sayuri Inoue, Mariana Janini Gomes
Department of Kinesiology and Sport Management, Texas A&M University, College Station TX, USA

1-20
Impact of neuroinflammation on cachectic phenotypes
Miriam Ferrer[1], Sarah Starosta[2], Xiaoyue Aelita Zhu[2,4], Xiang Zhao[1], Marco Pignatelli[5], Pavel Osten[1], Adam Kepecs[2,3], Tobias Janowitz[1]
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1-21
Naringenin to improve functional and behavioral outcomes by attenuating neuro-inflammation in mice with cancer cachexia.
Dakota Dustin[1]; Lauren Otto[2]; Avonti Basak Tukun[1]; Kate Marris[1]; Ali Kalhori[1] Leah Pyter[2]; Yael Vodovotz[1]; Noah Weisleder[3]; Miguel A. Lopez Perez[3]; Alexis Tucker[3]; Martha A. Belury[1]
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1-22
Pilot study of urine titin N-fragment in dogs with naturally-occurring cardiac cachexia
Lisa M. Freeman, John E. Rush, Emily T. Karlin
Cummings School of Veterinary Medicine, Tufts University, North Grafton, MA, USA

Poster session 2.2 **Cancer Cachexia II** (posters 3-34 to 3-42)
Chairs: Joanne Reid, Florian Strasser

3-34
Obesity accelerates muscle wasting in PDAC-induced cancer cachexia
Yabing Wang, Emily Kalmanek, Ashley Freeman, Kelsey Steckly, Carlos H.F. Chan, Erin E. Talbert
University of Iowa, Iowa City, IA, USA

3-35

A clinical model based on skeletal muscle radiation attenuation associated with efficacy of chemotherapy plus PD-1 antibody in gastric cancer

Chenfei Zhou[1,2#], Yan Sun[2#], Tao Liu[3], David P. J. van Dijk[2], Wenqi Xi[1], Jinling Jiang[1], Liting Guo[1], Feng Qi[1], Xuekun Zhang[4], Mengfan Jia[3], Jun Ji[5], Zhenggang Zhu[1,6], Sander S. Rensen[2], Steven W. M. Olde Damink[2*], Jun Zhang[1*]

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* These authors contributed equally to this work.

3-36

Fluid accumulation in palliative cancer patients with and without cacexia

Luisa V. Ramer, Danara Krug, Jan Porthun, Markus S. Anker

Deutsches Herzzentrum Charité, Campus Benjamin Franklin, Berlin, Germany

3-37

Reducing outcome variability in longitudinal models of preclinical cancer cachexia

Amber Willbanks, Ioanna Karras, Adolphus Adams, Richard Lieber, Ishan Roy

Shirley Ryan AbilityLab: Chicago, Illinois, USA

3-38

Anorexia accounts for major body weight loss but has no impact on muscle function in a colorectal cancer cachexia model

Yanshan Liang, Young-Yon Kwon, Sheng Hui

Department of Molecular Metabolism, Harvard T.H. Chan School of Public Health, Boston, MA, USA

3-39

Improving Patient and Caregiver Knowledge & Communication about Cancer Cachexia

Abigail Newell, Sabrina Pink, Maria Gonzalo, Rachel Saks, Marcy Sansbury, M. Claire Saxton

Cancer Support Community, Washington, DC, USA

3-40

One cycle of anthracycline chemotherapy reduces heart function and is inversely associated with higher blood oleic acid in women with breast cancer: a feasibility study

Kate Marris[1], Rachel M Cole[1], Daniel Addison[2], Patrick Ruz[2], Genevieve Sparagna[3], Ai Ni[4], Martha A Belury[1]

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3-41

Dissecting the GLIM Criteria in Advanced Cancer: Reduced Intake vs. Inflammation

Michael S. Yule[1,2], Andressa M. Machado[3], Leo R. Brown[4], Bruna M. M. Rocha[3], Amy McLuskie[2], Paula P. Lajolo[5], Jann Arends[6], Carlos E. Paiva[7], Duncan Brown[1], Iain Phillips[2], Donald C. McMillan[8], Yara C.P. Maia[3*], Richard J.E. Skipworth[4*] & Barry J.A. Laird[1,2*]

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3-42

Characterization of a cachectic subpopulation of skeletal muscle satellite cells in a Lewis-lung Carcinoma-induced model of murine cancer cachexia.

Alex Brown[1], Nicholás Collao[2], Michael De Lisio[2,3], Nadine Wiper-Bergeron[2*]

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Poster session 2.3 **Diagnosis of Sarcopenia I** (posters 5-05 to 5-12)
Chairs: Richard Skipworth, Faisal Beg

5-05

Associations of low lean mass by EWGSOP2, FNIH and EASO/ESPEN and MRI muscle composition with all-cause mortality across BMI classes

Jennifer Linge[1,2], Olof Dahlqvist Leinhard[1,2,3]

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5-06

Building Capacity in Computed Tomography (CT)-based body composition analysis: Development and implementation of an online education program

Vickie Baracos[1], Lisa Martin[2,] Merran Findlay[3-6], Abha Dunichand-Hoedl[1], Lauren Hanna[7], Judith D Bauer[7]

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5-07

Bioimpedance phase angle and thigh muscular assessment are promising approaches to assessing 30-day mortality risk after hip fracture in older people.

Paula Azevedo*[1], Thais Picoli[1], Victoria Soares[1], Jessica Ferreira[1], David Gumieiro[2], Filipe Leal-Pereira[1], Juli Souza[1], David Pereira[1], Sergio Paiva[1] e Marcos Minicucci[1]

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5-08

Defining sarcopenia: New MRI cut-off values for low muscle mass

***Jona Van den Broeck*[1], *Steven Heymsfield*[2], *Erik Cattrysse*[1], *Hubert Raeymaekers*[3], *Aldo Scafoglieri*[1]**

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5-09

Exploring the link between sarcopenic obesity and hepatic steatosis in patients with NAFLD

***Ali Kalhori*[1], *Rachel M. Cole*[1], *Avonti Basak Tukun*[1], *Dakota Dustin*[1], *Kate Marris*[1], *Stephan Zarich*[1], *Na Li*[2], *Arunak Kolipaka*[3], *Ai Ni*[4], *Martha A. Belury*[1]**

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5-10

Comparing predictive ability of sarcopenia definitions using muscle ultrasound for clinical outcomes among older inpatients

***Nicola Merz*[1], *Rahel Zehnder*[3], *Lisa Meyer*[2], *Andreas Limacher*[4], *Anna K Eggimann*[3]**

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5-11

Predictors and clinical correlates of Frailty in heart failure

***Tania Garfias-Veitl*[1,2], *Nozima Khaytmatova*[1], *Guglielmo Fibbi*[1], *Ryosuke Sato*[1,2], *Mirela Vatic*[1,2], *Wolfram Doehner*[3,4,5], *Stefan D. Anker*[3,5,6], *Stephan von Haehling*[1,2]**

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5-12

Assessing the validity of serological biomarkers in estimating muscle mass: a retrospective cross-sectional NHANES analysis

Christian Arias*, *Michael Owen-Michaane

Columbia University Institute of Human Nutrition, Columbia University Irving Medical Center, USA

Poster session 2.4 **Muscle Wasting & Sacopenia II** (posters 6-16 to 6-24)
Chairs: Peggy Cawthon, Bill Evans

6-16
Radiation reduces fibro/adipogenic progenitor-derived follistatin-like 1 to impair myoblast differentiation
Cooper Brabrook[1*], Nicolas Collao[1*], Laura Meseiller[2], Isabel Gonzalez[2], Paul Nguyen[3], and Michael De Lisio[1,2,4]
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6-17
Impact of *Ilk1* and *Fermt2* AAV-mediated knockdown on sepsis-induced muscle weakness
Alexander Pacolet[1], Sarah Vander Perre[1], Inge Derese[1], Chris Van den Haute[2,4], Sarah Derde[1], Rik Gijsbers[3,4] & Lies Langouche[1]
[1]Laboratory of Intensive Care Medicine, Department of Cellular and Molecular Medicine, KU Leuven, Leuven, Belgium; [2]Research Group for Neurobiology and Gene Therapy, Department of Neurosciences, KU Leuven, Leuven, Belgium; [3]Molecular Virology and Gene Therapy, Department of Pharmaceutical and Pharmacological Sciences, KU Leuven, Leuven, Belgium; [4]Leuven Viral Vector Core, Biomedical Sciences, KU Leuven, Leuven, Belgium

6-18
The co-existence of sarcopenia and cognitive impairment: prevalence and the association with healthy aging in the kora-age study
Marie-Theres Huemer[1], Barbara Thorand[1, 2], Eva Grill[2, 3], Lars Schwettmann[4, 5], Annette Peters[1, 2]
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6-19
A novel role for extracellular matrix dysregulation in the development of muscle wasting in individuals with chronic kidney disease
Luke Baker[1], Robert Ashford[2], Matthew Graham-Brown[3], Alice Smith[4], Emma Watson[2]
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6-20
BIO101, a drug candidate to counter-act age-related sarcopenia: towards Phase 3 program
Waly Dioh[1], Cendrine Tourette[1], Roger A Fielding[2], Jean Mariani[1,3], Rob Van Maanen[1], Stanislas Veillet[1]
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6-21

Pathological changes in skeletal muscle throughout colon cancer trajectory-multi center study

Alaa A. Al-Masud[1] **, Nasser A. Alsanea**[1,6], **Vera Mazurak**[2] **, Vickie Baracos**[2] **, Raha Alahmadi**[3] **, Shaima A. Alothman**[4], **Hanan A. Henidi**[5], **Saeed Alshlwi**[6] **, Dalal Alshamari**[7] **, Meshal Alsharafa**[1]

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6-22

Loss of skeletal muscle mass is associated with poor shorter survival and immunosuppressive tumor microenvironment in advanced lung cancer

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6-23

Impact of miRs modulation and inflammatory response on body composition changes in patients with gastrointestinal cancer

***Federica Tambaro*[1], Giovanni Imbimbo[1], Maria Ida Amabile[2], Giulia Lauteri[3], Veronica Rizzo[4], Cesarina Ramaccini[1], Giuseppe Nigri[3], Alessio Molfino[1], Maurizio Muscaritoli[1]**

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6-24

Different miRs patterns associate with changes in body in composition in patients with systemic sclerosis

***Federica Tambaro*[1], Edoardo Rosato[1], Antonietta Gigante[1], Maria Ludovica Gasperini Zacco[2], Roberta Belli[3], Cesarina Ramaccini[1], Maurizio Muscaritoli[1]**

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Poster session 2.5 **Therapeutic Development (clinical)** (posters 9-01 to 9-11)
Chairs: Tobias Winkler, Nicholas Brisson

9-01

Neuromuscular electrical stimulation (NMES) for sarcopenia in people with long-term conditions: a protocol for a systematic review and meta-analysis

***Siyue Kong*[1], Emma Watson[1], Daniel March[1], Gordon McGregor[2], James Burton[1]**

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9-02

A synbiotic improves muscle strength, mass and performance in older Australians: preliminary results from a randomized, controlled trial

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9-03

Can astaxanthin supplementation improve human body composition and muscle function

Taesoo Kim[1], Seon-Ho Eom[2], Chul-Hyun Kim[2], Sangmok Jung[3], Yong Hun Jo[1], Sungsin Jo[1], Yong Seok Lee[1], Young C. Jang[4], Hyeongseok Oh[2], Hyunwoung Shin[1¶]

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9-05

Combined GDF8 and activin A blockade in healthy volunteers: safety, efficacy, and pharmacokinetics

Dinko Gonzalez Trotter[1], Stephen Donahue[1*], Chris Wynne[2], Shazia Ali[1], Prodromos Parasoglou[1], Kusha Mohammadi[1], Jason Mastaitis[1], Robert Pordy[1], Gary A. Herman[1]

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*Former employee

9-06

CT-Derived Psoas Muscle Measurements are Associated with Increased Mortality in Venovenous Extracorporeal Membrane Oxygenation

William Miller[1], Athena Brooks[1], Bridget Dillon[1], Heidi Fazio, Melissa Brunsvold[3], Levi Teigen[4]

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9-08

menac - a randomised, open-label trial of a multimodal intervention (exercise, nutrition and anti-inflammatory medication) plus standard care versus standard care alone to attenuate cachexia in patients with incurable lung or pancreatic cancer undergoing systemic anti-cancer therapy

clinicaltrials.gov id: nct02330926

Barry J A Laird[1], Tora S. Solheim[2], Trude R. Balstad[3], Marie Fallon[1] and Stein Kaasa[4]
(on behalf of the MENAC trial group: Guro Birgitte Stene[3], Vickie Baracos[5], Asta Bye[6], Olav Dajani[4] Andrew Eugene Hendifar[7], Florian Strasser[8], Martin Robert Chasen[9], Matthew Maddocks[10], Melanie R. Simpson[11], Eva Skovlund[11], Gareth Owen Griffiths[12], Jonathan Hicks[13], Janet Shirley Graham[13], Fiona Kyle[14], Joanna Bowden[15])

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9-09

Efficacy and safety of anamorelin in pancreatic cancer patients with cachexia: a prospective observational study

***Ryosuke Matsukane*[1], *Haruna Minami*[1], *Nao Fujimori*[2], *Keijiro Ueda*[2], *Takanori Tanaka*[3], *Masako Hashimoto*[4], *Saki Kuwahara*[4], *Satoshi Hirai*[1], *Shigeru Ishida*[1] *Yoshihiro Ogawa*[2], *Takeshi Hirota*[1,4]**

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9-10

Efficacy and safety of ponsegromab, a first-in-class, monoclonal antibody inhibitor of growth differentiation factor 15, in patients with cancer cachexia: a randomized, placebo-controlled, phase 2 study

Jeffrey Crawford[1], John D. Groarke[2], Susie M. Collins[3], Shannon Lubaczewski[4], Eric J. Roeland[5], Tateaki Naito[6], Andrew E. Hendifar[7], Marie Fallon[8], Koichi Takayama[9], Timothy Asmis[10], Richard F. Dunne[11], Isik Karahanoglu[2], Carrie A. Northcott[12], Magdalena A. Harrington[2], Michelle Rossulek[13], Ruolun Qiu[14], Aditi R. Saxena[2]

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9-11

BIO101: a drug candidate to reduce GLP1-RA-induced muscle mass or function loss in patients with obesity.

***Rob Van Maanen*[1], *Claudia Ferreira*[1], *Mathilde Latil*[1], *Serge Camelo*[1], *Sandrine Rabut*[1], *Stanislas Veillet*[1], *Pierre J. Dilda*[1], *Waly Dioh*[1], *Marc-Andre Cornier*[2]**

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Poster session 3.1 **Cachexia – Mechanisms, basic** (posters 2-01 to 2-11)
Chairs: Andrew Judge, Nicholas Greene

2-01

Novel genetic variants in *DRAIC* and *RFX3* confer risk for weight loss in people with chronic obstructive pulmonary disease

Joe W. Chiles*[1], Alison Rocco[1], Vinodh Srinivasasainagendra[2], Harry B. Rossiter[3], Richard Casaburi[3], Anna Thalacker-Mercer[4], Rakesh P. Patel[5], J. Michael Wells[1], Emily S. Wan[6], Edwin K. Silverman[6], Michael H. Cho[6], Craig P. Hersh[6], Bruce M. Psaty[7], Sina A. Gharib[8], Yan Gao[9], George T. O'Connor[10], Leslie A. Lange[11], Hemant K. Tiwari[2], Merry-Lynn N.McDonald[1] for the TOPMed Investigators

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2-02

A scoping review examining diagnostic criteria for the cardiac cachexia condition

Omar Alrfooh, Donna Fitzsimons, Patrick Stark, Gareth Thompson

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2-03

Hepatic Yap1 activates systemic catabolism and muscle loss during organ repair: evidence for a liver-derived common mechanism with cancer cachexia.

Tewfik Hamidi[1#], Yanlin Jiang[2#], Tyler Robinson[2], Andris Kronbergs[3], Ernie Au[2], Joseph Rupert[4], Xiaoling Zhong[2], Siangsin Lal[2], Tiffany Liang[5], Alexander Robling[6], April Hoggatt[6], Robson Carvalho[9], Sarah Cury[9], Clark Wells[7], Teresa Zimmers[8§*], and Leonidas Koniaris[1§*]

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2-04

Multi-kinase inhibitor Sorafenib triggers cachexia by disrupting the activity of distinct chromatin regulators

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2-05

Investigating Post-Translational Modifications of NIK Protein in Muscle Atrophy

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2-06

Vincristine induced delayed body weight gain and stunted musculoskeletal growth in pediatric mice

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2-07

The LEAP2 response to cancer-related anorexia-cachexia syndrome

Salil Varshney[1], Kripa Shankar[1], Haiming L. Kerr[2], Lindsey J. Anderson[2], Nathan P. Metzger[1], Deepali Gupta[1], Omprakash Singh[1], Sean B. Ogden[1], Subhojit Paul[1], Francisco Piñon[1], Sherri Osborne-Lawrence[1], Corine P. Richard[1], Connor Lawrence[1], Bharath K. Mani[1,3], Jose M. Garcia[2], Jeffrey M. Zigman[1, 4, 5, *]

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2-08

KPC pancreatic cancer disrupts the skeletal muscle circadian transcriptome in a FoxP1-dependent manner

Jeremy B. Ducharme[1,2], Daria Neyroud[1,2], Martin M. Schonk[1,2], Miguel A. Gutierrez-Monreal[2,3], Zhiguang Huo[4], Karyn A. Esser[2,3], Sarah M. Judge[1,2], & Andrew R. Judge[1,2]

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2-09

Mutual de-differentiation of adipocytes and tumor cells in the macroenvironment of pancreatic cancer cachexia

Sephora Jean[1,4,11], Brittany R. Counts[10], Omnia Gaafer[2,4,10], Sara Ota[10], Hyun C. Roh[2,4], Sha Cao[3,4], Denis C. Guttridge[6,8], Michael C. Ostrowski[7], Leonidas G. Koniaris[9,11], Teresa A. Zimmers[1,2,10,11]

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2-10

The role of tumor specific IGFBP-3 in the onset and progression of skeletal muscle wasting in murine models of pancreatic cancer

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2-11
Attenuation of skeletal muscle lipid hydroperoxides is sufficient to restore skeletal muscle atrophy and weakness associated with cancer cachexia in mice
***Takuya Karasawa*[1,2], *Justin L. Shahtout*[1], *Shinya Watanabe*[1], *Edwin R. Miranda*[1], *Drake Watkins*[3], *Kyle Spainhower*[3], *Phaedra Ghazi*[3], *Dennis Fix*[1], *Martin McMahon*[3], *Eric Snyder*[3], *David H. Lum*[3], *Micah Drummond*[1], *Katsuhiko Funai*[1]**
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Poster session 3.2 **Cancer Cachexia III** (posters 3-13 to 3-23)
Chairs: Joanne Reid, Florian Strasser

3-13
Deciphering C/EBPβ-Mediated Tumor Effects on Cachexia and Its Modulation
***Aisha Saleh*[1], *Nadine Wiper-Bergeron*[1]**
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3-14
Male sex, overweight/obesity, low IL-4 and other biomarkers of cachexia in BIOPAC patients with pancreatic adenocarcinoma
***Tetiana Korzun*[1#], *Shauna Rakshe*[1#], *Sidsel C. Lindgaard*[2#], *Inna Chen*[2], *Julia S. Johansen*[2*], *Teresa A. Zimmers*[1*]**
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3-15
Tumour-induced alterations in single-nucleus transcriptome of atrophying muscles indicate enhanced protein degradation and reduced oxidative metabolism
***Samet Agca*[1], *Aylin Domaniku-Waraich*[1], *Sevval Nur Bilgic*[1], *Melis Sucuoglu*[1], *Meric Dag*[2], *Sukru Anil Dogan*[2], *Serkan Kir*[1]**
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3-16
Cachexia in hospitalized patients with chronic disease and outcome: a national database analysis
***Mitja Lainscak*[1, 2], *Tina Zupanic*[3], *Daniel Omersa*[4], *Ivan Erzen*[1, 3], *Jerneja Farkas*[1, 2, 3]**
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3-17
Sex-specific aberrant myelopoiesis and its role in cancer cachexia initiation
***Alice Tate*[1], *Lisa Ek Orloff*[1], *Jame Vanhie*[1], *Alex Brown*[2], *Nadine Wiper Bergeron*[2,3], and *Michael De Lisio*[1,2,3]**
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3-18

Impact of the emerging cancer cachexia-biomarker TIMP-1 on the liver

Vanessa Brunner, Chris D. Hermann, Benjamin Schoeps, Olga Prokopchuk, Damjan Manevski, Daniel Häußler, Julian Frädrich, Achim Krüger

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3-19

Identifying individuals with cancer cachexia using data from electronic health records (EHR) linked to insurance claims

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3-20

Cancer Cachexia: Real-World Prevalence

Julien Grosjean[1,2], Stefan Darmoni[1,2], Badisse Dahamna[1,2], Mélanie Daligault[1], Yann Colardelle[3], Richard Weiskopf[4], Markus Anker[5]

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3-21

Cancer Cachexia epidemiological landscape: lifetime prevalence and severity of cachexia in a population-based longitudinal study

Bhumi J Bhatt, Vickie E Baracos

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3-22

Is malnutrition assessed by MUST, SGA, GLIM and cachexia related with survival in outpatient advanced cancer?

Andressa Miranda Machado[1], Michael S. Yule[2], Bruna Maria Malagoli Rocha[1,3], Taysa Machado Menezes[1], Letícia Oliveira Cardoso[1], Paula Philbert Lajolo[4], Barry J Laird[2], Carlos Eduardo Paiva[5], Yara Cristina de Paiva Maia[1]

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3-23

Comparison of adiposity-specific microRNAs expression in subcutaneous and visceral adipose tissue of patients with gastrointestinal cancer

Alessio Molfino[1], Federica Tambaro[1], Valentina Pace[1], Simona Orlando[1], Giovanni Imbimbo[1], Giuseppe Nigri[2], Maria Ida Amabile[3], Maurizio Muscaritoli[1]

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Poster session 3.3 **Diagnosis of sarcopenia II** (posters 5-01 to 5-04 + 5-13 to 5-15)
Chairs: Richard Skipworth, Faisal Beg

5-01

Norm-reference values of phase angle for low muscle quality in a Korean population

Seon-Ho Eom[1], Kiwan Kim[2], Chang Won Won[3], Soojung Choi[4], Young-Jin Jo[1], Chul-Hyun Kim[1]¶

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5-02

Adoption of Routine Clinical Assessment of Sarcopenia and Sarcopenic Obesity in Prostate Cancer Patients on Androgen Deprivation Therapy

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5-03

Classification algorithm for low appendicular lean mass in hospitalized older adults: A classification regression tree approach

Luis Carlos Venegas-Sanabria[1,2], Daniela Arias Blanco[2], Miguel German Borda[4,5], Luisa Fernanda Murcia-Soriano[1], Diana Marcela Ramos-Caballero[3], Alejandra Tordecilla-Sanders[3], Gabriela Garcia-Laguna[3]

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5-04

Mid-regional pro-adrenomedullin is associated with sarcopenia in geriatric patients

Mirela Vatic[1,2], Guglielmo Fibbi[1,2,3,] Tania Garfias-Veitl[1,2], Ryosuke Sato[1,2], Emanuele Marzetti[4], Stephan von Haehling[1,2]

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5-13

Developing an AI-Driven X-Ray Segmentation Model for Accurate Sarcopenia Diagnosis: Overcoming DEXA Limitations

Hyeon Su Kim[1], Deog-Yoon Kim[2], Yong-Chan Ha[3], Yong-Kyun Lee[4], Hyunwoo Park[5], Shinjune Kim[1], Jun-Il Yoo[6]*

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5-14
Skeletal muscle index optimal thresholding for prognosis in metastatic non-small-cell lung cancer
José Leão Mendes, Nuno Pimenta, Paula Ravasco
Centre for Interdisciplinary Research in Health, Universidade Católica Portuguesa, Portugal
ABSTRACT TOPIC – Diagnosis of sarcopenia

5-15
Exploring the Obesity Paradox: Body Composition and Outcomes in Older Women with Hip Fractures
Marcos Minicucci*[*1], Thais Picoli[1], Victoria Soares[1], Jessica Ferreira[1], David Gumieiro[2], Filipe Leal-Pereira[1,2], Taline Lazzarin[1,2], David Pereira[1], Raquel Ballarin[1,2] e Paula Azevedo[1]
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Poster session 3.4 **Muscle Wasting & Sarcopenia III** (posters 6-25 to 6-32)
Chairs: Wolfram Doehner, Sabbah Hussain

6-25
Aging and exercise differentially modulate mercs and contractile dynamics in skeletal muscle
Ryan J. Allen[1], Ana Kronemberger[1], Qian Shi[2], Marshall Pope[3], Elizabeth Cuadra-Muñoz[1], Wangkuk Son[1], Long-Sheng Song[2], Ethan J. Anderson[4], Renata O. Pereira[2], Vitor A. Lira[1*]
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6-26
ATAD2: A Novel Regulator of Muscle Cell Proliferation, Differentiation and Autophagy
Sami Sedraoui[1,2*], Alaa Moamer[1,2*], Tomer Jordi Chaffer[1,2], Dominique Mayaki[1], Jean-Philippe Leduc-Gaudet[3], Felipe Broering[1], Laurent Huck[1], Marco Sandri[1,6,7], Gilles Gouspillou[4], Sabah Hussain[1,5]
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6-27
Revisiting the cholesterol paradox in chronic heart failure: the potential role of skeletal muscle mass Results from the Studies Investigating Co-morbidities Aggravating Heart Failure (SICA-HF)
Ryosuke Sato[1], Tania Garfias-Veitl[1,2], Mirela Vatic[1,2], Guglielmo Fibbi[1,2], Wolfram Doehner[3,4,5], Stefan D. Anker[3,5,6], Stephan von Haehling[1,2]
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6-28
Ketone bodies in heart failure: metabolic changes and muscle health in cardiac patients
***Guglielmo Fibbi*[1,2,3], *Tania Garfias-Veitl*[1,2], *Ryosuke Sato*[1,2], *Mirela Vatić*[1,2], *Wolfram Doehner*[4,5,6], *Stefan D. Anker*[4,5,6], *Stephan von Haehling*[1,2]**
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6-29
Effect of current smoking on fat-free mass in COPD patients
***Irena Sarc*[1,2], *Tatjana Kosten*[1], *Andraz Jug*[1], *Tomaz Hafner*[1]**
[1]University Clinic of Respiratory and Allergic Diseases Golnik, [2]Faculty of Medicine, University of Ljubljana

6-30
Satellite cells during skeletal muscle regeneration in survivors of critical illness
Adela Krajcova, Lucie Genserova, Frantisek Duska
Department of Anaesthesia and Intensive Care, Charles University 3rd Faculty of Medicine and Kralovske Vinohrady University Hospital, Prague, Czech Republic

6-31
Vitamin D signaling is essential for maintaining skeletal muscle and adipose mass during weaning
Shubhi Khare*, Neha Jawla*, G Aneeshkumar Arimbasseri
Molecular Genetics Laboratory, National Institute of Immunology, Aruna Asaf Ali Marg, New Delhi, India

6-32
Histidyl dipeptides preserve skeletal muscle mass during heart failure
Mamata Chaudhari, Benjamin Doelling, David Hoetker, Yibing Nong, Shahid P Baba
University of Louisville, Louisville, USA

Poster session 3.5 **Therapeutic Development (pre-clinical) I** (posters 10-01 to 10-07)
Chairs: Paola Costelli, Jeffrey Crawford

10-01
Exon 2 is the key pro-myogenic mediator of the lncRNA CYTOR
***Zeinabou Niasse-Sy*[4,5], *Ajda Lenardic*[2], *Bar-Nur Ori*[2], *Johan Auwerx*[1], *Martin Wohlwend*[3]**
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10-02
Early adolescent genotoxic stress leads to a reduction in skeletal muscle stem cells and persistent damage of the niche.
***Ashley Ontiri*[1], *Sabrina DeStefano*[1], *Danny Panken*[1], *Cathy Yang*[1], *Vijitha Puviindran*[1], *John Bachman*[2], *Elena Torres Ponce*[1], *Joe V Chakkalakal*[1]**
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10-03

Molecular characterization of cachexia in a novel model for the study of head and neck cancer

***Patrick D. Livingston*[1], Natalia M. Weinzierl[1], Nicholas A. Jamnick[1], Chandler S. Callaway[1], Leah J. Novinger[1,4], Schuyler Lee[2], Bifeng Gao[2], Douglas J. Adams[3], Christian D. Young[1,4], Andrea Bonetto[1,4]**

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10-04

Potential anti-cachexia properties of novel dual-MEK inhibitor IMM-1-104

Peter J. King, Sarah Kolitz, Kevin D. Fowler, Jason M. Funt, Benjamin J. Zeskind, Brett M. Hall

Immuneering Corporation, Cambridge, MA, San Diego, CA, and New York, NY USA

10-05

Musclin restrains muscle atrophy and NMJ degeneration in mouse models of ALS

***Andrea David Re Cecconi*[1], Mara Barone[1], Massimo Tortarolo[1], Federica Palo[1], Lorena Zentilin[2], Gianni Sorarù[3], Giovanni Nardo[1], Caterina Bendotti[1] and Rosanna Piccirillo[1]**

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10-07

ASCA101 as innovative multi-target therapeutic drug for cancer cachexia

***Sorim Nam*[1], Euna Choi[1], Changhoon In[1], Minhyuk Yun[1], Chaulmin Pai[1]**

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Poster session 4.1 **Cancer Cachexia IV** (posters 3-24 to 3-33)
Chairs: Andrea Bonetto, Tobias Janowitz

3-24

Assessing microRNAs expression in patients newly diagnosed with breast cancer and their association with changes in body composition

***Alessio Molfino*[1], Simona Orlando[1], Federica Tambaro[1], Maria Ida Amabile[1], Valentina Pace[1], Giovanni Imbimbo[1], Carmen Gallicchio[1], Maurizio Muscaritoli[1]**

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3-25

Adiposity specific micrornas in cancer patients: analysis of plasma levels according to fat distribution assessed by CT-scan

***FedericaTambaro*[1], Giovanni Imbimbo[1], Valentina Pace[1], Giolia Lauteri[2], Simona Orlando[1], Veronica Rizzo[3], Maria Ida Amabile[4], Giuseppe Nigri[2], Maurizio Muscaritoli[1], Alessio Molfino[1]**

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3-26

Analysis of body composition parameters and toxicities in patients with metastatic breast cancer (BC) treated with CDK4/6 inhibitors

***Alessio Molfino*[1], Giovanni Imbimbo[1], Marica Pellegrini[1], Maria Ida Amabile[2], Carmen Gallicchio[1], Massimilano Ardovino[1], Veronica Rizzo[3], Simona Pisegna[4], Andrea Botticelli[4], Maurizio Muscaritoli[1]**

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3-27

The effect of sex on circulating undercarboxylated osteocalcin in tumor-bearing mice receiving chemotherapy

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3-28

Anamorelin Efficacy in Non-Small Cell Lung Cancer Patients with Cachexia: Insights from ROMANA 1 and ROMANA 2

***Barry J. A. Laird*[1*], *Richard Skipworth*[2*], *Philip D Bonomi*[3], *Marie Fallon*[1], *Stein Kaasa*[4], *Ruben Giorgino*[5], *Donald C. McMillan*[6**], *David C. Currow*[7**]**

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3-29

Increased nivolumab clearance correlates with elevated GDF15 serum levels in patients with metastatic non-small cell lung cancer

Maaike M. Hofman[1,2], Bram C. Agema[1,3], Juliette H.R.J. Degens[4], Daan P. Hurkmans[1,2], Daphne W. Dumoulin[2], Annemie M.W.J. Schols[5], Stijn L.W. Koolen[1,3], Christianne Groeneveldt[2], Wouter R.P.H. van der Worp[5], Lizza E.L. Hendriks[6], Cor H. van Leest[7], Joachim G.J.V. Aerts[2], Ron H.J. Mathijssen[1], Anne-Marie C. Dingemans[2], Ramon C Langen[5], Sander Bins[1]

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3-30

The Clinical Significance of Weight Loss During Concurrent Chemoradiotherapy (CCRT) in stage III Non-Small Cell Lung Cancer (NSCLC): Impact on Treatment Strategy and Outcomes

Peiyu Qiu[1], Ramon CJ Langen[1], Francesco Cortiula[2, 3], Fariba Tohidinezhad[2], Juliette Degens[4], Michelle Steens[4], Lizza EL Hendriks[5], Sarah Debakker[5], Martina Bortolot[3,5], Ardy van Helvoort[1,6], Dirk de Ruysscher[2], Annemie MWJ Schols[1] and Wouter RPH van de Worp[1]

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3-31

The development of muscle mass, muscle strength, and muscle function in patients with lung cancer during oncological treatment

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3-32

Impact of Cachexia on the Survival of EGFR-Mutant Lung Cancer Patients on Osimertinib Therapy

Lanyi Nora Chen[1,4], Xin Ma[2,4], Benjamin Herzberg[1,4], Brian S. Henick[1,4], Anup K. Biswas[3,4], Catherine A. Shu[1,4], Swarnali Acharyya[3,4]

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3-33
Identifying pretreatment blood metabolic markers associated with weight loss in head and neck cancer patients
***Ronald C. Eldridge*[1], *Nabil F. Saba*[2], *Andrew H. Miller*[2], *Evanthia C. Wommack*[2], *Jennifer C. Felger*[2], *Deborah W. Bruner*[1], *Canhua Xiao*[1]**
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Poster session 4.2 **Muscle wasting & sarcopenia IV** (posters 6-09 to 6-15)
Chairs: Wolfram Doehner, Sabbah Hussain

6-09
Delayed skeletal muscle regeneration in an accelerated ageing mouse model
***Suvham Barua*[1,3], *Elia Angelino*[1,3], *Lorenza Bodo* [1], *Alessio Menga* [1], *Daniela Talarico*[2], *Andrea Graziani*[1,3]**
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6-10
Investigating muscle-derived SPMs as a potential treatment for muscle wasting
***Jasmine Foster*[1], *Thomas Wilkinson*[1], *Neil Greening*[1], *Luke Baker*[1]**
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6-11
Targeting reactive lipid carbonyls to protect against muscle wasting
Katsuhiko Funai
Department of Nutrition & Integrative Physiology, University of Utah

6-12
Impact of deleting MuRF1 or MuRF2 on skeletal muscle function – male vs. female
***Volker Adams*[1], *Antje Augstein*[1], *Antje Schauer*[1], *Beatrice Vahle*[1], *Siegfried Labeit*[2,3], *Axel Linke*[1]**
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6-13
The role of hepatokines in MASLD associated muscle wasting
***Amy Rose Fumo*[1], *Pauline Morigny*[1], *Honglei Ji*[1], *Adriano Maida*[1], *Ana Jimena Alfaro*[1], *Karsten Motzler*[1], *Christine von Törne*[2], *Annette Feuchtinger*[3], *Maria Rohm*[1,4,5]**
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6-14
MyoMed-205 counteracts titin hyper-phosphorylation, muscle dysfunction and atrophy in an animal model of HFpEF
***Beatrice Vahle*[1], *Antje Schauer*[1], *Antje Augstein*[1], *Siegfried Labeit*[2,3], *Axel Linke*[1], *Volker Adams*[1]**
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6-15
Angiotensin Type 2 Receptor Deficiency Exacerbates Physical Decline and Cardiac Muscle Wasting in Aged Mice
***Michael Abadir*[1], *Ruth Marx*[2], *Laura Powell*[2], *Jeremy Walston*[2]**
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Poster session 4.3 **Therapeutic Development (pre-clinical) II** (posters 10-08 to 10-14)
Chairs: Paola Costelli, Jeffrey Crawford

10-08
GDF-15 neutralizing antibody visugromab overcomes cancer cachexia
***José Medina-Echeverz*, *Neha Vashist*, *Sabrina Genßler*, *Thorsten Ross*, *Marlene Auer*, *Kathrin Klar*, *Felix Lichtenegger*, *Eugen Leo*, *Christine Schuberth-Wagner*[1]**
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10-09
Repurposed relics: selective β – blockers as a treatment for cancer-associated cachexia
***Mit Joshi*[1], *Bhoomika M. Patel*[2]**
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10-10
Dual Targeting of Y5 and Ghrelin Receptors: A New Strategy for Treating Cancer Cachexia
***Jenna E Hunt*[1], *Camilla Lund*[1], *Brian Chen*[2], *Marc Schneeberger*[2], *Christoffer Clemmensen*[3], *Annette G Beck-Sickinger*[4], *Søren L Pedersen*[1], *Keld Fosgerau*[1]**
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10-12
Pharmacological inhibition of USP-19 attenuates cancer cachexia-induced muscle atrophy
***Vignesh Karthikaisamy*[1-4, *, §], *Natalie Page*[6, §], *Darren M. O'Hara*[6], *Aaron N. Cranston*[6], *Colin R O'Dowd*[6], *Xavier Jacq*[6], *Richard Wilkinson*[6], *Stephanie Burton*[6], *Hayley Gibson*[6], *Joana Costa*[6], *Daniel Longley*[6], *Matthew Helm*[6], *Chris Mc Givern*[6], *Steven Shepherd*[6], *Christina Bell*[6], *Peter Hewitt*[6], *Mary McFarland*[6], *Hugues Miel*[6], *Steven Whitehead*[6], *Lauren Proctor*[6], *J. S. Shane Rountree*[6], *Mark Wappett*[6], *Stephan Herzig*[1-3, 5], *Timothy Harrison*[6], *Mauricio Berriel Diaz*[1-3]**
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10-13
Bimagrumab Prevents Semaglutide-Induced Muscle Mass Loss in Diet-Induced Obese Mice
***Morten Lundh*[1], *Anitta Kinga Sárvári*[1], *Nicolas Eskesen*[1], *Nina Sonne*[1], *Line Zachariassen*[1], *Jacob Nersting*[1], *Simone Bossi*[1], *Marco Tozzi*[1]**
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10-14
Loss of hindlimb muscle mass does not explain the loss of lean mass in semaglutide-treated mice
***Takuya Karasawa*[1,2], *Ran Hee Choi*[1], *Cesar A. Meza*[1], *Subhasmita Rout*[1], *Katsuhiko Funai*[1]**
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POSTER ABSTRACTS

1-01

RNA-sequencing and global proteomics of diaphragm weakness in female rats after myocardial infarction

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Introduction: Myocardial infarction (MI) leads to diaphragm abnormalities that contribute to the systemic pathophysiology post-MI. This process has been extensively studied with emphasis on males. However, effects of MI on diaphragm abnormalities in females and mechanisms involved in the dysfunction are yet to be elucidated. Our current study sought to identify global transcriptome and proteome changes associated with diaphragm abnormalities in an animal model of chronic stage MI.
Methods: The coronary artery was ligated to cause MI in adult female Sprague-Dawley rats or a sham procedure. We measured diaphragm force and fiber cross-sectional area, while target genes were identified using RNA-Sequencing (RNA-Seq) and Mass spectrometry was utilized for global proteomic modifications (n = 4/group).
Results: MI decreased maximal diaphragm specific force by ~20% ($p < 0.05$) without changes in cross-sectional area of type I, IIA, or IIb/d fibers. A total of 379 were differentially expressed genes out of 11526 identified. MI upregulated 318 genes and downregulated 61 genes in the diaphragm. Gene Ontology analysis revealed pathway enrichment of transcription regulator complexes, positive regulation of protein ubiquitination, mitochondrion, and negative regulation of phosphorylation. Global proteomic analysis identified upregulation of neuron death, cellular response to oxygen, immobilization stress, and mitochondrial electron transport chain with some key proteins being PHHB1, COX7C, NDUS2, and NQO2. Downregulated pathways include translation, peptide synthetic processes, hydrocarbon catabolic processes, and glutathione metabolism with key proteins being RS13, RL13, and Agrin.
Conclusion: Overall, these data indicate maladaptive contractile, metabolic signaling, and remodeling of the female diaphragm in chronic MI where impairments in translation pathway/downregulation of ribosomal protein precedes fiber atrophy and neuromuscular junction abnormalities contribute to inspiratory dysfunction. These findings present potential biological targets and pathways to investigate in the cause and prevention of MI induced diaphragm dysfunction in females.

1-02

Untargeted metabolomic profiling of dogs with heart failure shows metabolic differences associated with cardiac cachexia

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Introduction: Cardiac cachexia is common in pet dogs with naturally-occurring heart failure (HF). Metabolomics studies in patients with HF have shown numerous metabolic alterations, but have not reported whether cardiac cachexia was present. Therefore, it is unknown whether there are metabolomic effects of cardiac cachexia that are independent from those of HF. The objective of this study was to compare the metabolic profiles of dogs with HF and cardiac cachexia to dogs with HF without cachexia and to dogs without HF or cachexia.
Methods: Three groups of dogs with myxomatous mitral valve disease were enrolled: 1) HF with muscle loss; 2) HF without muscle loss, and 3) asymptomatic without muscle loss. Metabolomic profiles were analyzed from serum samples using ultra-high-performance liquid chromatography–tandem mass spectroscopy. Dogs in the three groups were compared, with statistical significance defined as $P<.05$ with low false discovery rate ($q<.10$) and nominal statistical significance defined as $P<.05$ but $q>.10$.
Results: Thirty dogs were enrolled: HF with muscle loss (n=10), HF without muscle loss (n=10), and asymptomatic disease without muscle loss (n=10). Numerous metabolites were significantly (n=201) or nominally significantly (n=366) different among groups. For example, when comparing the HF groups with and without muscle loss, lipids were the predominant metabolite differences, including many medium- and long-chain dicarboxylates and dicarboxylate acylcarnitines, which suggest mitochondrial dysfunction.
Conclusions: These results support some metabolic differences associated with cardiac cachexia that are independent from those known to occur as the result of HF.

1-03

Effects of dietary linoleic acid on insulin resistance and skeletal muscle atrophy in a mouse model of cancer cachexia

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Introduction: Cancer cachexia (CCx), e.g., the involuntary loss of muscle and fat, affects 30-80% of cancer patients. Insulin resistance plays a role in the progression of CCx. This study tests the hypothesis that linoleic acid (LA), an essential nutrient, reduces insulin resistance and preserves skeletal muscle in mice with CCx.
Methods:
In this 2x2 study design, 36 CD2F1 male mice were randomized to a control (Con) or a LA fortified diet (LA). Two weeks later, mice were randomized and inoculated with $0.5x10^6$ C26 adenocarcinoma cells (+) or phosphate-buffered saline (-). Body weight, food intake, grip strength, insulin resistance, and body composition were measured then mice were euthanized when 10% weight loss from peak body weight and/or tumor size $\geq$ 1 cm were achieved. A two-way ANOVA was carried out, with an alpha level of 0.05 considered significant.
Results: Body weights and weights of quadriceps and white adipose tissues were significantly lower while liver and spleen were significantly higher among tumor groups. From pre-inoculation to post-inoculation period, mean fasting glucose levels decreased significantly by 31% only among Con+. During pre-inoculation, LA had unexpectedly more insulin resistance than Con, but there was no significant effect of diet in post-inoculation period. Tumor (vs. saline) significantly increased MuRF-1 (11.15 ± 3.0 vs. 0.97 ± 0.1) and atrogin-1(10.12 ± 1.8 vs. 1.0 ± 0.2) transcripts in quadriceps which was similar in gastrocnemius muscle. LA-diet had no effects on MuRF-1or Atrogin-1 mRNA. There were no significant differences of either tumor or diet in grip strength and body composition.
Conclusions: The LA-diet group maintained fasting glucose levels but had higher insulin resistance. Diet had no effect on tissue weights or mRNA markers of ubiquitin proteases. Further study will be conducted with longer exposure to LA-diet to evaluate its effect on muscle function during the progression of CCx.

1-04

The effects of cardiac cachexia on the myogenic capacity of satellite cells

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Introduction: There is a growing body of evidence suggesting that cardiac cachexia is the partial result of a decrease in the myogenic capacity of muscle stem cells (MuSC). Often MuSCs experiencing the chronic inflammation present within the cachexic muscle tissue begin their differentiation process by developing into myoblasts but fail to progress further. The degree to which this dysfunctional MuSC behaviour is responsible for muscle wasting in cachexia is unclear and no mechanism has been reported. Therefore, we aim to investigate the features of the inflammatory cardiac cachexia muscle

environment and how they correlate with the abundance of undifferentiated MuSCs.
Methods: Over eight weeks the pharmaceutical monocrotaline was used to induce cardiac cachexia in age and sex matched mice (n=8). Following termination, RNA sequencing was performed on the gastrocnemius muscles to determine which cytokines correlate with differentiation defects. Flow cytometry was used to measure the number of cells expressing the white blood cell marker CD45 in the hind limb muscles. Finally, the tibialis anterior muscles will be stained for the MuSC marker Pax7 to determine the abundance of quiescent MuSCs. An increased abundance of which will indicate an inability of MuSCs to progress through their differentiation process.
Results: The staining process and sequencing analysis are still underway.
Male mice which received monocrotaline showed a reduction in body weight, lower tibialis anterior weights, and a greater abundance of white blood cells in their hind limb muscle tissue.
Conclusion: The reduction in body and tibialis anterior weights and a greater abundance of white blood cells in males who received monocrotaline all indicate that this group experienced a higher degree of chronic inflammation. This result is consistent with the scientific literature as males are more effected by cardiac cachexia.

1-05
Biomarkers and Mechanisms Related to Cancer-Induced Cardiac Cachexia

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Introduction: Cancer-induced cachexia affects up to 80% of patients with cancer and causes death in up to 80% in those with advanced cancer. The authors identified available evidence in cancer-induced cardiac cachexia in human and non-human models over a ten-year period (2011-2021) by examining the contribution of biomarkers and other factors leading to the development and progression of cardiac cachexia.
Methods: A systematic review was conducted, and eligibility criteria included randomized controlled trials, retrospective, prospective, descriptive animal, cadaver, and human studies. There were 15 (fifteen) animal studies and 4 (four) human studies that met the eligibility criteria and were included.
Results: Four common biomarkers were identified in animal studies including Tumor Necrosis Factor-alpha (TNF-α), Atrogin-1, Muscle RING-finger protein-1 (MuRF1), and Interleukin-6 (IL-6). Atrophied hearts showed decreased myocyte size, decreased sarcomeric proteins, and an increase in the b-myosin heavy chain which is indicative of muscle atrophy. In a few of the animal studies ubiquitin conjugation activity (E2) did not increase in the heart showing that the UPS was not upregulated. Cardiac muscle loss was the result of a reduction in cardiomyocyte size and all sarcomeric proteins. Cathepsin and LC3 were upregulated. However, LC3-II was significantly higher in male hearts (smaller hearts). This supported autophagy as the main driver in cancer-induced cardiac cachexia. In one human study, those with pre-cachexia and cachexia had significant cardiac findings. Cardiac wasting was examined in deceased patients retrospectively. Out of those with a cancer diagnosis, 30.5% developed cancer-associated cachexia, had significantly lower melatonin levels, and had lower heart weights compared to non-cachectic patients and those with a non-cancer and non-cardiovascular diagnoses.
Conclusion: Although the search was extensive, we found only a limited number of high-quality studies. The evidence indicates that cancer-induced cardiac cachexia in the reviewed animal studies appear to be driven mostly by autophagy.

1-06
Sex-dependent effects of monocrotaline on cachexia

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Introduction: The monocrotaline (MCT) model of cardiac cachexia is a pharmaceutical approach to pulmonary hypertension, often used to study heart failure and muscle wasting in murine models. However, little is known of how MCT, a pyrrolizidine alkaloid derived from plants, leads to peripheral changes in organ function and body mass, and sex differences have not been adequately compared.
Methods: MCT (200mg/kg) was applied to 10-12 week old male and female C57BL/6N mice weekly, for 8 weeks. Body weight, feeding behaviour and stool output were monitored over the experimental period. In the final week, endurance was measured via a treadmill fatigue study. Upon termination, organs were weighed and processed for histochemistry. Skeletal muscles were analyzed via flow cytometry and RNA-seq.
Results: Males were more susceptible to MCT-induced weight loss, manifesting at Week 5. Liver mass was reduced in male mice but no change in lung wet:dry ratio or heart mass was observed in either sex. Skeletal muscle mass was reduced in male mice which coincided with an increase in leukocyte infiltration. A significant decrease in white and brown fat was also observed in males. No differences in stool output or feeding behaviours were observed in either sex, however, endurance was decreased in females but not males. RNA-seq analysis of the gastrocnemius muscle showed no significant changes in gene expression when compared within either the male or female cohort, but when pooled, genes associated with mitochondrial function, translation, and cytoskeletal dysfunction (including Tuba4a) were reduced.
Conclusion: These data suggest that there are mice display sex-dependent responses to MCT, and that molecular and physiological changes are derived from MCT toxicity and not cardiac dysfunction. As such, MCT may not be a suitable model for cardiac cachexia in mice and further research using this model should consider sex-dependent responses.

1-07
Lung cancer has sex dependent effects on the musculoskeletal system

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Several lines of evidence suggest that cancer cachexia (CC) may be sex-dependent. We and others have shown **that CC associate with severe bone deterioration even in the absence of metastasis to bone.** Lung cancer patients are at high risk to develop CC. In these patients the presence of osteoporosis **associate with reduced survival. Here we aimed to** characterize the sex-dependent effect on the musculoskeletal system due to the **Lewis LungCancer, LLC.** At four months C57BL6 mice were inoculated s.c. and intrascapularly with 1×10^6 LLC cells and sacrificed after 3 weeks of tumor burden. The LLC induced body wasting in male but not female mice. Severe muscle and fat wasting was observed in male but not in female mice. To study changes in bone mass, femura were analyzed by means of μCT. The LLC male mice exhibited severe loss of trabecular bone compared to controls, but surprisingly the LLC tumor did not affect females mice. Osteocytes are master regulators of bone homeostasis and secrete factors that target

muscle. Therefore, we performed RNAseq on osteocytes isolated from these mice to characterize their molecular signatures. Analysis revealed that LLC tumor has different effects on male as compared to female osteocytes. In male tumor-bearing mice, gene clusters associated with ossification, mineralization and extracellular matrix organization were significantly different from controls, whereas in females, inflammatory pathways were significantly different from controls. We propose that male mice most likely have an accelerated bone loss due to tumor as shown by bone matrix breakdown whereas osteocytes in females are just beginning to change into inflammatory cells by 3 weeks. Future studies will include time courses to determine if estrogen is responsible for this delayed response to lung cancer and to determine if prevention of the inflammatory phenotype in osteocytes will reduce CC, muscle loss and increase survival.

1-08

The IL-8/CXCR2 pathway as a potential therapeutic target in pancreatic cancer cachexia and related muscle wasting

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Introduction: Pancreatic cancer is one of lethal cancers, with over 70% patients experiencing cachexia complications. Chronic inflammation is a key contributor to the cachexia phenotype, including muscle tissue loss. We have identified that interleukin-8 (IL-8) serum levels are associated with disease status and cachexia in pancreatic cancer. Therefore, we are interested in the role and impact of IL-8 in pancreatic cancer-associated cachexia and muscle wasting.
Methods: We established a co-culture model between murine pancreatic cancer cells and mature muscle cells to mimic their interaction. To investigate the therapeutic potential of targeting IL-8 in pancreatic cancer, we utilized an orthotopic pancreatic cancer model, which successfully induced weight loss and muscle atrophy in mice.
Results: The co-culture of murine pancreatic cancer cells and mature muscle cells resulted in decreased levels of muscle fiber-related proteins such as myosin heavy chain (MYH) and myoglobin. Since murine models lack the *IL-8* gene, we used IL-8 homologs instead. Among various IL-8 homologs, CXCL15 was found to be the most effective at inducing cachectic muscle loss. We identified that CXCL15 increases the interaction between MYH and the E3 ligase protein MuRF1, and significantly increases poly-ubiquitination on lysine 48 of MYH, indicating that IL-8 induces muscle loss through a degradation pathway. Additionally, IL-8 was found to increase the transcription of MuRF1 through NF-κB activation, which can be suppressed by the IL-8 receptor antagonist SB225002. In our animal model, CXCL15 levels in both serum and tumor tissue increased, accompanied by impaired muscle strength after pancreatic tumor inoculation. Administration of SB225002 during cancer progression was sufficient to suppressed pancreatic tumor-induced muscle wasting, restore muscle function, and improve survival.
Conclusions: We demonstrated that IL-8 mediates muscle atrophy through the CXCR2/NF-κB/MuRF1 axis. Targeting this pathway emerges as an effective therapeutic approach in pancreatic cancer.

1-09

Pancreatic Cancer Induces Population-Specific, Heterogeneous Activation of Cachexia Genes and Reverts Differentiation in Skeletal Muscle Myocytes

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Introduction: Skeletal muscle preservation in pancreatic cancer has been unsuccessful. Knowledge is generally limited to whole tissue transcriptomics in wasted muscle. Here we sought to investigate changes specific to myonuclei and myofibers during progression of pancreatic cancer cachexia.
Methods: 12-week-old male C57BL6/J mice were implanted orthotopically with KPC^{32908} pancreatic tumor cells or underwent sham surgery (controls), n=5/group. Beginning day (d) 9, tissues were harvested every 3 days until d18. We interrogated myonuclei by single-nucleus (sn) RNA-sequencing (seq), myofibers by RNAscope and immunofluorescence (IF), and whole muscle by bulk RNAseq. Quadriceps and gastrocnemius muscles were used for analysis.
Results: As expected, bulk RNAseq showed a gradual increase in the expression of cachexia mediators including *Cepbd*, *Foxo1*, *Bnip3*, *Trim63*, and *Fbxo32*. However, prior to overt muscle wasting, d12 snRNAseq showed transcriptional heterogeneity defining specific myonuclear populations. Myonuclei were proportionately increased with cancer (40%) vs controls (37%), p=0.003. Of 7 myonuclei sub-populations, 2 were enriched in controls and 4 in cancer. Control-enriched sub-populations expressed differentiated muscle markers, including *Maf*, *Myh4*, and *Ckm*. Cancer-enriched sub-populations had diverse signatures—Group 1: $Maf^{Hi}Myh4^{Hi}$ with altered circadian rhythm, Group 2: $Maf^{Hi}Myh4^{Hi}$ with altered mesenchymal cell proliferation, Group 3: $Maf^{L\text{-}o}Myh1^{Hi}Myh2^{Hi}$, and a cancer-only Group 4: $Maf^{L\text{-}o}Myh4^{L\text{-}o}Myh1^{Hi}Myh2^{Hi}$ with high atrogene expression. Bulk RNAseq revealed decreasing *Myh4* and *Maf* with increasing *Myh1* and *Myh2* during cachexia progression. Muscle *Maf* declined with weight loss (r=0.699; p=0.001). RNAscope demonstrated abundant *Maf* in control versus minimal expression in cancer by d18. Myh4 protein decreased by IF while Myh2 was abundant during late cachexia.
Conclusions: Our results identify population-specific heterogeneity in cachexia gene activation rather than a global increase of cachexia mediators equivalently across the muscle. Furthermore, our findings implicate tumor-induced Maf loss leading to myofiber dedifferentiation. Future studies should determine the sufficiency of Maf to prevent skeletal muscle wasting in pancreatic cancer.

1-10

Optimization of a mouse model of pancreatic cancer to simulate the human phenotypes of metastasis and cachexia

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Introduction: Pancreatic ductal adenocarcinoma (PDAC) patients present with both distant metastases and cancer induced cachexia leading to high mortality rates. The mouse models used to study PDAC do not sufficiently recapitulate the human phenotypes of metastasis and cachexia, making it challenging to understand the pathogenesis of this disease and develop therapeutics to treat it. Here we optimized an orthotopic mouse model of PDAC to recapitulate the human disease.
Methods: Orthotopic surgeries were performed in which variables including the generation of metastatic pancreatic cancer cell lines, number of implanted cells, location of implantation site, age, and sex of mice, were tested to optimize rates of metastasis and cachexia. At endpoint, digital spatial profiling was utilized to compare the tumor microenvironments between the primary and metastatic lesions and RNA-seq analysis was performed to compare gene expression profiles in muscles from mice with and without metastases.
Results: Orthotopic implantation of $1x10^3$ KPCML1 metastatic cells into the head of the pancreas significantly increased the rate of metastasis from 20% in 10-week-old mice to 70% in 6-month-old mice, independent of sex. This did not occur with a separately generated KPCMS1 metastatic cell line, which exhibits a gene expression profile that is characteristically more metabolic than "EMT" like. In KPCML1 mice, the immune microenvironment was conserved between primary and metastatic tumors. Cachexia endpoints, including loss of adipose and muscle mass, were also achieved in PDAC mice with and without metastasis, mirroring conditions in patients. We also found that cachectic muscles from PDAC mice with metastasis exhibited similar transcriptional profiles to muscles from mice without metastasis.
Conclusion: Thus, this model is likely to be advantageous in both advancing our understanding of PDAC and cachexia, as well as in evaluating novel therapeutics.

1-11

Differential impact of chemotherapy and cachexia in a preclinical colorectal cancer model: a comparative analysis of 5-FU, paclitaxel, and cisplatin by biological sex

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Introduction: Cancer cachexia (CC), a wasting syndrome affecting ~50-80% of cancer patients, leads to unintentional body weight and muscle mass loss. Females present delayed severity in CC development than males. Chemotherapy, a commonly used cancer treatment, can aggravate muscle wasting and weakness, exacerbating CC and mortality. To date, the mechanisms associated with muscle wasting due to cancer and chemotherapy remain incompletely defined. This study aims to investigate the effects of chemotherapy and biological sex on CC.
Methods: Eight-week-old male and female BALB/c mice received $1x10^6$ Colon-26-adenocarcinoma (C26) cells or PBS-control injected bilaterally (n=7-10/group/sex). Twelve days after, tumor-bearing mice received two cycles of 75% of the maximum tolerated dose per kg/week of chemotherapy (5-fluorouracil (5-FU), paclitaxel (PTX), or cisplatin (Cis)) or saline as C26-control.
Results: When compared to PBS-control the C26-control male mice had ~15% lower tumor-free body mass (TF-BM), gastrocnemius, and plantaris ($p<0.021$-0.025); while TF-BM and muscles of C26 chemotherapy-treated male mice showed no significant differences from PBS-control. Conversely, C26-female mice did not show significant TF-BM or muscle loss compared to PBS-control. C26 chemotherapy-treated groups in both sexes, however, had tumors ~50% of the weight of C26-controls. This led to the calculation of TF-BM and muscle wasting ratios (WR) relative to grams of tumor. The TF-BM, gastrocnemius and plantaris WR of C26-male mice were ~3.2 times greater ($p<0.021$-0.025) in Cis-treated groups compared to non-treated control. In C26-females, TF-BM, gastrocnemius, and plantaris WR were ~4.1 times greater ($p<0.024$–0.034) in 5-FU-treated groups compared to non-treated control.
Conclusion: The increase WR indicates cachexia exacerbation with greatest TF-BM and muscle loss relative to tumor size. Muscle loss was exacerbated with Cis in C26-male mice and with 5FU in C26-females. These findings underlie potential biological sex divergence in the chemotherapy side effects providing valuable insights into future interventions to preserve muscle mass.

1-12

Liver metastases accelerate muscle wasting in lung cancer cachexia

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Introduction: Lung cancer is a leading cause of death worldwide and is often accompanied by muscle wasting, *i.e.* cachexia. Despite affecting a majority of lung cancer patients, cachexia remains understudied and currently has no cure. The liver represents a common site of metastases and is associated with poor prognosis in patients with lung cancer. We have previously demonstrated that liver metastases (LM) exacerbate cachexia in murine models of colorectal cancer, however, whether LMs heighten muscle wasting in lung cancer is unknown. Here, we aimed to characterize the impact of LMs on skeletal muscle health in a mouse model of lung cancer cachexia.
Methods: C57BL/6J male mice were injected with LLC tumor cells either subcutaneously, or intrasplenically (mLLC) to mimic hepatic metastases (n = 6-9/group). Upon sacrifice, tissues (muscles and liver) and plasma were collected for morphological and molecular analyses.
Results: Consistently, mLLC hosts displayed greater reductions in muscle weights (~ 18%), in line with decreased muscle torque (~17%) and reduced muscle cross-sectional area (~11%). On a molecular level, skeletal muscle from mLLC hosts had elevated levels of pStat3, Murf1, and Atrogin-1, suggesting enhanced protein catabolism. Mimicking metastatic disease, media collected from LLC-hepatocyte mixed cultures promoted greater C2C12 myotube wasting. Plasma proteomics identified 211 and 131 differentially expressed proteins in mLLC hosts compared to control animals and subcutaneous LLC hosts, respectively. Top regulated pathways in mLLC hosts included Neutrophil Degranulation, BAG2 Signaling, Acute Phase Response, Regulation of Insulin-like Growth Factor Transport and Uptake by IGFBPs, Hedgehog Ligand Biogenesis, and Cachexia Signaling.
Conclusions: Overall, our findings demonstrate that LMs accelerate muscle wasting and weakness in a mouse model of lung cancer cachexia. This work highlights the need for animal models that mimic advanced cancer, thus providing a better understanding of the mechanisms that mediate cachexia.

1-13

Cachectic tumours promote gut alterations through JAK/STAT pathway in *Drosophila* larvae

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Introduction: Cancer-associated cachexia (CAC) is a complex and deadly metabolic syndrome associated with several cancers (colon, pancreas,…). It is characterised by rapid involuntary weight loss, perturbs many organs, and leads to the atrophy of the adipose tissue and skeletal muscles. We investigate here the effect of CAC on the gastrointestinal system, a key organ responsible for digestion, absorption, and energy metabolism regulation.
Methods: We developed Drosophila larvae models of CAC using localized Notch-driven wing disc overgrowth. Notch activation alone causes hyperplastic overgrowth without muscle or adipose tissue wasting. However, when combined with epithelial polarity impairment, it results in neoplastic growth and peripheral tissue wasting. Since these two tumour types are similar in size, it suggests that neoplastic tumours produce specific pro-cachectic factors. We monitored alterations in the gut using qPCR and imaging techniques to follow cellular populations. RNA sequencing of normal and tumoural wing discs identified candidate mediators, which were then tested by genetic screen.
Results: We observed that cachectic tumours promote two distinct events in the larval gut: atrophy and early alteration of the adult midgut precursor (AMP) niche. The niche becomes disorganized before any other signs of CAC appear, resulting in a significant decrease in AMP numbers at the onset of the syndrome. The low AMP numbers were not caused by cell death, suggesting that these progenitors are differentiating prematurely. Genetic functional screening identified the tumour-secreted Jak/Stat pathway ligand Upd3 (homologous to mammalian IL-6), as a mediator of the stem cell depletion.
Conclusion: The study demonstrates that the gut is affected by tumours inducing CAC in Drosophila larvae, and suggests that intestinal cell type alterations could represent a para-neoplastic syndrome associated with CAC. Further investigations are needed to better understand the link between intestine remodelling and cachexia and its relevance in mammalian models.

1-14

The role of glucocorticoid receptors in regulating skeletal muscle regeneration in cancer cachexia

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Introduction: Cancer cachexia is a paraneoplastic multifactorial syndrome impacting approximately 80% of cancer patients. In response to tumor-related stress and inflammatory cytokines Glucocorticoid hormone (GC) secretion increases in the system, acting via the glucocorticoid receptor (GR) orchestrating catabolic processes, mobilizing energy from stores of carbohydrates, fats, and proteins. This chronic mobilization induces muscle energy catabolism via the ubiquitin-proteasome pathway, suppresses muscle protein synthesis through Akt signaling, and amplifies systemic inflammation, contributing to muscle atrophy. Another mechanism contributing to muscle atrophy is the defect of skeletal Muscle Stem Cells (MuSCs) to differentiate in response to cachectic microenvironments. Interestingly MuSC GR knockout mice model exhibited precocious differentiation in response to injury, suggesting potential implications for muscle regeneration in cachectic animals. Given that, we hypothesize that increased activity of the GR, driven by elevated levels of endogenous GCs, impairs the differentiation of MuSCs in cancer cachexia.
Methods: To evaluate whether the loss of GR in MuSCs enhances muscle regeneration in cachectic mice, we utilized the MuSC-specific GR knockout mouse model. Cancer cachexia was induced by inoculating Lewis lung carcinoma cells. We then assessed body weight and composition, conducted in vitro differentiation assays of primary myoblasts, and analyzed tibialis anterior (TA) muscle regeneration by comparing the counts of Pax7 and MyoG positive cells between GR knockout and the wild-type (WT) control.
Results: Our findings indicate no difference in the composition of lean versus fat mass between the two groups. Histological examination of TA sections revealed no evidence of tissue regeneration. Additionally, primary myoblast differentiation assays demonstrated a slight reduction in both the differentiation index and myotube diameter in GR knockout myoblasts compared to WT control.
Conclusion: In conclusion, this research aims to understand the mechanisms of cancer cachexia mediated by GR in MuSCs.

1-15

Effect of age on cancer cachexia pathogenesis in male and female mice

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Introduction: Cancer cachexia causes progressive weight loss and muscle wasting, leading to reduced quality and length of life for cancer patients. Few studies have investigated cachexia in aged mice or females. With the median age of cancer diagnosis being 66 years, using murine models that translate to older individuals and both sexes is crucial. This study evaluated differential cachexia pathogenesis in male and female, young and aged mice with colon-26 adenocarcinoma (C26) tumors.
Methods: 106 male and female CD2F1 mice, aged 8-10 weeks or 19-21 months were injected subcutaneously with either vehicle (PBS) or 1 million C26 cells. At pre-determined humane endpoints (24-29 days post-C26 injection), tissues were collected, weighed, and flash frozen in liquid nitrogen for qPCR, Western blot, and histological analyses. Data were analyzed using 3-way ANOVA to determine tumor, sex, age, and interaction effects.
Results: Tumors decreased final body weight ($P<0.05$), with aged ($P<0.05$) and female ($P<0.01$) mice exhibiting less severe wasting, despite no difference in tumor or spleen mass between tumor-bearing groups. Similar to body weight, tumors decreased gastrocnemius, soleus, and plantaris muscle and epididymal adipose tissue mass (all $P<0.0001$), but gastrocnemius and plantaris muscle loss was less severe in aged ($P<0.01$) and female ($P<0.01$) mice. Heart mass was also decreased by tumor ($P<0.0001$), but females were largely protected ($P<0.0001$). In contrast, tumor increased liver mass ($P<0.0001$), with aged mice ($P<0.01$) and females ($P<0.05$) exhibiting increased mass.
Conclusions: Older mice from both sexes exhibited less severe cachectic atrophy, and females had further protection compared to males. Females expressing a potential “protective” phenotype, regardless of age, should be further explored. Utilizing both aged and female mice in pre-clinical studies is important for improved understanding of age and sex-specific pathogenesis. Further research is required to better understand molecular mechanisms driving age and sex differences in cachexia.

1-16

Restoring neuromuscular function in murine cancer survivors

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Introduction: While early detection and advancements in cancer treatment have increased survival outcomes, cancer survivors frequently experience debilitating skeletal muscle wasting, weakness, and fatigue. Yet, the underlying causes of persistent weakness experienced in cancer survivors are largely unknown, and animal models mimicking the long-term consequences of cancer and chemotherapy are sparse. Evidence suggests that impaired mitochondrial homeostasis underlies cancer- and chemotherapy-induced weakness, however, whether targeting mitochondria improves muscle function during cancer survivorship is unknown. Using a tumor resection model, we aimed to characterize the persistent muscle deficits in murine cancer survivors and determine whether targeting mitochondrial proteins ameliorated muscle function.

Methods: CD2F1 male mice were injected with Colon26 (C26) cells and treated with Folfiri (2x/week) for 3 weeks. Tumors were surgically resected, and animals were allowed to recover for 4 weeks. In a separate study, gastrocnemius and tibialis anterior muscles were injected with viral constructs to overexpress PGC1α or OPA1 following tumor resection. After 4 weeks of recovery, mice were assessed for neuromuscular function and euthanized for collection of skeletal muscles.

Results: Compared to controls, murine cancer survivors displayed persistent reductions in muscle mass (-14%), muscle torque (-15%), motor unit connectivity (-50%), and indices of oxidative metabolism including pyruvate (-44%) and succinate dehydrogenase (SDH: -80%) enzyme activity. In contrast, overexpression of PGC1α or OPA1 restored muscle mass (PGC1α: +12%; OPA1: +18%), muscle torque (PGC1α: +14%; OPA1: +22%), motor unit connectivity (PGC1α: +106%; OPA1: +98%), and indices of oxidative metabolism (SDH: PGC1α: +47%; OPA1: +37%) in murine cancer survivors.

Conclusions: Overall, our data demonstrate that overexpression of PGC1α or OPA1 improves neuromuscular function in murine cancer survivors. Mitochondrial targeting represents a potential strategy to improve muscle function and quality of life in the growing population of cancer survivors.

1-17

Melusin modulation of AKT-GSK3β signalling mitigates cachexia-induced muscle atrophy

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Introduction: Cachexia-induced skeletal muscle atrophy is the most severe comorbidity associated to advanced cancer and still represents an unmet clinical need. Chaperone proteins exert pivotal functions in cellular proteostasis and recent data suggest their involvement in different type of muscle atrophy. Herein, we evaluated whether the chaperone protein Melusin exerts an anti-atrophic role in cancer cachexia-induced muscle atrophy.

Methods: Cachexia-induced muscle atrophy was induced by subcutaneously injecting 10^6 of colon 26 (C26) cancer cells in BALB/c mice. Atrophy occurrence was evaluated by measuring both skeletal muscles weight and myofibers cross-sectional area (CSA). Melusin overexpression was achieved by intramuscular injection of AAV-9 vectors carrying human Melusin construct. RNAseq, RT-qPCR, Western blot, immunofluorescence, co-immunoprecipitations, proximity ligation assay and gel filtration chromatography were utilized to investigate the molecular role of Melusin in cancer cachexia-induced muscle atrophy.

Results: Melusin expression is significantly reduced during cancer cachexia-induced muscle atrophy. Remarkably, AAV 9-mediated Melusin overexpression in C26 tumor-bearing mice partially protects from cachexia-induced muscle weight reduction, CSA reduction and atrogenes rise. Melusin maintenance blocks GSK3β activation that occurs during muscle atrophy. Specifically, Melusin binds AKT, favouring its inhibitory phosphorylation on GSK3β. Melusin-mediated GSK3β inhibition leads to β-catenin accumulation and rise of its pro-trophic gene targets.

Conclusions: Melusin maintenance counteracts cancer cachexia-induced skeletal muscle atrophy by modulating, via AKT interaction, GSK3β-βcatenin signalling axis.

1-18

Development of home-cage and machine learning based physical function measure for pre-clinical cachexia modeling

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A major feature of cancer cachexia is progressive functional decline. However, in pre-clinical models of cachexia, there is no consensus on how to best measure whole-body function. Home-Cage assays have emerged as a method to obtain more sensitive outcomes due to lower costs and reduced stress responses of maze-based or human-animal interaction in physical performance measures. However, video home-cage monitoring approaches have not been evaluated in muscle wasting pre-clinical models. We developed a novel home-cage physical function assay using DeepLabCutTM, a machine learning-based markerless pose estimation video analysis tool.

Methods: Using a Lipopolysaccharide injection induced model of systemic inflammation and cachexia over 30 days, we compared our home-cage distance traveled to current conventional mice physical assessment assays (Open Field and Y-Maze ambulatory distance, Single-Limb and All-Limb Grip Strength, Rotarod, and Treadmill Fatigue Distance) in cachectic and control mice. DeepLabCutTM was used to process home-cage videos for position data which was analyzed using Python.

Results: In individual mixed effect models between lipopolysaccharide and vehicle groups, each assay had significant decline and recovery ($p<0.0001$) except for rotarod ($p>0.05$) within the 30-days. In analysis of recovery day duration, Home-Cage distance showed similar sensitivity for recovery (18.50±1.89) compared to maze-based distance-measured (18.80±2.96) in cachectic animals but was significantly more sensitive than grip strength (10.82±1.94), rotarod (10.33±1.36), and treadmill (12.33±1.64) assays ($p<0.05$). In comparative models, time trend comparison for Home-Cage showed similar functional decline and recovery to Open Field and Y-Maze distances but significantly improved compared to grip strength, rotarod, and treadmill assays ($p<0.05$).

Conclusions: Our analysis shows Home-Cage is at least equivalent to maze-based approaches to locomotion and superior to grip strength, rotarod, and treadmill assays. This Home-Cage monitoring approach, leveraging video monitoring and machine-learning, is a low-cost approach that is likely more feasible and accurate than current approaches to physical function in cachexia.

1-19

Altered autophagy and oxidative metabolism in rats with heart failure-associated skeletal muscle atrophy

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Skeletal muscle atrophy and metabolic dysfunction are hallmarks of heart failure (HF) and promote multiple negative outcomes, including physical disability, morbidity, and mortality. At the molecular level, HF is characterized by increased reactive oxygen species, mitochondrial dysfunction, and protein damage. Skeletal muscle relies on autophagy to remove damaged proteins. We aimed to evaluate autophagic activity and oxidative damage during HF-associated skeletal muscle atrophy. Methods: Eighteen 8-week-old male Wistar rats were injected with monocrotaline (HF group, n=11, MCT; 60mg/Kg) or saline (control group, C, n=7). 4 weeks following the injection, aerobic capacity and muscle functional analysis were evaluated in vivo and gastrocnemius muscles were collected for analysis. Results: At 4 weeks post-injection, MCT rats showed signs of heart failure. Furthermore, MCT administration led to a significant decrease in exercise tolerance (C 17.0±3.37, MCT 11.4±2.54min to exhaustion) and muscle function (20Hz: C 42.98±9.98, MCT 31.95±3.29; 60Hz: C 166.01±26.66, MCT 134.14±12.75; 120Hz: C 185.97±33.29, MCT 161.16±10.67nN-m). In the gastrocnemius muscle, muscle fiber cross-sectional area was decreased (C 3146±334, MCT 2694±364), oxidative phosphorylation (CI: C 1.0±0.70, MCT 0.248±0.15; CIII: C 1.0±0.481, MCT 0.436±0.29a.u.) and expression of antioxidant enzymes (SOD2: C 1.0 ±0.52, MCT 0.40±0.26a.u.; GPX C: 1.0±0.5, MCT 0.42±0.21) were impaired, while AMPK phosphorylation (C 1.0±0.66, MCT 2.61±2.03a.u.) and autophagy were markedly increased (LC3II/I: C 1.0±1.44, MCT 22.9±94a.u.) in rats with HF compared to their counterparts. Despite these changes, levels of protein oxidative damage in HF rats remained unchanged (C 1.0±.31, MCT 0.98±0.22) compared to controls, suggesting a potential compensatory mechanism linked to increased autophagic activity. Conclusions: Monocrotaline-induced HF is associated with skeletal muscle atrophy and dysfunction primarily due to altered oxidative metabolism and autophagic flux.

1-20

Impact of neuroinflammation on cachectic phenotypes

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Introduction: Cachexia, featured by weight and appetite loss, is common in cancer patients and leads to impaired whole body functions, reduced life quality and higher mortality. Inflammation is a critical contributing factor to cancer cachexia in both patients and mouse models. Here we aim to elucidate how systemic inflammation can dysregulate brain activities and mediate behavioral changes in mouse cancer cachexia model.
Methods: We used Colon-26 (C26) model of cancer cachexia and combined quantitative behavioral assays, cytokines evaluation, whole brain screening and neural circuit analysis to characterize the association between inflammation, neural activity and behavioral phenotypes.
Results: We confirmed a series of metabolic decay in cachectic C26 mice, including reduced feeding, muscle and fat mass, heat production, and elevation in muscle atrophy markers. Cachectic mice showed apathy-like behaviors, such as reduced motivation and increased effort-sensitivity. These changes happened most prominent in the last three days before the end point. We found that cytokines in brain was differentially regulated from in plasma between pre-cachectic and cachectic mice, and identified IL-6 as a major contributor of the inflammatory profile. IL-6 likely arose peripherally, entered brain via compromised blood-brain barrier, and activated astrocytes and microglia in several brain regions. Blocking IL-6 activity by a neutralizing antibody reduced plasma IL-6 levels, delayed cachexia onset, and improved mice survival. C-Fos whole brain screen suggested a sensing pathway from brain stem, area postrema (ArP), parabrachial nucleus (PBN), ventral tegmental area (VTA) and to forebrain regions relevant to motivation. Reward-inducing dopamine release in nucleus accumbens (NAc) was reduced in cachectic mice, which can be rescued by anti-IL-6 treatment.
Conclusions: We described a brain-specific inflammatory profile in C26 mouse model and its impact on brain motivation circuit. Targeting IL-6 rescued metabolic and behavioral deficits in cachectic mice, suggesting a promising therapeutic approach.

1-21

Naringenin to improve functional and behavioral outcomes by attenuating neuro-inflammation in mice with cancer cachexia.

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Introduction: Cancer cachexia is responsible for over 20% of cancer related deaths. Reduced physical activity and muscular function, and depressive behavior are consequences of cancer cachexia and have been linked to increased IL-1β and neuroinflammation. Naringenin is a phytochemical found in citrus fruits that has anti-inflammatory and anticancer activities and increases locomotor activity and reduces depressive-like behavior in various murine models. We propose to test the hypothesis that naringenin promotes physical activity and muscle function while reducing depressive-like behavior during cancer cachexia by attenuating neuroinflammation.
Methods: Mice (16 male, CD2F1) were implanted with electronic telemetry transmitters to monitor locomotor activity then fed a semi-purified diet supplemented with 2wt% naringenin (NAR) or without (CON). Two weeks later, mice were inoculated with colon-26 adenocarcinoma cells. Prior to inoculation and prior to sacrifice, muscle function was assessed using a grip strength meter, and the Aurora 1300A *in vivo* system to electrically stimulate maximal torque during dorsiflexion. Another cohort of tumor bearing mice will be given a diet with or without naringenin and an IL-1 receptor antagonist or placebo. Behavioral outcomes (sucrose preference, tail-suspension, voluntary wheel running), and protein levels of IL-1β in the brain will be measured.
Results: Tumor bearing (NAR) mice had significantly higher activity counts during the last three light phases before sacrifice (average of 63% higher, P=0.02) and significantly higher forelimb (4.28 vs 3.55gf, P=0.042) and all-limb (10.25 vs 8.76gf, P=0.018) grip strength. Electrically stimulated maximal torque was not significantly different between NAR and CON diet groups.
Conclusions: Tumor bearing (NAR) mice had significantly higher locomotor activity and grip strength, but not electrically stimulated dorsiflexion torque, compared to tumor bearing (CON) mice. The next aim of this study will determine if naringenin attenuates measurements of depressive-like behavior and neuro-inflammation, and if blocking IL-1β signaling reduces depressive-like behavior similar to naringenin.

1-22

Pilot study of urine titin N-fragment in dogs with naturally-occurring cardiac cachexia

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Introduction: Between 48-69% of pet dogs with naturally-occurring heart failure (HF) have muscle loss. Clinically-applicable biomarkers are needed to identify and monitor muscle loss in HF patients. Urine titin N-fragment is a marker of skeletal muscle atrophy in humans and in rodent and dog models of muscular dystrophy. Therefore, it may be a useful biomarker in dogs with naturally-occurring cardiac cachexia.
Methods: Urine was collected from three groups of pet dogs with myxomatous mitral valve disease: 1) HF with muscle loss; 2) HF without muscle loss, and 3) asymptomatic without muscle loss. Urine titin N-fragment was measured using a commercial mouse/rat ELISA that has been validated in dogs (IBL America, Minneapolis, MN). Urine titin N-fragment was normalized to urine creatinine.
Results: Twenty-five dogs were enrolled: HF with muscle loss (n=6), HF without muscle loss (n=10), and asymptomatic disease without muscle loss (n=9). Median age was 13 years (range, 9-15 years) and median weight was 9 kg (range, 3-26 kg). There was a significant difference in urine titin N-fragment/creatinine ratio among the three groups (P=0.007). Dogs with HF-muscle loss had significantly higher levels compared to dogs with asymptomatic disease without muscle loss (P=0.005) and higher levels compared to dogs with HF without muscle loss (P=0.09).
Conclusions: Larger and longitudinal studies are needed to fully evaluate urine titin N-fragment, but this pilot study suggests it may be a useful biomarker for muscle loss in dogs with HF.

2-01

Novel genetic variants in *DRAIC* and *RFX3* confer risk for weight loss in people with chronic obstructive pulmonary disease

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Introduction: Causes of weight loss (WL), as a marker of cachexia, in people with chronic obstructive pulmonary disease (COPD) are poorly understood. Identification of genomic risk variants associated with weight loss could improve understanding of its pathophysiology in COPD by identifying candidate genes for further study.
Methods: We performed whole genome sequencing analyses of significant WL in 17,211 participants with COPD across studies within the Trans-Omics for Precision Medicine (TOPMed) Initiative and the All of Us study. Participants were included if they were 40-85 years of age, had a cigarette smoking history, and had either evidence of spirometric obstruction or a clinical diagnosis code associated with COPD. WL was defined as at least 5% WL that was not regained by study's end or a final body mass index of <20kg/m^2. Both race-stratified and cosmopolitan analyses were performed in TOPMed using GENESIS, and in All of Us using SAIGE. Fixed-effects meta-analyses were performed between cohorts.
Results: In All of Us participants, 4,287 (48%) met our WL criteria. In TOPMed participants, 3,396 participants (40.6%) met our WL criteria. In All of Us, two genetic variants associated with WL in COPD reached genome-wide significance: 1) an intergenic variant (chr3:73345901) between *PPP4R2* and *PDZRN4* in cosmopolitan analyses (OR=0.21, SE = 0.27, p=5.8x10^{-9}, alternate allele fraction(AAF)=0.003) analyses and 2) chr5:45271359 (OR=2.43, SE = 0.16, p=2.0x10^{-8}, AAF=0.037) in Blacks. In meta-analyses, five variants within *DRAIC* significantly associated with WL among Black participants with COPD (lead variant chr15:69571341, exonic, OR=1.37, SE=0.051, p=1.29x10^{-9}, AAF=0.61-0.66). Meta-analysis of results from all study- and race-stratified cohorts identified two significant variants intronic to *RFX3* (chr9:3390983 and chr9:3391066, OR=1.53, SE=0.076, p=1.65x10^{-8}, AAF=0.86-0.99).
Conclusions: We identified multiple novel loci associated with WL in COPD. Further mechanistic study is needed to characterize affected cellular processes and may highlight opportunities for targeted therapeutics.

2-02

A scoping review examining diagnostic criteria for the cardiac cachexia condition

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Introduction: Cardiac cachexia is a complex condition marked by unintentional weight loss, changes in body composition, and disrupted inflammatory processes, impacting individuals with heart failure across various NYHA classes. Despite the existence of multiple definitions, there are no standardized diagnostic criteria to differentiate cardiac cachexia from other forms and to facilitate the recognition and risk assessment of chronic heart failure (CHF). This study explores the clinical definitions of cardiac cachexia (diagnostic criteria) found in the literature and evaluates the respective strengths and weaknesses of each definition.
Methods: A scoping review was conducted following the PRISMA-Sc guidelines. We searched for eligible English-language papers across the literature that reported the use of diagnostic criteria for cardiac cachexia in people with HF through various databases.
Results: Current definitions of cardiac cachexia reveal inaccuracies in diagnostic tools and the inadequacy of certain criteria for identifying heart failure patients with cachexia. Body composition measurements and weight loss cutoffs are neither standardized nor clearly defined for cachectic patients. The inclusion of comorbidities in cardiac cachexia criteria has negatively impacted diagnosis, as ideal body weight (dry weight) is often inaccurately assessed. Additionally, the overlap of biomarkers and cytokines between cardiac cachexia and other conditions complicates the identification of affected patients who are cachectic.
Conclusion: Future efforts are crucial in establishing a new clinical definition for cardiac cachexia, with a clear approach to addressing current weaknesses and strengths to improve prognosis and enhance outcomes for HF patients.

2-03

Hepatic Yap1 activates systemic catabolism and muscle loss during organ repair: evidence for a liver-derived common mechanism with cancer cachexia.

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Introduction: Recovery from critical illness involves a systemic catabolic response, associated with loss of muscle and fat mass. The transcriptional coactivator Yap1 mediates organ repair and organ size. We investigated the role of Yap1 in modulating the catabolic changes associated with liver injury and growth.

Methods: Murine models of partial hepatectomy and hepatocyte inducible Yap1 were examined. Metabolism was assessed using metabolic cages. RNA-sequencing was used to identify gene expression changes. Serum effect was tested on myotubes *in vitro*. Muscle-derived components were labelled and traced in the post-proliferative liver.

Results: Liver growth models induced severe catabolism, including significant body weight loss with approximately 25% and 50% loss of muscle and fat mass respectively. Both liver growth models resulted in elevated resting energy expenditure (REE) with the utilization of a mixed oxidative fuel source based on changes in respiratory quotient. Muscle from Yap1-induced hepatomegaly mice showed elevated branch chain amino acid catabolism and lipid oxidation. Serum from proliferating liver models induced myotube atrophy *in vitro*, suggesting secreted that hepatic factors may regulate muscle and fat loss. Muscle gene expression profiles identified pathway activation similar to those observed in cancer cachexia models. Pathway activation included ubiquitin-proteosome and *Trim63*. Tracer studies detected muscle-derived amino acids and lipids in the regenerating liver.

Conclusions: Liver proliferation induces a systemic catabolism that provides muscle-derived substrates to build the proliferative liver mass. Hepatic Yap1 activation is sufficient to induce this activity. The liver, through Yap1 activation, can directly regulate muscle and fat loss, as well as changing the metabolic state to a mixed oxidative source and elevating REE through secreted serum factors. Our data suggest that liver proliferation induces processes almost identical to those observed in cancer cachexia, suggesting that cancer cachexia may represent the pathological activation of the normal physiologic reparative process.

2-04

Multi-kinase inhibitor Sorafenib triggers cachexia by disrupting the activity of distinct chromatin regulators

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Introduction: Cachexia, a systemic metabolic disorder characterized by irreversible loss of skeletal muscle mass, is triggered by pro-inflammatory cytokines associated with chronic diseases like cancer, and additionally, by chemotherapeutics used in cancer therapy. In this study, we profiled the effects of tyrosine kinase inhibitor (TKI) class of drugs on skeletal muscle physiology.

Methods: We employed mouse satellite cell-derived primary muscle cells and C2C12-derived muscle cells as models to test the effect of TKIs Imatinib, Nilotinib and Sorafenib. We performed confocal microscopy, intracellular calcium transient measurements and mitochondrial functional analyses to characterize muscle cell dysfunction post TKI treatment. We utilized quantitative proteomics and transcriptomics to obtain an unbiased overview on the biological processes affected in TKI-triggered cachexia. Furthermore, we investigated the epigenetic outcomes of TKI-triggered cachexia using chromatin immunoprecipitation.

Results: We report that multi-kinase inhibitor Sorafenib triggers cachexia, characterized by severe loss of motor protein MyHC-IId, sarcomere disarray and phenotypic remodeling of muscle cells. System-wide multi-omics analyses revealed global transcriptional dysregulation and reduced protein synthesis in Sorafenib-treated muscle cells. Sorafenib-triggered cachectic phenotype originated from targeted attenuation of chromatin signalling on muscle-specific genes. Sorafenib obstructed the chromatin recruitment of SET1A histone methyltransferase, resulting in reduced H3K4 trimethylation and a corresponding decrease in chromatin association of transcriptionally active RNA polymerase II, specifically on protein-coding genes of MyHC-IId and sarcoplasmic reticulum calcium re-uptake pump SERCA1. Furthermore, Sorafenib greatly limited the expression of mitochondrial electron transport chain proteins by degradation of transcriptional co-activator PGC1α. Consecutively, impaired sarcoplasmic reticulum-mediated calcium handling, diminished mitochondrial respiration and insufficient ATP production resulted in contractile and metabolic dysfunction in Sorafenib-treated muscle cells.

Conclusion: We outline interconnected cellular pathways of protein homeostasis, energy production, muscle contraction, and the underlying transcriptional processes targeted in Sorafenib-triggered cachexia. Findings from this study would greatly facilitate the development of therapeutic regimens to alleviate muscle wasting.

2-05

Investigating Post-Translational Modifications of NIK Protein in Muscle Atrophy

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Background: The NF-κB-inducing kinase (NIK) is crucial in the noncanonical NF-κB signaling pathway, implicated in muscle atrophy. This study explores NIK's post-translational modifications in primary myotubes treated with EDAA2 ligand, SMI1 (a NIK inhibitor), and their combination. Western blot analysis showed distinct NIK protein band shifts under different treatments. EDAA2 ligand caused a double shift, suggesting phosphorylation. SMI1 treatment resulted in a faint NIK band, indicating NIK inhibition. Co-treatment produced a single, pronounced NIK band, highlighting a complex interplay

between activation and inhibition. Understanding these modifications may uncover therapeutic targets for muscle-wasting diseases.
Methods: Primary myotubes were cultured and treated with EDAA2 ligand, SMI1, and their combination. After treatment, proteins were isolated using RIPA buffer, quantified, separated by SDS-PAGE, transferred to a PVDF membrane, and probed with primary antibodies against NIK. Detection was done using enhanced chemiluminescence (ECL).
Results: EDAA2 ligand treatment led to a double shift in NIK bands, indicating post-translational modifications. SMI1 treatment showed a faint NIK band, suggesting inhibition. Co-treatment resulted in a single, prominent NIK band, indicating NIK accumulation. We tested for interference from other signaling pathways but found no similarities in the blots, leaving the cause of NIK accumulation unknown. One of the shifting bands in EDAA2-treated samples was due to phosphorylation, while the cause of the second shift is unidentified.
Conclusion: Post-translational modifications, particularly phosphorylation, significantly regulate NIK in primary myoblasts. NIK accumulation with combined EDAA2 and SMI1 treatment suggests a complex interplay between the noncanonical NF-κB pathway and other mechanisms. Further investigation is needed to identify the second shifting band and pathways involved in NIK accumulation, potentially offering new insights into muscle atrophy therapies.

2-06
Vincristine induced delayed body weight gain and stunted musculoskeletal growth in pediatric mice

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Introduction: 85% of children diagnosed with cancer are expected to survive their diagnosis. Cancer and chemotherapy contribute to poorer health outcomes. Despite the high survival rate, there is minimal research on the influence of pediatric chemotherapy on musculoskeletal physiology. Given that vincristine is a commonly prescribed chemotherapeutic for the treatment of CNS tumors in pediatric populations, the aim of the current research was to investigate the musculoskeletal consequences associated with vincristine in pediatric mice.
Methods: Vincristine was administered (1.0 mg/kg, 2x weekly, i.p.) to 4-week-old male C57BL/6J mice. Body mass was monitored daily. Vehicle (n=5) and experimental mice (n=8) were culled after 46 days. At time of euthanasia, skeletal muscle mass was assessed, along with *ex vivo* EDL muscle function testing. Changes in trabecular bone mass were measured via micro-CT in formalin-fixed femurs. Molecular abnormalities in skeletal muscle were measured by western blotting and qPCR.
Results: Vincristine-treated mice exhibited a progressively lower body mass (-16%, $p<0.05$) vs. the vehicle-treated animals. Skeletal muscle mass (gastrocnemius: -10%, $p<0.05$; tibialis anterior: -20%, $p<0.05$; quadriceps -19%, $p<0.05$) and e*x vivo* EDL muscle force were decreased in the vincristine-treated mice ($p<0.05$; -26%). The experimental mice displayed evidence of enhanced protein turnover, consistent with increased phosphorylation of $STAT3^{Tyr705}$ ($p<0.05$; 233%) and elevations in MuRF-1 (+499%, $p<0.05$) and MUSA1 (+233%, $p<0.05$) muscle ubiquitin ligase mRNA expression. Lastly, the animals administered chemotherapy exhibited decreased trabecular bone volume (BV/TV: -77%, $p<0.05$) and thickness (Tb.Th: -34%, $p<0.05$).
Conclusions: Our research highlights the impact of vincristine on muscle and bone in pediatric mice. Experimental mice yielded stunted development of skeletal muscle and bone, as evidenced by decreased skeletal muscle mass, increased cell signaling associated with muscle atrophy, and changes in trabecular bone. Future research will focus on the mechanisms responsible for the systemic long-term effects of chemotherapeutics in pediatric patients.

2-07
The LEAP2 response to cancer-related anorexia-cachexia syndrome

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Introduction: The hormone ghrelin serves a protective role in cancer-related anorexia-cachexia syndrome (CACS) – a condition in which plasma levels of ghrelin rise, its administration lessens CACS severity, and experimentally-reduced signaling by its receptor (GHSR) worsens fat loss and anorexia and accelerates death. Yet, actions for the related hormone liver-expressed antimicrobial peptide-2 (LEAP2), which is an endogenous GHSR antagonist and inverse agonist, are unexplored in CACS. Here, we investigated changes to plasma LEAP2 and the impact of LEAP2 in CACS.
Methods: After validating the occurrence of CACS in mice bearing tumors derived from inoculated Lewis lung carcinoma (LLC) and RM-9 prostate cancer cells, measures of CACS were determined in LLC and RM-9 tumor-bearing ghrelin-KO mice + wild-type (WT) littermates and LEAP2-KO mice + WT littermates. Also, plasma LEAP2 and ghrelin levels were determined in the mouse CACS models and in human subjects with cancer cachexia vs. weight-stable cancer vs. non-cancer controls.
Results: Plasma ghrelin was unchanged but plasma LEAP2 and LEAP2/ghrelin ratios were lower by 56.7-55.9% and 79.7-66.7%, respectively in the two CACS mouse models. Compared to WT littermates, ghrelin deletion exaggerated losses of tumor-free body weight and fat mass, reduced food intake, reduced soleus muscle weight, and/or lowered grip strength in LLC and RM-9 tumor-bearing mice. LEAP2 deletion lessened reductions in tumor-free body weight and fat mass and increased food intake in LLC or RM-9 tumor-bearing mice. In a 55-subject cohort of patients with CACS or weight-stable cancer, plasma LEAP2/total ghrelin ratio was negatively correlated with 6-month weight change preceding blood collection.
Conclusions: These data demonstrate that ghrelin deletion exacerbates CACS in LLC and RM-9 tumor-bearing mouse models while contrastingly, LEAP2 deletion reduces measures of CACS in these tumor-bearing mouse models. Further, they suggest that lower plasma LEAP2/ghrelin ratio protects against greater weight loss in patients with cancer.

2-08
KPC pancreatic cancer disrupts the skeletal muscle circadian transcriptome in a FoxP1-dependent manner

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Cancer cachexia is a debilitating metabolic disorder characterized by an involuntary loss of body and muscle mass that contributes to increased morbidity and mortality. We previously found that the

transcriptional repressor protein Forkhead box P1 (FoxP1) is increased in skeletal muscle of mice and humans with pancreatic cancer and is required for cancer-induced muscle wasting in mice. Herein, we expand on these findings and use ChIP-seq to identify direct FoxP1 targets in skeletal muscle of cancer-free mice and mice with KPC pancreatic tumors. Promoter regions bound by FoxP1 were enriched for genes which regulate skeletal muscle proteostasis, including proteasomal, autophagy, and mitophagy genes, as well as core clock genes that direct circadian rhythm. Based on these findings, we further investigated the impact of pancreatic cancer and skeletal muscle-specific FoxP1 knockout ($FoxP1^{SkmKO}$) on the skeletal muscle circadian transcriptome. In wild-type (WT) mice, KPC tumors caused substantial disruption to clock output genes (COGs), with only 30% of COGs showing similarity between muscles from cancer-free and KPC mice. Notably, genes linked to lipid and carbohydrate metabolism lost their rhythmicity, and genes related to muscle atrophy, including those annotating to autophagy, proteasomal, and inflammatory pathways, became rhythmic in response to KPC tumors in WT but not $FoxP1^{SkmKO}$ mice. Pancreatic cancer also altered the temporal distribution of peak gene expression, with COGs shifting from a uniform distribution around 24 hours to clustered peaks at activity offset and onset in WT but not $FoxP1^{SkmKO}$ mice. These findings demonstrate a significant disruption to clock output genes in skeletal muscle of mice with pancreatic tumors that is dependent on FoxP1.

2-09

Mutual de-differentiation of adipocytes and tumor cells in the macroenvironment of pancreatic cancer cachexia

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Introduction: Pancreatic cancer cachexia involves involuntary loss of adipose tissue and skeletal muscle, leading to increased morbidity and mortality in patients and murine models of pancreatic ductal adenocarcinoma (PDAC) cachexia. PDAC induces significant adipose tissue remodeling, altering cellular composition, biological processes, and metabolic pathways to meet the metabolic and inflammatory demands of cachexia. Previous data indicated changes in adipose tissue cell subtypes, underscoring the need to understand the heterogeneity and transcriptional and cellular importance of adipose tissue during cachexia progression. Adipocytes exhibit plasticity, transitioning into adipocyte progenitor cells (APCs) through de-differentiation. The mechanisms behind adipose tissue loss in cancer cachexia, particularly the role of de-differentiation, remain largely unknown. We hypothesize that changes in cellular subtypes and gene expression within the adipose microenvironment promote inflammation, lipolysis, and adipocyte de-differentiation in PDAC cachexia.
Methods: A time-course study using an orthotopic murine model of progressive cachexia examined adipose tissue changes in response to PDAC. 12-week-old male C57BL/6J mice were implanted with $5x10^4$ KPC32098 tumor cells or underwent SHAM surgery. Epididymal white adipose tissue (eWAT) was collected at Day 0, 9, 12, 15, and 18. Single-nucleus RNA sequencing (snRNA-seq) was performed on eWAT on day 12, and bulk RNA sequencing was done over time.
Results: snRNA-seq revealed tumor cells within eWAT, confirmed by bulk sequencing and histology. Adipocytes, APCs/MSCs, and endothelial cells reduced, while macrophages and tumor cells increased in PDAC mice. Adipocytes showed decreased expression of differentiation markers. Bulk RNA-seq data showed decreased expression of lipid storage and adipose-derived stem cells genes. PDAC altered adipocytes' identity, downregulating the TCA cycle and respiratory electron transport. Ex vivo/in vitro coculture of eWAT with KPC32908 cells confirmed these findings. We also observed decreased mitochondrial fatty acid beta-oxidation and adipogenesis pathways, increased inflammation, mRNA metabolism, translation, and DNA replication. Tumor cells within adipose tissue exhibited decreased ductal and acinar markers, while MSCs markers increased, indicating a microenvironment conducive to tumor growth and invasion.
Conclusions: PDAC alters adipose cell composition and identity, with adipocyte mitochondrial dysfunction and subtype-specific de-differentiation as key mechanisms. Visceral WAT acts as a site for tumor micrometastasis, indicating interaction between tumor cells and adipocytes.

2-10

The role of tumor specific IGFBP-3 in the onset and progression of skeletal muscle wasting in murine models of pancreatic cancer

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Introduction: Pancreatic ductal adenocarcinoma (PDAC) is highly associated with skeletal muscle wasting (SMW). Findings from our lab in a non-metastatic model of PDAC, implicate Insulin-like Growth Factor Binding Protein-3 (IGFBP-3) as an inducer of TGF-β dependent ubiquitin proteasome pathway (UPP) activation and autophagy, and inhibitor of IGF-1 dependent anabolism. Here we test the hypothesis that IGFBP-3 regulates PDAC-induced SMW in a more clinically relevant, metastatic murine model.
Methods: C57BL/6J female mice (6-8 weeks) were randomized to one of three groups: 1) no tumor control (NTC) (n=10), 2) KP2-Luc parental murine tumor cells (n=10), or 3) IGFBP-$3^{-/-}$ KP2-Luc (n=10). Tumor cells were injected orthotopically. Lean mass was assessed longitudinally via dual energy x-ray absorptiometry (DEXA). Quadricep muscles were collected for protein and transcriptional analysis. Tibialis Anterior (TA) muscles were collected for histology and stained with Oil Red O (ORO) to highlight intramuscular lipids.
Results: KP2 mice experience significantly reduced survival ($T_{1/2}$=46 days) compared to IGFBP-$3^{-/-}$ mice that maintained 60% survival at day 90 ($p<0.0001$). IGFBP-$3^{-/-}$ mice lost significantly less lean mass from baseline to day 46 compared to KP2 mice ($p<0.0001$). Transcriptionally, KP2 mice displayed increased expression of *igfbp3, tgfbr1,* and UPP associated genes *fbxo32,* and *trim63* compared to NTC and IGFBP-$3^{-/-}$ mice. We also found the ratio of pFoxO1 (Ser253) to total protein levels were significantly reduced in KP2 mice ($p<0.05$ vs IGFBP-$3^{-/-}$) while no differences were seen in pAkt (Ser473) and pS6 (Ser235/236) expression. Additionally, expression of ULK1 and the ratio of LC3b II over LC3b I, markers of autophagy, are elevated in KP2 mice compared to NTC and IGFBP-$3^{-/-}$ mice ($p<0.05$) and correlate with increased ORO staining, a potential biomarker of autophagy.
Conclusions: These findings suggest that in metastatic models, tumor derived IGFBP-3 potentiates PDAC-related SMW via upregulating the UPP and autophagy, and not through inhibiting protein synthesis.

2-11

Attenuation of skeletal muscle lipid hydroperoxides is sufficient to restore skeletal muscle atrophy and weakness associated with cancer cachexia in mice

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Introduction: Cachexia is a devastating wasting condition known to affect over 50% of individuals with cancer with no effective therapy. Reactive oxygen species (ROS) are known to contribute to the development of cancer cachexia, yet downstream mechanisms of ROS-induced atrophy due to cachexia are largely unknown. Here, we provide preliminary evidence for the role of lipid hydroperoxides (LOOH) in cancer cachexia-mediated muscle wasting, using a xenograft mouse model combined with genome editing or nutraceutical treatments.

Methods: Mice with skeletal muscle-specific deletion of lysophosphatidylcholine acyltransferase 3 (LPCAT3-MKO), transgenic mice overexpressing glutathione peroxidase 4 (GPx4Tg), and mice treated with the LOOH-scavenger N-acetylcarnosine (NACar) were subcutaneously injected with $1x10^6$ Lewis Lung Carcinoma (LLC) cells. These models allowed us to investigate the potential effect of LOOH-neutralization on muscle weakness and atrophy with cachexia. Muscle mass and force-generating capacity were assessed at 3-week post-LLC cells injection. LOOH was assessed by quantifying malondialdehyde (MDA)-protein adducts.

Results: Injection of LLC resulted in a significant decrease in skeletal muscle mass and strength, which was associated with an increase in MDA-protein adducts. However, GPx4Tg, LPCAT3-MKO, and NACar-treated mice were significantly protected from muscle atrophy and weakness, with GPx4Tg and LPCAT3-MKO mice showing attenuated accumulation of MDA-protein adducts in muscle.

Conclusions: We provide evidence that LOOH contributes to the loss of muscle mass and force associated with cancer cachexia. The attenuation of muscle LOOH accumulation is sufficient to restore muscle function, highlighting a potential therapeutic target for preventing muscle.

3-01

The art of war: blocking the secretion of pro-cachectic factors from cachexia inducing cancer cells

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Introduction: Cachexia, characterized by progressive wasting of muscle and fat, is a major cause of mortality in cancer patient, but clinical options against cachexia remain limited due to the multifactorial nature of the disease. Several seminal studies demonstrated that tumour-cell released small extracellular vesicles (sEVs) containing key cachexins are necessary and sufficient to induce muscle and fat loss. Furthermore, it is now well known that cancer cells secrete more sEVs compared to non-cancerous cells. Hence, we examined whether decreasing the secretion of sEVs from tumour cells can inhibit cancer-induced cachexia.

Methodology: Cortactin (Cttn) was knocked-out (KO) using CRISPR/Cas9 technology in colon cancer cells and sEVs were isolated and quantified. Co-culture and pre-clinical studies were carried out to study the cachectic phenotype. Fluorescence-based high-throughput screening assay was performed to identify the drugs that decreases sEVs secretion.

Results: Loss of Cttn inhibited the release of sEVs. While C26 wild-type (WT) derived sEVs induced atrophy in myotubes and lipolysis in adipocytes, Cttn-KO sEVs did not induce atrophy or lipolysis. Proteomics analysis of sEVs highlighted the enrichment of cachectic proteins in WT-sEVs compared to KO-sEVs. Follow-up C26 pre-clinical studies highlighted that Cttn-KO tumour-bearing mice exhibited stable body weight, reduced tumour burden, and dramatically extended lifespan compared to mice bearing WT tumour. Remarkably, Cttn-KO prevented tumour-induced muscle, and fat loss. To use these findings for therapeutic benefit, we screened the library of FDA-approved drugs and identified several drugs that blocks the release of sEVs. Administration of sEVs inhibitor to the cachexic mice resulted in the abolishment of cancer-associated cachexia and prolonged survival.

Conclusion: Overall, these findings indicate that decreasing sEVs release from tumour might be a promising approach to treat cancer-cachexia, improve quality-of-life, and extend the lifespan of cancer patients.

3-02

Reassessing the role of progenitor cells in tumor-associated muscle wasting

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Introduction: Skeletal muscles contain myogenic and non-myogenic progenitor cells that proliferate and differentiate after tissue damage to restore myofiber, connective tissue, and blood vessel homeostasis. We previously showed that cancer-induced muscle wasting involves myofiber damage and impaired differentiation of myogenic progenitors, which coincided with aberrant accumulation of interstitial cells expressing both myogenic (*Pax7*) and non-myogenic (*Ly6a* & *Pdgfra*) progenitor cell markers. Here, utilizing scRNA-sequencing and Pax7-tdTomato reporter mice, we reassessed the fate of non-myogenic progenitor cells during cancer cachexia.

Methods: PBS (control) or $1x10^6$ Colon-26 carcinoma cells (C-26) were subcutaneously injected into the right flank of 12-week-old Pax7-CreER; Rosa26-LSL-Tdtomato mice (n=2/condition). Tamoxifen (1mg/10g b.w.) was administered by I.P. injection at days 12-17 post-PBS/C-26 injection to activate CreER and turn on tdTomato expression in $Pax7^+$ cells. After onset of cachexia (day 21), hindlimb muscles were harvested and digested to isolate resident mononuclear cells for scRNA-seq (10x Genomics). Transcriptomes from 16,427 (control) and 11,528 (C-26) cells were sequenced and integrated to identify cell types and their gene expression.

Results: Approximately 12 distinct mononuclear cell types were identified in both normal and cachectic muscles. Consistent with previous findings of muscle damage and inflammation during cancer cachexia, muscles from C-26 tumor-bearing mice had greater relative abundances of neutrophils (*Cxcr2*$^+$, *Retnlg*$^+$, *Mmp9*$^+$; +3.5-fold), monocytes/macrophages (*Adgre1*$^+$, *Mrc1*$^+$, *Itgam*$^+$; +1.35-fold), and inflammatory gene expression across multiple cell populations. However, in both control and C-26 muscles, *Pax7* and *tdTomato* transcripts were detected exclusively in myogenic progenitor cells, whereas *Ly6a* and *Pdgfra* transcripts were detected exclusively in non-myogenic progenitor cells such as FAPs (*Pdgfra*$^+$, *Fbn1*$^+$) or pericytes (*Cdh5*$^+$, *Pdgfrβ*$^+$). Validation of these findings by flow cytometry is currently underway.

Conclusions: These data suggest that non-myogenic progenitor cells do not express Pax7 and adopt a myogenic fate, which is therefore unlikely to contribute to impaired myogenesis, during cancer cachexia.

3-03

Improved immune response and energy metabolism in the C26 tumor-bearing mice exposed to IL4

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Introduction: Cancer cachexia is a multifactorial syndrome characterized by body weight loss and skeletal muscle wasting. Multiple mechanisms are involved, including mitochondrial abnormalities, energy metabolism alterations and systemic inflammation. Previous observations showed that interleukin-4 (IL4) administration to tumor-bearing (TB) mice resulted in improved muscle fitness, myogenesis and survival. Along this line, the present study was aimed to investigate whether IL4 administration improves skeletal muscle energy metabolism and the immune response in cancer hosts.
Methods: Ten-weeks-old Balb/c male mice were inoculated with 5 x 10^5 C26 colon carcinoma cells. Daily IL4 treatment (66.5 μg/kg) was performed by intraperitoneal injection. The gastrocnemius muscle was used to assess mitochondrial proteins (western blot) and respiration (high-resolution respirometry, Oroboros Instruments). Liver and gastrocnemius muscle were used to perform mass spectrometry based metabolomic analyses. Immunophenotype analysis on isolated splenocytes was performed by fluorescence-activated cell sorting.
Results: Treatment with IL4 counteracted the loss of body weight, muscle mass and muscle strength in TB mice, while further increased splenomegaly. The protein levels of the oxidative phosphorylation (OXPHOS) complexes II and III, cytochrome c and PGC-1α in the skeletal muscle were significantly increased in treated vs untreated TB mice. Consistently, the activity of OXPHOS complex II was improved in the C26 hosts administered IL4. Tumor and IL4-dependent modulations in both liver and skeletal muscle metabolomic profiles were observed. Myeloid-derived suppressor cells and regulatory T cells were significantly under-represented in the spleen of IL4-treated C26 hosts as compared to untreated mice.
Conclusions: Treatment with IL4 improves energy metabolism in the skeletal muscle of TB mice, possibly reflecting exercise-mimetic properties. The possibility that such beneficial action could be associated to the improved immune response, which is suggested by the reduced amounts of immunosuppressive cells in the spleen, remains to be investigated.

3-04

Temporal examination identifies features in cachexia etiology with sex-based heterogeneity

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Introduction: Due to the complexity of cancer cachexia, elucidating the mechanisms that drive the pathology has proven challenging. Heterogeneity among people with cachexia, including sex-specific differences, is implicated in the pathology but is poorly understood, complicating management and treatment. This study sought to examine motor unit perturbations as an emerging but contentious aspect of cachexia etiology.
Methods: To model cancer cachexia, male and female mice were implanted with colon-26 (C26) tumour fragments, and analysed at: 1. tumour palpation (pre-cachectic), 2. 10% body mass loss (mild cachexia), and 3. 25% body mass loss (severe cachexia). Analyses included: changes in body composition (via NMR-MRI), motor unit function (via electromyography) and muscle function (via grip strength assessment). Assessment of muscles included morphological parameters of neuromuscular junction and motor nerve architecture (via microscopy with computational re-construction).
Results: Features of cachexia, including loss of lean and fat mass, and grip strength, were observed at earlier timepoints in male mice than females. Motor unit dysfunction was observed early in males, and preceding muscle atrophy in both sexes. Males exhibited striking alterations of synaptic structures at the pre-cachectic timepoint; which were associated with a signature of inflammatory factors. Subsequent *in vivo* studies demonstrated that the inflammatory signature can drive the observed synaptic pathologies, and can be targeted to ameliorate disease features at least in part.
Conclusion: Our findings highlight notable sex-specific heterogeneity in the cachectic onset suggesting early protective qualities in females. Furthermore, neurological perturbations preceded muscle wasting, implicating the neuromuscular axis as a potential disease driver. The observed defects and associated mechanisms suggest disease events that may present opportunities for improved personalized diagnostic and/or therapeutic strategies.

3-05

The dynamic role of cardiac-infiltrating neutrophils in pancreatic cancer-induced cardiac dysfunction

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Introduction: Cardiac wasting and dysfunction are common consequences of cancer cachexia. Usually associated with cardiotoxic chemotherapies, cardiac damage is also present in chemotherapy-naïve cancer patients, implicating cancer itself as a contributing factor. However, the mechanisms by which cancer impairs cardiac function are unknown.
Methods: We modeled pancreatic ductal adenocarcinoma (PDAC)-induced cardiac dysfunction via orthotopic implantation of syngeneic pancreatic cancer cells derived from the genetically engineered KPC mouse (*Kras$^{G12D/+}$; Tp53$^{R172H/+}$; Pdx1-Cre*) in the pancreata of WT C57BL/6J mice. Neutrophils were depleted using both antibody-based and chemogenetic approaches. Cardiac wasting and damage were assessed via heart mass, echocardiography, and plasma troponin-I, creatine kinase-MB, and galectin-3. Immune infiltration was measured using flow cytometry, and cardiac gene expression was assessed by qPCR and bulk RNA sequencing.
Results: PDAC induced loss of heart mass compared to sham-operated controls, and echocardiographic analysis revealed left ventricular wall thinning, and decreased left ventricular mass and volume in tumor-bearing mice. RNA sequencing showed enrichment of inflammatory pathways in the hearts of PDAC mice, which was associated with infiltration of CD244-positive neutrophils into the myocardium. This neutrophil influx was accompanied by significant elevation in biomarkers of cardiac damage, including Troponin-I, Galectin-3, and creatine kinase-MB. Neutrophil depletion in tumor-bearing animals failed to mitigate cardiac wasting or the elevation in cardiac biomarkers. Neutrophil depletion in non-tumor-bearing mice significantly elevated cardiac biomarkers and elicited a pronounced sickness response.
Conclusions: Neutrophils infiltrate the myocardium of PDAC-mice but do not mediate wasting or cardiac damage. Our data identify a baseline cardioprotective role for neutrophils in healthy animals.

3-06

Myofiber-specific FoxP1 deletion protects against pancreatic cancer-induced muscle atrophy and weakness

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Cancer-induced skeletal muscle wasting affects up to 80% of cancer patients and is associated with reduced quality of life and survival. We previously identified the transcriptional repressor, Forkhead box P1 (FoxP1), as a downstream target gene of FoxO1 whose skeletal muscle expression is elevated in several mouse models of cancer cachexia as well as in cachectic cancer patients. Our results showed that FoxP1 upregulation in muscle is sufficient to induce pathological features of cancer cachexia, such as muscle wasting and weakness. In the current study, using skeletal muscle-specific FoxP1 knockout (*FoxP1*^{SkmKO}) mice, we demonstrate that the absence of FoxP1 is protective against muscle tissue wasting and myofiber atrophy in an orthotopic model of pancreatic cancer. Further, FoxP1^{SkmKO} prevented pancreatic cancer-induced diaphragm weakness, as measured by ex-vivo muscle function assessment. RNA-sequencing data revealed that tumor-free FoxP1^{SkmKO} have reduced expression of several atrophy-related genes, including myostatin, *Fbxo32*/atrogin-1, *Trim63*/MuRF1 and *Eif4ebp1*, compared to wild-type mice. In tumor-bearing mice, FoxP1 deletion attenuated the cancer-induced dysregulation of genes annotating to pathways such as *regulation of cellular protein catabolic process*, *regulation of proteolysis* and *ubiquitin transferase regulator activity*. In summary, these data support that myofiber FoxP1 is a negative regulator of muscle mass that mediates pancreatic cancer-induced atrophy.

3-07

A dual target PERPetrator in pancreatic cancer and cachexia

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Introduction: Cancer cachexia is a multifactorial syndrome entailing muscle and fat wasting, inflammation, and metabolic dysfunction. Pancreatic cancer has the highest incidence of cachexia at around 80%. However, there are no FDA approved therapy for cachexia in the clinic yet. One of the reasons is the failure of preclinical therapies to demonstrate success in the clinic. Most preclinical studies utilize 6-8 weeks old mice which roughly corresponds to a human age of ~ 20 years. However, the median age of diagnosis of pancreatic cancer is ~70 years.

Methods: Given widespread physiology, microenvironment, and metabolism differences in young and aged skeletal muscle, we sought to study cancer cachexia in mice aged at 78 weeks, which corresponds to a human age of approximately 60 years. Our previously published study reported little difference in tumor growth or survival between the two cohorts, yet significant alterations in the muscle transcriptome.

Results: Transcriptomic analysis of the aged and the young cohorts led us to discover Perp, a p53/p63 target gene, as a novel tumor promoter and a target in cachectic muscles. TCGA analysis demonstrated pancreatic cancer patients with increased expression of Perp having a significant survival disadvantage. Downstream analysis showed novel functions and previously unreported localization of Perp in the pancreatic tumor. Moreover. Perp was increased prior to the induction of atrophy genes in cachectic muscles and inhibiting it by novel small molecule compounds rescued atrophy.

Conclusion: Together, we present Perp as dual target in pancreatic cancer and cachexia and a therapeutic avenue that may have been overlooked if not for the use of a more age-appropriate model of pancreatic cancer.

3-08

Interleukin 6 induces complex and dose-dependent response to pancreatic cancer

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Introduction: We, and others, recently showed that interleukin 6 (IL-6) signals in the liver to disrupt hepatic metabolism in pancreatic ductal adenocarcinoma (PDAC) cachexia. Here we investigate how tumor location and levels of secreted IL-6 impact PDAC T-cell infiltration and cachexia development.

Methods: We induced murine PDAC by injecting, orthotopically into the pancreas, the PDAC cell line *Kras*^{G12D}*; p53*$^{R172H/+}$*; Pdx1-cre* (OT-PDAC^{parental}), which does not produce IL-6. We also implanted genetically-engineered cells that overexpress IL-6 (OT-PDAC^{IL6}). We modulated these conditions by implanting PDAC cells into wild type or whole-body *Il6*$^{-/-}$ and by injecting cells subcutaneously.

Results: While *Il6*$^{-/-}$ mice are resistant to OT-PDAC^{parental} cachexia, we found that OT-PDAC^{IL6} in *Il6*$^{-/-}$ mice caused severe body mass loss, upregulation of muscle wasting genes, and impaired hepatic metabolism. At 5 days post-implantation, OT-PDAC^{IL6} tumors produced 100-fold higher IL-6 levels than OT-PDAC^{parental}, while remaining histologically similar. However, by 10 days post implantation, OT-PDAC^{IL6} tumors were undetectable by histology or qPCR, despite evident muscle wasting. By flow cytometry analysis, the OT-PDAC^{IL6} tumor microenvironment exhibited increased tumor-infiltrating T-cells and natural killer cells, and decreased T-regulatory cells. While OT-PDAC^{parental} mortality was 100% at day 13, OT-PDAC^{IL6} and sham mouse survival were equivalent (87.5%) at 76 days post-implantation. CD4/CD8 T-cell depletion prevented tumor clearance. Hepatic metabolism and muscle mass recovery slowy after tumor clearance. When implanted subcutaneously, PDAC^{IL6} tumors produce high levels of IL-6 prior to being immunologically cleared. Neither subcutaneous PDAC^{parental} or subcutaneous PDAC^{IL6} induce cachexia.

Conclusions: This work defined a careful interplay of tumor site and IL-6 production. OT-PDAC^{parental} stimulates IL-6 production that is sufficient to induce cachexia and hepatic dysfunction. Conversely, 100-fold tumor IL-6 overexpresion resulted in both cachexia and a durable tumor clearnce through an anti-tumor T-cell response. While the immune response occurred regardless of implantation site, orthotopic tumors were necessary to induce cachexia.

3-09

Tumor-derived CTGF drives PDAC-induced cancer cachexia

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Introduction: Cancer-associated cachexia is a multifactorial syndrome characterized by the involuntary loss of body and skeletal muscle mass (with or without fat loss) that increases resistance to cancer treatments, decreases muscle function and quality of life, and is a strong predictor of reduced survival. However, there are currently no approved targeted therapies for these individuals, highlighting a major gap in the field. In recent work, we analyzed serum from patients with pancreatic ductal adenocarcinoma (PDAC), and identified high levels of Connective Tissue Growth Factor (CCN2/CTGF). CTGF significantly correlates with indices of cachexia such as skeletal muscle depletion and myosteatosis, thereby linking CTGF with key cachexia phenotypes. CTGF is a multifunctional, matricellular protein which functions in extracellular remodeling during chronic pathological insults. In mouse models of cachexia, we have found that Ctgf is upregulated in tumors at time points prior to muscle wasting, indicating CTGF production by murine PDAC tumors is also linked with cachexia.
Methods: To test the role of CTGF in mediating cancer cachexia we systemically neutralized CTGF through treatment with the anti-CTGF antibody (FG-3019) in two different mouse models of pancreatic cancer cachexia, the PANC-1 xenograft model and the orthotopic KPC model. To complement these findings, we implanted the pancreas of mice with tumor fragments derived from WT PANC-1 cells or PANC-1 cells genetically deleted for CTGF, and further analyzed the tumor cell secretome, *in vitro*.
Results: We found that systemic and genetic targeting of CTGF blocked pancreatic tumors from secreting key circulating mediators of cachexia, including IL6, TNFα, and IL1β, and inhibited key measures of cachexia, including body weight loss and wasting of muscle and fat.
Conclusions: These data therefore identify CTGF as a novel, therapeutically targetable modulator of PDAC-associated cachexia, whose production from pancreatic cancer cells may drive cachexia through promoting the secretion of cachexia-associated cytokines.

3-10

Therapeutic targeting of mitochondrial permeability transition in a mouse model of pancreatic cancer cachexia

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Introduction: Mitochondrial alterations are well-known in cancer cachexia, but how they relate to the muscle pathology remains unclear. Our recent studies highlight an event known as mitochondrial permeability transition (mPT) as a mechanism that can generate muscle phenotypes that are seen in cancer cachexia, including atrophy and mitochondrial respiratory dysfunction. Whether mPT may be involved in muscle pathology with cancer cachexia is untreated.
Methods: To test whether mPT is involved in cancer cachexia, we incubated muscle fiber bundles in tumor conditioned media (TCM) and assessed the Ca^{2+} threshold for mPT. To examine this *in vivo*, male C57BL6 mice received subcutaneous injections of pancreatic cancer (KPC) cells in each flank and muscle fiber bundles were assessed for the Ca^{2+} threshold for mPT. To test whether targeting the mPT-promoting protein Cyclophilin D (CypD) confers protection to skeletal muscle in a mouse model of pancreatic cancer cachexia, we generated mice with inducible skeletal muscle knockout of the gene encoding the mPT-promoting protein cyclophilin D (CypD; mkoPPIF). We inoculated male mkoPPIF and $PPIF^{fl/fl}$ littermates in each flank with KPC cells. At sacrifice (28-35 d post-inoculation), hindlimb muscles were weighed and assessed for mitochondrial respiration.
Results: TCM reduced the Ca^{2+} threshold for mPT and this was prevented by an inhibitor that targeted CypD. Similarly, tumor-bearing mice had a reduced Ca^{2+} threshold for mPT compared to non-tumor-bearing mice, suggesting that there is a higher probability of mPT in skeletal muscle with cancer cachexia. Consistent with this idea, hindlimb muscles from tumor-bearing mkoPPIF mice were larger (p=0.007) and had a higher maximal mitochondrial respiratory capacity (p=0.0006) than those from tumor-bearing $PPIF^{fl/fl}$ mice.
Conclusions: Our data suggests there is a higher probability of mPT in skeletal muscle with pancreatic cancer cachexia and that genetic knockout of the mPT-promoting protein CypD can provide some protection to skeletal muscle.

3-11

Flux studies of energy metabolism in cancer cachexia

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Background: Cancer cachexia is a metabolic wasting syndrome that reduces the survival and quality of life in cancer patients. Despite its impact, limited understanding exists for the metabolic mechanisms involved, making cachexia a significant unresolved challenge. In particular, the underlying alterations of systemic nutrient utilization in cancer cachexia remain largely unknown.
Method: To determine the alterations in systemic nutrient utilization in cancer cachexia, we systematically quantified fluxes of energy metabolism in the C26 cancer cachexia model using in vivo isotope tracing approaches. To control for metabolic effects from tumor growth, in addition to the cachectic C26 (cxC26) group, we also used a non-cachectic (ncxC26) group. To isolate cachexia-specific metabolic changes independent of reduced food intake, both cxC26 and ncxC26 mice were fed an equal, gradually reduced amount of food, based on the daily intake of cxC26 mice. Both groups were infused with 13C tracers for 8 major energy nutrients to determine their circulatory turnover fluxes and their contribution to the TCA cycle in host tissues.
Results: The cxC26 mice exhibited higher circulatory turnover flux of glucose, alanine, and glutamine than the food intake-controlled ncxC26 mice, which had lower glucose, alanine, and glutamine circulatory turnover flux than the ad libitum ncxC26 mice. In contrast, there were no significant changes in the circulatory turnover of lactate, valine, glycerol, palmitate, and 3-hydroxybutyrate in the cxC26 mice. Additionally, in the cxC26 mice, there was an increased preference for glucose as a fuel source in tumor and brain, and for glutamine in the spleen and kidney, compared to the ncxC26 TB mice under reduced food intake.
Conclusions: In this study, we identified that the unrelenting nutrient depletion by host tissues and tumors represents a maladaptation to limited food intake resulting from anorexia in cancer cachexia.

3-12

Hsp70/90-carrying EVs potentiate muscle wasting during chemotherapy-induced cancer cachexia

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Introduction: Cancer cachexia is a wasting syndrome characterized by weight loss and muscle wasting, which is a major determinant of cancer mortality. Chemotherapy is commonly

employed as a therapeutic approach to treat cancer. However, it often triggers or exacerbates cachexia. This study investigated how chemotherapy drugs, 5-Fluorouracil (5-FU) and Cisplatin (CDDP), stimulate muscle wasting in tumor-bearing mice.
Methods: We conducted in vitro and in vivo experiments to elucidate the mechanisms through which 5-FU and CDDP treatment impact muscle wasting in the murine KPC pancreatic adenocarcinoma model. **Results:** Our results revealed that pre-treating KPC cells with 5-FU and CDDP at therapeutic concentrations increased their capacity to induce myotube catabolism, and their therapeutic doses exacerbated muscle wasting in KPC tumor-bearing mice. Additionally, the drugs significantly increased the release of heat shock protein Hsp70/90-containing EVs from KPC cells, resulting in elevated circulating Hsp70/90 while reducing tumor growth. Increased release of Hsp70/90-containing EV is caused by the upregulation of Rab27a/b, which controls EV release. Further, 5-FU and CDDP activate NF-κB p65 to upregulate Rab27a/b in KPC cells. Furthermore, blocking EV release through the ablation of Rab27a/b effectively suppressed 5-FU and CDDP-stimulated muscle wasting measured by body weight, muscle mass and function, catabolic markers, and physical activity.
Conclusions: our findings reveal a novel mechanism of chemotherapy-stimulated muscle wasting, which can be targeted for therapeutic intervention to improve chemotherapy outcomes.

3-13
Deciphering C/EBPβ-Mediated Tumor Effects on Cachexia and Its Modulation

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Cancer is one of the leading causes of death in Canada, claiming 80,000 lives annually. Approximately 30% of these deaths are not due to tumour burden but rather cancer cachexia, a multifactorial paraneoplastic syndrome that affects most patients with advanced cancers.
Our lab has previously established that C/EBPβ expression in the tumour is a critical factor in promoting muscle atrophy. To deepen our understanding of C/EBPβ's role, we are investigating its function within the tumour microenvironment, focusing on how its expression modulates tumour biology and contributes to muscle atrophy in cancer cachexia.
Methods: We performed RNA sequencing on genetically modified Lewis lung carcinoma (LLC) cell lines, including LLC with C/EBPβ knockout (LLC C/EBPβ KO) and LLC with C/EBPβ over-expression (LLC C/EBPβ OE), to identify transcriptional changes within the tumour associated with cachexia. To further complement our analysis, a focused high-throughput drug screen was conducted on LLC cells to assess the impact of pharmacological modulation of C/EBPβ expression.
Results: The analysis elucidated mechanisms within the tumour contributing to cachexia, identifying key genes in pathways related to systemic inflammation and muscle atrophy. A high-throughput drug screen revealed that while some compounds down-regulated C/EBPβ expression, approximately 38% of the tested drugs—including anti-neoplastics, statins, anti-hypertensives, and glucocorticoids—up-regulated C/EBPβ expression. This suggests that commonly prescribed medications may have unintended effects on C/EBPβ expression, potentially influencing the progression of cancer cachexia.
Conclusion: These findings advance our understanding of C/EBPβ's role in the tumour microenvironment and its contribution to cancer cachexia. The identification of key pathways and potential pharmacological modulators of C/EBPβ opens new avenues for targeted therapy in the treatment of both cancer and cachexia.

3-14
Male sex, overweight/obesity, low IL-4 and other biomarkers of cachexia in BIOPAC patients with pancreatic adenocarcinoma

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Introduction: We sought biomarkers for cachexia in patients with newly diagnosed pancreatic adenocarcinoma (PDAC).
Methods: BIOPAC is a Danish prospective data/biorepository of patients with pancreatic cancer (NCT03311776). We assessed variables associated with cachexia (defined as weight loss ≥5% *or* weight loss ≥2% with BMI≤20) in 1,757 patients enrolled from 2008-2022.
Results: Cachexia was significantly associated with male sex (OR 1.45 [1.15-1.85]), habitual weight corresponding to overweight BMI category (OR 1.61 [1.24-2.09] or obese BMI category (OR 2.65 [1.86-383]), disease stage 3 or 4 (OR 1.48 [1.13-1.94]), diabetes (OR 1.39 [1.05-1.85]), and current smoking status (OR 1.88 [1.37-2.61]). Logistic regression of cachexia versus plasma biomarkers in a subset with available data (*n*= 430) demonstrated IL-4 levels as significantly associated with cachexia in the presence of the above covariates (OR 0.71 [0.56-0.88]). Cox proportional hazards regression analysis of patients with available survival data (*n*=1585) showed differences in overall survival by cachexia status; however, differences were not significant when stratified by disease stage (cachexia HR 1.08 [0.96-1.22]). Univariable analysis for biomarkers of cachexia in patients with Stage 1,2 disease revealed increased thrombocytes and increased plasma CCL23, CCL7/MCP3, CXCL1, IL-21, IL-6, and LAP-TGFB, along with reduced FAS ligand, while cachexia in Stage 3,4 disease associated to increased TRAIL and decreased TNFSF14 (unadjusted p<0.05). Males with cachexia showed poorer overall survival than males without cachexia (p=0.044). Men also showed poorer overall survival versus women (P=0.019).
Conclusions: This large cohort study reproduces earlier observations on enhanced PDAC cachexia severity and mortality in men and newly establishes overweight/obesity as risk factors for cachexia, independent of diabetes. The inverse association between plasma IL-4 levels and cachexia aligns with rescue of muscle wasting in cachexic mice by IL-4 therapy. Future studies will validate biomarkers in an independent cohort and investigate factors and mechanisms contributing to cachexia in PDAC.

3-15
Tumour-induced alterations in single-nucleus transcriptome of atrophying muscles indicate enhanced protein degradation and reduced oxidative metabolism

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Background: Tumor-induced skeletal muscle wasting, a key feature of cancer cachexia, has significant implications for patient survival. The associated loss of muscle mass presents a major clinical challenge, linked to reduced chemotherapy tolerance and increased frailty. Understanding the molecular mechanisms of muscle atrophy is crucial for developing new treatments.
Methods: Lewis lung carcinoma tumors were utilized to induce cachexia and muscle atrophy in mice. Single-nucleus libraries of the tibialis anterior (TA) muscle from tumor-bearing mice and their non-tumor-bearing controls were constructed using 10X Genomics applications following the manufacturer's guidelines. RNA sequencing results were analyzed with CellRanger software and

Seurat R package. Mitochondrial oxygen consumption in TA muscle was measured using an Oroboros O2k-FluoRespirometer. Mouse primary myotubes were treated with a recombinant Ectodysplasin-A2 (EDA-A2) protein to activate EDA-A2 receptor (EDA2R) signaling and study changes in gene expression and oxygen consumption.
Results: Tumor-bearing mice were sacrificed while exhibiting moderate cachexia. Average TA muscle weight was reduced by 11% in these mice. A total number of 12335 nuclei, comprising 6422 nuclei from the control group and 5892 nuclei from atrophying muscles were studied. The analysis of single-nucleus transcriptomes identified distinct myonuclear gene signatures and a shift towards type IIb myonuclei. Muscle atrophy-related genes, including *Atrogin1*, *MuRF1* and *Eda2r* were upregulated in these myonuclei, emphasizing their crucial roles in muscle wasting. Gene set enrichment analysis demonstrated that EDA2R activation and tumor inoculation led to similar expression patterns in muscle cells including the stimulation of NFκB, JAK-STAT and TGFβ pathways and the suppression of myogenesis and oxidative phosphorylation. Muscle oxidative metabolism was suppressed by both tumors and EDA2R activation.
Conclusions: This study provides single-nucleus resolution insights into tumor-induced transcriptional changes in muscle tissue, highlighting the detrimental effects on oxidative metabolism. These findings advance the understanding of the molecular mechanisms driving muscle wasting in cancer cachexia.

3-16
Cachexia in hospitalized patients with chronic disease and outcome:
a national database analysis

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Background: Cachexia remains frequent in patients with chronic diseases and is associated poor performance and outcome. The International Classification of Diseases (ICD) has codes for cachexia but information about use in clinical practice as well as association with outcome is scarce. In this study, we aimed to investigate prevalence of cachexia coding in hospitalized patients with chronic diseases and their outcome.
Methods: This was a retrospective analysis of the National Hospital Health Care Statistics Database using the 10th revision of the ICD codes. In timeframe 2004 – 2019, cachexia codes (R64, C80.9 and B22.2) were linked with codes of cancer, chronic heart failure, chronic obstructive pulmonary disease and chronic kidney disease. The primary endpoint the discharge code of cachexia; secondary endpoints were length of hospital stay, in-hospital and post discharge all-cause mortality.
Results: Over 16 years, 5.484.103 hospitalisations were screened; cachexia was coded 19,348 times (0.35%) in 14089 patients (67±13 yo, 42% women). From 2004 to 2019, prevalence of cachexia increased steadily from 1.2% to 1.9%, which was most prominent for cancer and COPD. At one year post discharge, 49% patients with cachexia were dead as compared to 26% in patients without cachexia. In Cox multivariate analysis, cachexia predicted post-discharge death in any of chronic diseases (hazard ratio of 1.28 in heart failure to 1.47 in chronic kidney disease).
Conclusions: In our report from a national hospitalisation database we found that ICD-10 coded cachexia at discharge was rare in patients with chronic disease. When diagnosed, it was associated with higher hazard of post discharge mortality.

3-17
Sex-specific aberrant myelopoiesis and its role in cancer cachexia initiation

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Background: Male cancer patients are 30% more likely to develop cachexia compared to female patients; however, the underlying etiology remains unknown. Myelopoiesis in the bone marrow induces systemic and skeletal muscle inflammation in individuals with cancer cachexia which contributes to muscle atrophy and lipolysis. It remains unknown; however, the extent to which differences in myelopoiesis during cancer cachexia initiation contributes to the sex-based differences in cachexia incidences. Thus, we aimed to identify sex-based differences in myelopoiesis during cancer cachexia initiation.
Methods: Male and female mice aged 12 weeks were randomized into a sham (n=20) or cachexia (n=60) condition. Mice in the cachexia condition were inoculated subcutaneously with Lewis Lung Carcinoma (LLC) cells to induce cachexia, and sham mice received PBS. Mice were sacrificed 2-, 2.5-, and 3.5-weeks post-injection and hematopoietic stem cells (HSCs), and myeloid progenitors were quantified by flow cytometry.
Results: In males, HSC content was elevated at 2-, 2.5-, and 3.5-weeks compared to sham ($p<0.05$); however, this elevation was only observed at 2.5 weeks in females ($p<0.01$). When compared to sham multipotent progenitor content was higher at all time points ($p<0.01$) in males, however, females had higher content at 2.5-weeks compared to sham and 2-weeks ($p<0.05$). Long-term HSC content was higher at 3.5-weeks compared to sham, 2-, and 2.5-weeks ($p<0.01$) in males; although, in females this elevation occurred at 2.5-weeks ($p<0.05$). Granulocyte-monocyte progenitors were elevated in males at 2.5-weeks compared to 2- and 3.5-weeks ($p<0.0001$) but did not change in females. Megakaryocyte-erythroid progenitors were elevated at 3.5-weeks in males compared to 2.5-weeks ($p<0.0001$) and at 2.5-, and 3.5-weeks in female compared to 2-weeks ($p<0.05$).
Conclusion: These results suggest that LLC inoculation induces aberrant myelopoiesis primarily in males during the initiation of cancer cachexia. Therefore, aberrant myelopoiesis may contribute to the sex-based differences in cancer cachexia prevalence.

3-18
Impact of the emerging cancer cachexia-biomarker TIMP-1 on the liver

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Introduction: Cachexia is a multifactorial wasting syndrome characterized by severe body weight loss, muscle wasting, and profound metabolic disruptions, associated with many inflammatory diseases including cancer. In most cancer types, Tissue inhibitor of metalloproteinases-1 (TIMP-1), an emerging proinflammatory cytokine, is elevated in both primary tumors and blood of patients. Increased TIMP-1 levels are associated with poor disease outcome and impact on homeostasis of the liver, the key regulator of systemic metabolism. Here, we present data on the link between blood levels of TIMP-1, liver functionality including TIMP-1-associated metabolic changes, and patient outcome during cancer cachexia.
Methods: Weight loss (WL), blood levels of TIMP-1, C-reactive protein, ferritin, gamma-glutamyl transferase, albumin, and total

protein were assessed in colorectal cancer (CRC; n=82) and pancreatic cancer (PC; n=84) patients. Targeted mass-spectrometry-based metabolomics was performed on plasma samples from cachectic (n=7) and non-cachectic (n=9) PC patients, and from healthy and PC-bearing TIMP-1-competent and -deficient mice.
Results: Plasma levels of TIMP-1 significantly correlated with WL and compromised liver function. In cachectic CRC patients, grouped by their extent of WL, significant differences in survival based on TIMP-1 plasma levels were observed. Integration of TIMP-1 levels with liver functionality parameters into the TIMP-1/liver cachexia (TLC) score enabled reliable stratification of CRC and PC patients into low (LO), intermediate (IM), and high (HI) risk categories. Additionally, analysis of plasma metabolite classes in PC patients and PC-bearing mice revealed significant alterations during cachexia, correlating with plasma levels of TIMP-1. Genetic engineering of PC-bearing mice demonstrated the pivotal role of TIMP-1 in causally affecting these metabolic changes in the liver during pancreatic cancer cachexia.
Conclusion: The easily accessible liquid biopsy marker TIMP-1 harbors significant prognostic value and may contribute to a deeper understanding of factors governing the alteration of hepatic metabolism during cancer cachexia. Currently, we investigate the associated molecular mechanism.

3-19
Identifying individuals with cancer cachexia using data from electronic health records (EHR) linked to insurance claims

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Introduction: An international consensus recognized the following Fearon criteria as diagnostic of cancer cachexia: 1. weight loss >5% in 6 months; 2. weight loss >2% in 6 months with a starting BMI <20 kg/m^2; or 3. weight loss >2% in 6 months with sarcopenia. Available scientific literature on the epidemiology of cancer cachexia relies primarily on clinical trial data. The purpose of this study was to explore the prevalence of cancer cachexia using real world data (RWD).
Methods: This study analyzed the Optum Market Clarity (Optum Inc., Eden Prairie, MN) database to identify individuals ≥18 years old with newly onset cancer (solid or hematologic malignancy) based on ICD-10 diagnosis codes in claims or EHR data between October 1, 2016, and September 30, 2021. Cachexia was defined using the Fearon criteria above and was identified both in the 12 months before (“pre-index”) and 12 months after (“post-index”) the cancer index date. The prevalence of clinical concepts related to cachexia (eg, ICD-10 codes for abnormal weight loss) was also estimated.
Results: The study population consisted of 3,139,723 adults with newly onset cancer in claims or EHR, including 176,077 with 2+ bodyweights pre-index and 264,254 with 2+ bodyweights post-index. The prevalence of cachexia was 23.8% pre-index, 37.4% post-index, and 40.8% pre- or post-index. Post-index, the prevalence of cachexia was 25.0%-78.3% for solid tumors and 36.9%-52.8% for hematologic malignancy; prevalence was highest for pancreatic cancer (78.3%) and gastrointestinal cancer (63.9%) and lowest for eye cancer (25.0%) and prostate cancer (25.5%).
Conclusions: Based on repeated bodyweight measurements in RWD, nearly 40% of individuals with newly onset cancer met Fearon criteria for cachexia in the 12 months after their diagnosis. These findings suggest that cancer cachexia is common among those newly diagnosed with cancer. The impact of cachexia on cancer outcomes in RWD should be further explored.

3-20
Cancer Cachexia: Real-World Prevalence

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Background: Care and research of patients with cancer cachexia has been impeded by physician awareness and education; and limited real-world prevalence data. We hypothesized that healthcare professionals use subjective judgment for diagnosing cancer cachexia, rather than the established criteria; and that real-world prevalence of cancer cachexia, based on SCWD definitions is greater than when using only subjective judgment.
Methods: We assessed prevalence of cachexia in cancer patients, at a French center containing two types of real-world digitized data: (a)"structured": coded diagnoses and procedures; (b)"unstructured": uncoded clinical narratives/reports: discharge summaries, procedure results, letters. Two sequential searches covering 2018-2023 (1) determined the prevalence of cachexia in all cancer patients using ICD codes and unstructured data; (2) examined data of high-prevalence colorectal, pancreatic, and non-small-cell lung cancers determining (a)prevalence of cachexia in these cancers; (b)extent to which clinicians' judgment for the diagnosis of cachexia was supported by data; (c)extent to which the diagnosis of cachexia was not made despite data indicating cachexia's presence.
Results: 76,547 of 737,906 patients had cancer; 1,856 (2.42%) of these had cachexia: 349 identified by code, 1,236 by unstructured data, 271 by both. ICD search retrieved only 33.4% of cachexia patients. Of the 6,946 with colorectal, pancreatic, or non-small-cell lung cancer, ICD search found 254 with cachexia; 127 of the 254 had data supporting the diagnosis. An additional 1340 with BMI or weight loss data meeting SCWD criteria were not diagnosed "cachectic". Searching unstructured data for all three cancers identified 439 additional cachectic patients: totaling 2,033.
Conclusions: (1) Standard ICD code searching underestimated the prevalence of all and high-prevalence-cachectic cancers;
(2) Many cachexia cases were not diagnosed, although data indicated its presence;
(3) Many cachexia cases "diagnosed" by judgment were not supported by the data;
(4) Increasing provider awareness of cancer cachexia definitions, and proper coding would likely improve care and research for the disorder.

3-21
Cancer Cachexia epidemiological landscape: lifetime prevalence and severity of cachexia in a population-based longitudinal study

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Introduction: Lifetime prevalence and severity of cachexia are not known.
Methods: Real-world data of patients in Alberta, Canada (~ 4.37 mi population) was acquired from the Alberta Cancer Registry, certified by the North American Association of Central Cancer Registries. The search was indexed at start of 1st line palliative chemotherapy for advanced-stage disease in patients ICD-confirmed cancers (pancreas, biliary tract, gastroesophageal, small cell (SCLC) and non-small cell lung (NSCLC), colorectal, breast, prostate, hematologic, skin/connective tissue) between 1/1/2013–31/12/2022. Data collected include weight, height, diagnosis, age, sex and systemic therapy treatments. Primary outcome was lifetime prevalence as defined by cumulative % weight loss (WL) from the

start of 1st line therapy, until death. WL was graded (WLG) according to Martin et al. (2015), Grade 0-4 to reflect the severity of cachexia.
Results: The cohort comprised N=12,561 patients; 70.6% (8874/12561) had died. BMI at baseline was variable median overall BMI loss over disease until death was -3.1 kg/m^2. Cumulative median %WL was -9.5% (IQR 11.8). WL showed intra-individual variability, with 9.3% showing WLG 0 and 11.1% of patients attaining WLG 1, WLG 2 was reached by 13.9%, WLG 3 by 30.2% and WLG 4 35.5% of the population. Prevalence according to WLG differed by primary cancer and sex (P<0.001). The rank order from least to most WL was biliary<SCLC<skin/connective <prostate<NSCLC<hematologic<pancreas<colorectal <breast<gastroesophageal. Median days to attain Grade 4 differed by cancer (P< 0.001); gastroesophageal 190 days [95% CI 160-219], breast cancer (370 days, [333-407] and pancreas (155 days [136-174]. Grade 4 WL was more prevalent in women (39.6% vs. 31.6% in men; p<0.001).
Conclusions: We provide the first epidemiological estimates of lifetime prevalence of cachexia in a population-based dataset. Cachexia is prevalent across all incurable cancers. Patients with breast cancers have the same lifetime prevalence of cachexia as gastroesophageal and pancreatic cancers.

3-22

Is malnutrition assessed by MUST, SGA, GLIM and cachexia related with survival in outpatient advanced cancer?

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Introduction: Nutritional status critically influences survival outcomes in patients with advanced cancer. Tools such as the Patient-Generated Subjective Global Assessment (PG-SGA), the Malnutrition Universal Screening Tool (MUST), the Global Leadership Initiative on Malnutrition (GLIM) criteria, and cachexia classification are commonly used to assess nutritional status. However, their effectiveness in predicting both short and long-term survival remains underexplored. This study evaluates the relationship between these nutritional assessment tools and survival at multiple time points in outpatients with advanced cancer in Brazil.
Methods: Conducted in a public hospital in Brazil, this study included 84 outpatients with advanced cancer. Nutritional status was assessed using PG-SGA, MUST, GLIM criteria, and cachexia classification (Fearon, 2011). Survival was evaluated at 90, 180, 365, and 730 days using Kaplan-Meier and Cox regression analyses.
Results: The PG-SGA was significantly associated with 730-day survival (x^2=9.12, p=0.01). MUST correlated with survival at 90, 180, and 365 days (x^2=13.04, p=0.00; x^2=10.19, p=0.00; x^2=7.86, p=0.02, respectively). GLIM criteria were related to 90-day survival (x^2=6.76, p=0.00), while cachexia classification was associated with 90 and 180-day survival (x^2=13.43, p=0.00; x^2=8.62, p=0.01, respectively).
Conclusion: This study suggests that nutritional assessment tools vary in their predictive capabilities for survival in advanced cancer patients. PG-SGA is linked to longer-term survival, while MUST, GLIM, and cachexia classification are more effective for short-term survival. Combining these tools may enhance the comprehensive assessment of nutritional status and survival outcomes. Further research is needed to validate these findings and investigate the clinical benefits of integrating these tools.

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Comparison of adiposity-specific microRNAs expression in subcutaneous and visceral adipose tissue of patients with gastrointestinal cancer

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Introduction: Cancer-induced adipose tissue (AT) depletion is an early event negatively affecting patients' outcomes. MiRNAs have been implicated in regulating multiple signaling pathways related to AT wasting, including inflammation. However, their roles in cachexia are only partially known.
This study aimed to assess the expression of AT-derived miRNAs associated with changes in subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT): i) among gastrointestinal (GI) cancer patients vs controls, ii) according to presence of cachexia and iii) according to C-reactive protein (CRP) level.
Methods: SAT and VAT biopsies were obtained from 18 naïve GI cancer patients and 4 controls. The presence of cachexia was assessed. Total RNA was extracted from SAT and VAT specimens. We identified miRNAs involved in AT metabolism in cancer and measured them by RT-qPCR.
Results: We found higher levels of miR-128 (p=0.006), miR-155 (p<0.001) and lower of miR-144 (p<0.001) in SAT vs VAT of cancer patients. Cachectic patients showed a tendency in upregulating miR-128 (p=0.07) and a significant upregulation of miR-26 (p=0.006) and downregulation of miR-144 (p=0.007) in SAT vs VAT.
Higher levels of miR-155 (p<0.001) and lower of miR-144 (p<0.001) were present in SAT compared to VAT in cancer patients with lower BMI. Cancer patients with high CRP levels showed a significant different modulation of miR-128 (p=0.02), miR-155 (p=0.04) and mir-144 (p=0.02) in SAT compared to VAT.
Conclusions: Our preliminary data showed a different modulation of adipose tissue specific miRNAs between SAT and VAT of patients with cancer and with cachexia.

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Assessing microRNAs expression in patients newly diagnosed with breast cancer and their association with changes in body composition

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Introduction: Changes in body composition often occur in women diagnosed with breast cancer (BC), negatively impacting on patient's prognosis. MiRNAs' expression and their release was shown to be involved in skeletal muscle (SM) and adipose tissue (AT) metabolism during cancer. For this reason, we aimed to evaluate circulating miRNAs between i) BC patients vs controls ii) among BC patients according to changes in body weight (stable, WS; loss, BWL; gain, WG) and iii) according with body composition parameters.
Methods: We collected plasma samples from newly diagnosed BC patients and controls and measured specific SM and AT miRNAs by RT-qPCR. Data were statistically analysed, as appropriate.
Results: We enrolled 24 patients with BC (BMI 27.10 ± 3.97 kg/m^2) and 9 controls (BMI 24.19 ± 3.90 kg/m^2). We observed un upregulation of miR-15b (p=0.004), miR-21.5, miR-26a, miR-29a, miR-29b (p<0.001), miR-155 (p=0.011) and miR-486 (p=0.049) in BC vs controls. Among BC patients, we observed an upregulation for miR-26a (p=0.028) and a trend of miR-29a (p=0.051) in WG vs WS. Interestingly, miR-26a was lower in BWL vs WG (p=0.014),

whereas miR-29a was higher in BWL vs WS (p= 0.043). Additionally, in BC patients the levels of miR-15b and miR-133a positively correlated with BMI (r=0.487, p=0,021; r=0.551, p=0.008, respectively) and with fat mass index (r=0.434, p=0.043; r=0.471, p=0.027, respectively). Significant correlations were also observed between fat-free mass index and the levels of miR15b (r=0.425, p=0.049), miR-21.5 (r=0.480, p=0.024) and miR-133a (r=0.448, p=0.037).
Conclusions: Our data showed a modulation of circulating miRNAs involved in SM and AT metabolism in BC patients, as well as significant correlations with body composition parameters.

3-25
Adiposity specific micrornas in cancer patients: analysis of plasma levels according to fat distribution assessed by CT-scan

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Introduction: Changes in adipose tissue (AT) in cancer represent an early event with negative impact on patient's outcomes. Circulating miRNAs may originate from cancer cells and act in periphery at different levels promoting cachexia.
We evaluated differences in specific circulating miRNAs, linked to AT alterations between i) GI cancer patients and controls, ii) cachectic and non-cachectic cancer patients and iii) according to adiposity level by CT-scan.
Methods: Patients with GI cancer and controls with benign diseases were considered. Cachexia was assessed and adiposity evaluated by CT-scan for subcutaneous AT area (SAT), visceral AT area and the total AT area (TAT). We identified miRNAs involved in AT metabolism in cancer and measured them in plasma by RT-qPCR.
Results: We enrolled 37 naïve GI cancer patients. Cachexia was present in 49%. Patients with cachexia presented with a lower BMI and lower SAT compared to non-cachectic ($p<0.05$). In cancer patients, we found higher levels of miR-26a, miR-128, miR-155 and miR-181a vs controls ($p<0.05$). Cancer patients with overweight/obesity showed lower levels of miR-26a ($p<0.04$). MiR-26a and miR-181a were higher in cachectic, as well as non-cachectic patients vs controls ($p<0.001$). Differences between cachectic patients and controls were confirmed for miR-155 ($p<0.001$) and interestingly were not present between non-cachectic vs control ($p=0.072$). Moreover, miR-155 tended to be higher in cachectic vs non-cachectic patients ($p=0.087$). We found that miR-155 was higher in cachectic patients with low TAT compared to those without cachexia and high TAT ($p<0.05$).
Conclusions: We confirm a modulation of specific miRNAs involved in AT metabolism in cancer and cachexia. MiR- 155 levels were higher in those patients with cachexia and low adiposity with implications in the development of nutritional and metabolic alterations in GI cancer patients.

3-26
Analysis of body composition parameters and toxicities in patients with metastatic breast cancer (BC) treated with CDK4/6 inhibitors

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Introduction: We analyzed in BC treated with CDK4/6 inhibitors (CDK4/6i) i) changes in subcutaneous adipose tissue (SAT), visceral adipose tissue (VAT), skeletal muscle area (SMA) and skeletal muscle index (SMI) before and after treatment with CDK4/6i and ii) whether the changes in these parameters were associated with toxicities
Methods: We considered metastatic ER+/HER2- BC patients undergoing treatment with CDK 4/6i, collected clinical data and registered the rate of discontinuation or dose reduction due to adverse events. We analysed CT scan images before treatment (T0) and at the second oncology visit (T1), calculating SAT, VAT, SMA and SMI.
Results: 70 metastatic BC patients were enrolled. Median time of observation at T1 was 4 months. 68 patients experienced at least one G1-G2 adverse event, whereas 34 at least one G3-G4. Dose reduction due to toxicity was registered in 17 patients (24%), whereas discontinuation in 24 patients (15 for disease progression, 9 for adverse events). SMA at baseline inversely correlated with the number of adverse events (G3-G4) ($r=-0.30$; $p=0.039$). Changes in body composition were not associated with G3-G4 toxicities. However, in patients with dose reduction, we observed overtime (T0-T1) an increase in median VAT (118 vs 135; $p=0.023$). In patients not discontinuing the treatment, we observed overtime an increase in mean SMA (127 ± 23 vs 131 ± 22, $p<0.05$) and median VAT (119 vs 131, $p<0.05$). We observed greater reduction in median VAT (Δ%) in patients who discontinued the therapy ($p<0.05$). ΔVAT (%) (reduction) was more pronounced in those patients who discontinued therapy for disease progression ($p=0.01$).
Conclusions: Changes in muscularity and adiposity were associated with toxicities, treatment discontinuation or dose reduction in patients with breast cancer treated with CDK4/6i.

3-27
The effect of sex on circulating undercarboxylated osteocalcin in tumor-bearing mice receiving chemotherapy

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Introduction: Osteocalcin (OC) is a bone-derived hormone, and its undercarboxylated form(ucOC) can regulate muscle mass and exercise responses. Cancer and treatment can induce muscle loss and metabolic and physical dysfunction. We previously reported that FOLFOX (5-fluorouracil, leucovorin, oxaliplatin) chemotherapy lowers plasma ucOC levels in male mice. While sex can affect OC levels, there are gaps in sex, cancer, and chemotherapy interaction to regulate OC and the relationship to the IL-6 cytokine family and physical function. Circulating ucOC's relationship to physical

function and circulating IL-6 and LIF levels were examined using the colon-adenocarcinoma (C26) model and FOLFOX chemotherapy administration in male and female mice,
Methods: In vivo, male and female CD2F1 (Balb/c, 12 weeks) injected with C26 tumor cells or PBS and three cycles of vehicle or FOLFOX 9 days after tumor inoculation (N=9-14/group).
Results: Males and females had no baseline differences in plasma ucOC. Sex impacted FOLFOX's effect on circulating ucOC. In male mice, FOLFOX alone decreased ucOC, while C26 alone increased ucOC. FOLFOX attenuated the C26 increase in ucOC. FOLFOX alone increased ucOC in females, but there was no effect of C26 alone, while FOLFOX increased ucOC independently of C26. Sex-affected ucOC level is associated with muscle mass and function. Control female muscle mass was negatively associated with ucOC, and ucOC was positively associated with RTF in FOLFOX females.
Conclusion: As expected, circulating ucOC in control male mice was positively associated with muscle mass, but FOLFOX and C26 ablated this relationship. However, in control females, ucOC was negatively associated with muscle mass but positively associated with circulating LIF and endurance capacity in tumor-bearing or chemotherapy mice. A better understanding of how sex interacts with cancer and chemotherapy to regulate the relationship of ucOC with muscle mass, physical function, and inflammatory cytokines is warranted.
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3-28

Anamorelin Efficacy in Non-Small Cell Lung Cancer Patients with Cachexia: Insights from ROMANA 1 and ROMANA 2

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Background: Cancer cachexia presents a significant challenge, but the ghrelin agonist anamorelin shows promise as a potential treatment. This study examined whether the baseline systemic inflammatory response (SIR) (measured by the modified Glasgow Prognostic Score [mGPS]), low BMI or greater weight loss, was associated with a differential treatment effect of anamorelin in people with cachexia and non-small cell lung cancer (NSCLC).
Methods: ROMANA 1 and ROMANA 2 were double-blind, placebo-controlled, randomised phase 3 trials that enrolled people with inoperable stage III/IV NSCLC with cachexia (≥5% weight loss within 6 months or body mass index [BMI] <20 kg/m^2). Patients were randomised 2:1 to anamorelin 100 mg once daily or placebo, for 12 weeks. This is a post-hoc analysis of efficacy endpoints (body weight, body composition (Lean body mass [LBM], Fat Mass [FM]), stratified by baseline mGPS, BMI and weight loss and measured in the modified intent-to-treat pooled population.
Results: 795 patients had available data. Anamorelin improved body weight (p<0.001) and body composition parameters (LBM, FM, p<0.01) in all mGPS groups. In patients with mGPS=2, anamorelin increased weight >5% and improved hand grip strength (HGS) and the Functional Assessment of Anorexia Cachexia Therapy Anorexia/Cachexia Subscale (FAACT A/CS). In patients with BMI <20 kg/m^2 at baseline or weight loss ≥10% in the prior 6 months, anamorelin led to significant increases in body weight from baseline (p<0.001) versus placebo. Patients with weight loss ≥10% in the prior 6 months showed the highest improvements in LBM (p<0.001). Patients with BMI <20kg/m^2 at baseline showed the highest improvements in FM (p<0.001).
Conclusion: Anamorelin improved body composition parameters in all patients, as well as physical function and symptom burden, particularly in patients with systemic inflammation, BMI<20kg/m^2 and weight loss≥10%. These results highlight the anabolic mechanisms of anamorelin irrespective of weight loss or systemic inflammation (high risk groups).
NCT Identifiers: ROMANA 1: NCT01387269; ROMANA 2: NCT01387282

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Increased nivolumab clearance correlates with elevated GDF15 serum levels in patients with metastatic non-small cell lung cancer

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Introduction: Cancer cachexia impairs responsiveness to immunotherapy. As nivolumab clearance inversely relates to therapy response, this study explored the relationship between nivolumab pharmacokinetics (PK), body composition and serum cachexia biomarkers.
Methods: Patients (154) with advanced NSCLC treated with nivolumab monotherapy according to standard of care were included. At baseline, C-reactive protein (CRP), interleukin (IL)6, growth differentiation factor (GDF) 15 and -8, adiponectin and leptin were measured. Skeletal muscle mass (SMM), subcutaneous and visceral adipose tissue (SAT and VAT) were measured at the first lumbar vertebra on computed tomography images at baseline, week 6, and week 12 and adjusted for height squared (SMMi, VATi, SATi). Early body weight loss was defined as >2% weight loss during the first 42 (±10) days. The nivolumab PK model structure was based on previous work. Clearance and covariate relationships (cachexia parameters and patients characteristics) were stepwise assessed in this cohort.
Results: Out of 154 patients, 149 provided samples for nivolumab PK analysis, and 117 for serum cachexia biomarkers. Men showed higher clearance compared to women (p<0.001). Nivolumab clearance positively correlated with baseline GDF15 (p<0.001) and CRP (p<0.001). Weight loss and changes in SMMi were not significantly associated with clearance. Serum GDF15 concentrations (median 2406 pg/ml, IQR 1655-3900) were not different between patients with early weight loss and stable weight. Patients with elevated GDF15 levels (>2000 pg/ml) had significantly worse overall survival (HR = 1.70, 95%CI 1.13-2.5).
Conclusion: This study demonstrates that nivolumab clearance significantly correlates with baseline GDF15 serum levels, and that elevated GDF15 levels associate with poor survival in patients with metastatic NSCLC.

3-30

The Clinical Significance of Weight Loss During Concurrent Chemoradiotherapy (CCRT) in stage III Non-Small Cell Lung Cancer (NSCLC): Impact on Treatment Strategy and Outcomes

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Introduction: Cancer cachexia, highly prevalent in NSCLC, has been associated with diminished quality of life and a decreased overall survival (OS). This study investigates the predictive value of weight loss during treatment in NSCLC patients undergoing CCRT, assessing its impact on OS, progression free survival (PFS), treatment-related toxicities, and the administration of adjuvant durvalumab immunotherapy.
Methods: All consecutive patients with stage III NSCLC treated between May 2018 and 2022 with CCRT followed by durvalumab at MAASTRO clinic were retrospectively evaluated. Patient's demographics, clinical data, and treatment related toxicities were collected. Excluded were patients with incomplete data or who did not finish CCRT. The remaining patients were categorized by body weight change during CCRT using maximally selected rank statistics into a weight stable and weight losing group (cut-off >3% weight loss). Kaplan-Meier survival analysis and Cox regression assessed the impact of weight loss on OS.
Results: 96/199 (48.2%) patients had > 3% of weight loss (-7.7±4.3%) during CCRT, for the others weight varied 1.8±5.8%. Average OS was significantly shorter in weight losing group (OS: 36.7±2.5 months) compared to the weight stable group (OS: 44.4±3.0 months, P=0.005, HR=1.875). Weight loss during CCRT correlated with gross tumor volume (r=-0.2159, P=0.0063) and was more frequently accompanied by the development of anorexia (P=0.004) and esophagitis (P=0.001) compared to the weight stable group. 65/96 (67.7%) of the weight losing patients had a PS0-1 after CCRT, while this was 88.3% for the weight stable group (P=0.005). Patients with a PS0-1 (109/199) were admitted to adjuvant immunotherapy, which significantly improved OS independent of weight loss (OS: 51.7±2.8 vs. 37.3±2.5 months, P<0.0001).
Conclusions: Weight loss during CCRT is associated with an increased risk of toxicities, decreased PS and reduced eligibility for adjuvant durvalumab, which negatively impact outcome. Therefore, early diagnosis and treatment of cachexia during CCRT may improve treatment efficacy and outcome.

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The development of muscle mass, muscle strength, and muscle function in patients with lung cancer during oncological treatment

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Introduction: Sarcopenia and cachexia in patients with lung cancer at the time of diagnosis are linked to negative outcomes. Despite this, knowledge about changes in skeletal muscle mass, strength, and function during oncological treatment remains limited. Additionally, less than half of patients with lung cancer receive optimal treatment due to anticipated treatment tolerance issues. Research indicates that muscle mass affect treatment tolerance, suggesting that better evaluation of a patient's physical capacity at diagnosis could reduce the risk of chemotherapy-induced toxicities. This study aims to evaluate changes in muscle mass, strength, and function in patients with lung cancer undergoing chemotherapy and assess the association with treatment-related complications, quality of life, and survival.
Methods: This prospective cohort study will include 180 participants. Measurements will be taken at diagnosis and at 3 and 6 months during oncological treatment. These assessments will include muscle mass (bioelectrical impedance analysis and CT scans at L3), muscle strength (dynamometry for handgrip strength and 1 RM leg press), and muscle function (5-times and the 30-second sit-to-stand test, and both maximal and habitual gait speed over 10 meters). Sarcopenia will be defined according to the EWGSOP2 criteria, while cancer cachexia will be defined using the international consensus criteria by Fearon et al. (2011). Chemotherapy-induced toxicity will be evaluated using the CTCAE template.
Results: The study will examine associations between muscle parameters and outcomes, providing estimates of regression coefficients and odds ratios. It is expected to offer insights into how sarcopenia and cachexia impact treatment tolerance and survival in lung cancer. Patient recruitment will begin September 2024 and preliminary results will be presented at the conference.
Conclusion: By identifying specific patterns of muscle deterioration associated with treatment complications, the findings may inform personalized treatment strategies and improve clinical management, potentially enhancing treatment tolerability, quality of life and survival rates.

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Impact of Cachexia on the Survival of EGFR-Mutant Lung Cancer Patients on Osimertinib Therapy

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Background: Lung cancer is the leading cause of cancer-related mortality. Recently, molecular targeted therapies have transformed the treatment landscape for certain lung cancer subtypes. For instance, the EGFR tyrosine-kinase inhibitor (TKI), Osimertinib, has significantly improved the survival of patients with EGFR-mutant lung cancer. Although osimertinib selectively targets mutant-EGFR with minimal physiological side effects, some osimertinib-treated patients still undergo debilitating weight loss and develop symptoms of cachexia. Cachexia is characterized by unintentional weight loss and a decline in muscle mass and function and is a known poor

prognostic factor for cancer patients. Since the incidence of cachexia is associated with poor survival in most cancers, we investigated whether cachexia is associated with poor outcomes in osimertinib-treated EGFR-mutant lung cancer patients.
Materials and Methods: In a retrospective pilot study of 56 patients receiving first-line osimertinib treatment for metastatic EGFR-mutant NSCLC, we defined on-treatment weight loss as a loss of ≥5% body weight after 6 or 12 months of treatment. We examined patient characteristics, differences in progression-free survival (PFS), time on treatment with osimertinib, and overall survival (OS) for patients with and without on-treatment weight loss.
Results: Our study found that 12 of 26 osimertinib-treated patients (46%) experienced on-treatment weight loss. Despite no significant differences in patient or disease characteristics, patients with weight loss had markedly worse overall survival (HR 4.91, 95% CI 1.56-15.5, p = 0.007) compared to those without weight loss, though their PFS and treatment duration were similar.
Conclusion: Our study has revealed the prevalence of weight loss in patients receiving osimertinib-targeted therapy, suggesting that targeting cachexia in osimertinib-treated EGFR-mutant lung cancer patients positively impact their overall survival.

3-33
Identifying pretreatment blood metabolic markers associated with weight loss in head and neck cancer patients

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Introduction: Despite its high prevalence and detriment to prognosis, early biomarkers for cancer cachexia are not well established. We aimed to identify pretreatment metabolic markers predictive of weight loss within the first year of head and neck cancer (HNC).
Methods: In 185 newly diagnosed HNC subjects on standard therapy, high-resolution liquid chromatography-mass spectrometry extracted untargeted metabolites from pretreatment plasma samples. Patient weight was recorded pretreatment and at 6 weeks, 1, 3, 6, and 12 months post-treatment. Our outcome was maximum weight loss during follow-up as a percentage of pretreatment weight. Linear regression models analyzed metabolites associated with percent weight loss adjusting for body mass index, age, sex, HPV status, smoking history, cancer stage, and a feeding tube. Nominally significant metabolites (P<0.05) were further analyzed via pathway analysis to identify enriched metabolomic profiles associated with weight loss during cancer recovery.
Results: The cohort averaged 59.3 years of age, was 75% male, 81% white, and 48% HPV positive. The median maximum weight loss during follow-up was 11.7% (IQR: 6.5%, 16.3%). The distribution when patients experienced maximum weight loss was 14% at 6 weeks, 23% at 1 month, 29% at 3 months, 20% at 6 months, and 14% at 12 months. Seventy-one of 960 analyzed metabolites were significantly associated with weight loss; 49 of these were elevated. Pathway analysis revealed that elevated levels of pretreatment metabolites involved in bile acid biosynthesis (P=0.0003), de novo fatty acid biosynthesis (P=0.002), and glycerophospholipid metabolism (P=0.004) were strongly associated with greater weight loss consistent with cancer cachexia. No meaningful differences were observed when stratified by HPV status.
Discussion: Pretreatment metabolic markers, namely bile acids and fatty acids, in HNC patients' blood may predict significant weight loss, indicative of cachexia. This finding suggests potential for early identification and intervention strategies, improving patient outcomes and quality of life.

3-34
Obesity accelerates muscle wasting in PDAC-induced cancer cachexia

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Pancreatic ductal adenocarcinoma (PDAC) patients are severely impacted by cachexia, a multifactorial syndrome of unintentional weight loss of skeletal muscle and adipose tissue. While obesity is known to be a contributing factor to the development of PDAC, little is known about the relationship between obesity and cachexia.
Methods: Medical record data were collected from 190 consecutive PDAC patients enrolled in our institutional biorepository. Body composition was assessed on CT images taken during routine care. Total cross-sectional area of skeletal muscle (SKM), subcutaneous adipose tissue (SAT), and visceral adipose tissue (VAT) were assessed at the third lumbar vertebrae and values were normalized to height^2 (SKMI, SATI, VATI), as previously described. For patients with follow-up scans (n=100), changes in body composition between scans were calculated and normalized to the days between scans. For 121 patients with available serum, circulating myostatin was measured by ELISA, as elevated myostatin has previously been associated with obesity.
Results: Patients with pre-illness obesity had greater weight loss at diagnosis (10.8% versus 6.5%, p=.004). For the 174 patients with available at-diagnosis scans, obese males and females had higher SKMI (p<0.0001), SATI (p<0.0001), and VATI (p<0.0001) compared to non-obese PDAC patients. For 100 patients with follow-up scans and persistent cancer, greater decreases in SATI (p=0.04) and VATI (p=0.003) were associated with higher body mass index (BMI). Surprisingly, larger decreases in SKMI were also associated with higher BMI (p=0.008). Circulating myostatin was not different between obese and non-obese patients (2231 pg/ml versus 2184 pg/ml, p=0.71). As previously reported, serum myostatin was significantly associated with SKMI (p=0.01) but was not related to VATI (p=0.655) or SATI (p=0.345).
Conclusions: PDAC patients with higher BMIs have accelerated wasting of both adipose tissue and skeletal muscle, but circulating myostatin levels were not associated with increased adiposity.

3-35
A clinical model based on skeletal muscle radiation attenuation associated with efficacy of chemotherapy plus PD-1 antibody in gastric cancer

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Introduction: Biomarkers for PD-1 antibody-based therapy in gastric cancer (GC) are urgently needed. We aimed to assess the role of body composition parameters in guiding treatment of chemotherapy plus PD-1 antibody in GC patients.
Methods: Clinical information of GC patients underwent

chemotherapy plus PD-1 antibody (IO cohort, n=120) or chemotherapy alone (CTx cohort, n=82) following surgical resection was reviewed as the training set. Tumor regression grade (TRG) was recorded. TRG 0/1 was classified as good response and TRG 2/3 was poor response during analysis. Body composition parameters were detected based on computed tomography (CT) images at the L3 level using SliceOmatic software, and their associations with patients' outcomes were analyzed. Data of patients from an independent center was collected as the external validation set (n=43).
Results: In the training set, high skeletal muscle radiation attenuation (SMRA), neutrophil to lymphocyte ratio (NLR) <2.65, and weight loss <5% were associated with TRG0/1 in the IO cohort but not in the CTx cohort. SMRA was an independent prognostic factor of progression-free survival (HR=0.333, 95%CI 0.115-0.970, *P*=0.044). A clinical model consisting of SMRA, NLR and weight loss was established, and stratified patients into 3 groups (group 1: high SMRA with NLR <2.65 and weight loss <5%, group 2: high SMRA with NLR ≥2.65 and/or weight loss ≥5%, and group 3: low SMRA). When treated with chemotherapy plus PD-1 antibody, patients in group 1 showed higher TRG0/1 rate (27/40, 67.5%, *P*<0.001) than those in group 2 (26/63, 41.3%) and group 3 (2/17, 11.8%). In the validation set, patients who were stratified into group 1 also had higher TRG0/1 rate than other 2 groups (13/17, 76.5%, *P*=0.045).
Conclusion: The clinical model consisting of SMRA, NLR and weight loss can effectively identify GC patients who respond well to chemotherapy plus PD-1 antibody.

3-36
Fluid accumulation in palliative cancer patients with and without cacexia
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3-37
Reducing outcome variability in longitudinal models of preclinical cancer cachexia

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Introduction: Longitudinal pre-clinical models are an important tool for understanding the role of physical function in cancer cachexia. However, these models are prone to physiologic heterogeneity, both over time and due to variability in animal body composition. This reduces sensitivity when estimating muscle wasting and monitoring inflammatory markers. Herein, we developed a pipeline that accounts for differing rates of disease progression and initial body composition changes, thereby reducing variability and increasing sensitivity to cachexia-specific pathologies.
Methods: Initial body weight and echoMRI fat and lean mass were recorded 1 week prior to pancreatic cancer implantation. Mice were euthanized by week (time model) and binned by disease event (early, palpable, midpoint, morbid) post-hoc. Early was defined as 2 weeks post-implantation. Palpable was based on palpation performed 3x/week and defined when a mass was detected in the abdomen. Midpoint was 10 days post-palpable. Morbid animals were those that met sickness criteria for euthanasia. Ex-vivo quadriceps mass and serum biochemistry were analyzed.
Results: Quadriceps mass by weeks in our time model showed a high % coefficient of variation (%CV) at multiple timepoints (max %CV = 13.023). When grouped by event, max %CV decreased to 11.306. Mixed effects analysis of serum biomarkers TNFα and GDF-15 showed a significant interaction effect between disease event and cancer (p=0.0001 and 0.0017) but not between time and cancer (p>0.25). Variability was further reduced for quadriceps mass by performing an ANCOVA with initial fat mass, lean mass, or body weight. ANCOVA by initial fat mass resulted in the greatest reduction (67%) in max %CV (4.727).
Conclusions: Variability in muscle wasting and inflammation was significantly reduced by disease-based event binning coupled with ANCOVA of initial fat mass. We propose this as a robust method to improve detection of cachexia-associated outcomes in longitudinal models of preclinical cancer cachexia.

3-38
Anorexia accounts for major body weight loss but has no impact on muscle function in a colorectal cancer cachexia model

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Introduction: Reduced food intake, or anorexia, is frequently implicated in contributing to body weight loss and tissue wasting in cancer cachexia. However, the extent to which anorexia alone accounts for these effects, including body weight loss, tissue wasting, and other cachectic phenotypes, especially impaired muscle function, remains inadequately characterized. This study aims to rigorously address these gaps using a well-established mouse model of cancer cachexia.
Methods: We used mice subcutaneously injected with a cachectic Colon-26 (cxC26) cell line as our cancer cachexia model and mice bearing a non-cachectic Colon-26 (ncxC26) cell line as controls. To meticulously delineate the effects of anorexia, we developed an isocaloric restriction experimental strategy, where we fed the cxC26 and ncxC26 groups the same amount of food, matching the daily food intake of a cxC26 ad lib group. We further had a third group of ncxC26 ad lib group to gauge the phenotypes of non-cachectic ad lib mice. Across these groups, we measured body weight, body composition, energy expenditure, fecal energy excretion, muscle mass, key muscle atrophy markers, muscle protein, grip strength, physical activity, and maximum exercise capacity.
Results: The body weight and body composition of the ncxC26 isocaloric group closely matched those of the cxC26 isocaloric group. At the same time, the two groups had no difference in energy expenditure or fecal energy excretion. The non-cachectic and cachectic groups also exhibited comparable muscle protein wasting under isocaloric feeding. In contrast, muscle function measurements-including grip strength, physical activity, and maximum exercise capacity-dropped significantly in the cxC26 isocaloric group, while the ncxC26 isocaloric group remained unchanged compared to the ncxC26 ad lib group.
Conclusion: Neither energy expenditure nor energy excretion contributes to body weight loss in the C26 model. Instead, anorexia accounts for body weight loss in the model. Anorexia, however, has no impact on muscle function.

3-39
Improving Patient and Caregiver Knowledge & Communication about Cancer Cachexia

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Introduction: Although nearly 80% of advanced stage cancer patients experience cachexia, patient knowledge and communication about cachexia are low. To create a cachexia lexicon, or shared language for providers, patients, and advocates, we co-developed an engagement tool to increase awareness of and communication around cachexia among patients and caregivers. In this study, we evaluated the efficacy of the engagement tool in increasing knowledge and communication around cachexia among patients and caregivers.
Methods: We fielded a pre- and post-test design survey with 191 patients with cancer and caregivers to evaluate the engagement tool. Survey participants: 1) reported baseline knowledge and communication around cachexia; 2) reviewed the tool: 3) rated the

tool for clarity, acceptability, and resonance; 4) re-assessed knowledge and communication. Data were analyzed using descriptive statistics, t-tests, and McNemar's tests.
Results: Participants included 156 patients and 35 caregivers. The most common diagnoses were breast (32%), colorectal (14%), lung (13%), ovarian (9%), and pancreatic (7%) cancers, and 39% had cachexia. Average self-rated knowledge increased significantly after reviewing the engagement tool from pre-test (M=2.05, SD=1.04) to post-test (M=3.66, SD=1.05), t (190) =4.83, p <.001, with a large effect size (Cohen's d = 1.5). Based on McNemar's tests, the accuracy of knowledge around symptoms increased significantly among 53% of participants (p <. 001) at post-test, in addition to accurate knowledge of the diagnoses at highest risk for cachexia (17%, p <. 001) and the providers who manage cachexia symptoms (58%, p <.001). Seventy-seven percent of participants were willing to talk to their provider about cachexia at post-test compared to 39% at pre-test.
Conclusion: Findings demonstrate that the engagement tool can increase awareness and communication about cancer cachexia. Coordinated dissemination of the tool in diverse venues and formats may encourage communication around the condition, increase diagnosis, and connect patients and caregivers with supportive care.

3-40
One cycle of anthracycline chemotherapy reduces heart function and is inversely associated with higher blood oleic acid in women with breast cancer: a feasibility study

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Introduction: Anthracycline chemotherapy (AC) leads to cardiotoxicity in many breast cancer patients by inducing inner mitochondrial damage and disrupting the electron transport chain.
This study was conducted to determine the feasibility of accrual and estimate the effect size of one cycle of AC on heart function and erythrocyte and mitochondrial lipidome changes in breast cancer patients.
Methods: Women, with stage I-III breast cancer who were planning with their oncology team to undergo AC treatment were recruited for this prospective feasibility study. Patients underwent blood sampling and cardiac magnetic resonance imaging at two clinical visits, before and after any one cycle of AC. HPLC-MS/MS was used for mitochondrial lipidomic analysis.
Results: Difficulty recruiting due to the timing of capturing newly diagnosed breast cancer patients, exacerbated by the COVID-19 pandemic, resulted in a total enrollment of 14 women, 3 who withdrew before starting the study, and 3 discontinued after visit 1.
After one cycle of AC, T2, a subclinical biomarker of heart failure and an established measurement of edema, significantly increased (p=0.031).
Targeted lipidomic analysis on cardiolipin (CL), the inner mitochondrial membrane phospholipid, revealed the ratio of LA-rich to oleic acid (OA)-rich was negatively correlated with T1, an indicator of myocardial fibrosis, at visit 1 (p=0.026). OA-rich CL, (%72 carbons), was positively associated with T1 at visit 1 (p=0.026) and visit 2 (p=0.019). OA content in erythrocytes was positively correlated with T2 at visit 1 (p=0.050) and visit 2 (p=0.011).
Conclusions: Despite the small sample size, the negative effects of AC on heart function are apparent. OA-rich CL and OA in erythrocytes appear to be related to subclinical markers of heart failure. We plan to test our hypothesis that dietary LA will preserve cardiac contractile function, mitochondrial function, and LA-rich and OA-poor CL species in mice with mammary cancer, treated with AC.

3-41
Dissecting the GLIM Criteria in Advanced Cancer: Reduced Intake vs. Inflammation

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Introduction: The Global Leadership Initiative on Malnutrition (GLIM) have recommended a criteria for the diagnosis of malnutrition. The patient must meet at least one phenotypic criterion and at least one aetiological criterion - either reduced food intake or inflammation (the latter defining cachexia). The aim of the present study was to assess which of these aetiological criteria most effectively predicts overall survival (OS) in advanced cancer.
Methods: Data from biobanks in Scotland and Brazil were combined for analysis. Inclusion criteria were: age ≥18 years, cancer stage III or IV, and able to provide consent. Weight loss (WL) was selected as the phenotypic criterion of choice, as preliminary analysis demonstrated it to be a superior predictor of OS. Malnutrition (WL + inflammation) was defined as >5% WL over 6 months and a CRP ≥3mg/l. Malnutrition (WL + reduced intake) was defined as >5% WL over 6 months and reduced food intake. Survival was assessed using Kaplan-Meir, log-rank tests and cox proportional hazard models.
Results: There were 176 patients. Malnutrition (WL + inflammation) and malnutrition (WL + reduced intake) were observed in 37.8% (HR: 2.268 [CI: 1.543 to 3.335], p<0.001) and 26.3% (HR: 1.739 [CI: 1.190 to 2.542], p=0.005) of patients respectively, with both increasing the risk of death. In multivariate analysis malnutrition (WL + inflammation) (HR: 1.656 [CI: 1.047 to 2.619], p=0.034) remained a significant predictor of OS whilst malnutrition (WL + reduced intake) did not. Median survival for patients with malnutrition (WL + inflammation) was 2.14 (CI: 1.74 to 4.90) vs. 9.5 (6.94 to 13.64) months for those without (p<0.001).
Conclusion: The inflammatory component of GLIM appears superior compared to reduced intake in predicting OS. Therefore, whilst GLIM has multiple potential combinations, all treated with equal regard, these data suggest that the inflammatory aetiological component, should be hierarchical to others.

3-42
Characterization of a cachectic subpopulation of skeletal muscle satellite cells in a Lewis-lung Carcinoma-induced model of murine cancer cachexia.

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Introduction: Cancer cachexia is a paraneoplastic syndrome that causes ~20% of cancer-related deaths. Cachexia reduces body

weight and skeletal muscle mass, corresponding with decreased cancer treatment effectiveness and survival. Cachexia causes muscle damage, yet our lab and others have demonstrated that satellite cells, the skeletal muscle stem cells responsible for muscle maintenance and regeneration, fail to differentiate in cachectic muscle.
Methods: Twelve-week-old male C57BL/6 mice were inoculated with subcutaneous Lewis-lung carcinoma cells (500K/flank) and tumours were allowed to grow for 3.5 weeks. Skeletal muscle from tumour-bearing and Sham mice were collected and single-cell RNA sequencing was performed. Cell clusters and subclusters were analyzed using the Seurat pipeline and trajectory and pseudotime analyses were performed with Monocle3.
Results: Mice with 3.5-week tumours had significantly reduced changes in body mass (-3.0 g), lean mass (-1.6 g), fat mass (-1.6 g), and reduced gastrocnemius/soleus complex cross-sectional area (-296.9 μm^2) compared to Sham. Satellite cells in 3.5-week tumour-bearing mice demonstrated downregulation of gene expression related to muscle regulation and contraction and extracellular matrix organization, and an upregulation in expression of genes known to impair differentiation compared to Sham. Subclustering analysis revealed a distinct population of satellite cells that were abundant in 3.5-week tumour-bearing mice (75%) compared to Sham (1%) and were characterized by genes known to promote quiescence and impair differentiation (*Sox3*, *Junb*, *Cebpb*). Trajectory analysis revealed branching of the cachectic satellite cell subcluster from quiescent cells and away from activated and committed cells.
Conclusions: Our findings demonstrate a distinct transcriptional change in satellite cells in cachectic skeletal muscle, and for the first time reveal a novel subcluster of cachectic satellite cells that are in line with enhanced quiescence and impaired differentiation phenotypes that have previously been observed.

4-01
A Comparison of Established Diagnostic Criteria for Cachexia and Their Impact on Prognostication in Patients with Oesophagogastric Cancer

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Background: Cachexia is common in oesophagogastric cancer, yet heterogeneity in its definition has hindered clinical utilisation. This study aims to compare the two established cachexia definitions (Fearon's consensus definition and the Global Leadership Initiative on Malnutrition [GLIM] criteria) and their relationship with survival in patients with oesophagogastric cancer. Prognostic differences between the three GLIM phenotypical criteria (weight loss, low BMI and low radiological muscularity) were also explored.
Methods: Consecutive patients with newly diagnosed oesophagogastric cancer over a 2-year study period (2019-2020) were identified from a prospectively maintained regional database. Involuntary weight loss, BMI, CT body composition analyses and neutrophil-lymphocyte-ratio were recorded at diagnosis. The primary outcome of interest was overall survival.
Results: Overall, 465 patients (66.9% male, median 71 years) were diagnosed with oesophagogastric cancer during the study period. Cachectic proportions differed between definitions (Fearon: 59.1% vs. GLIM: 44.1%). Patients who met either definition had shorter survival than those who met neither (p<0.001). Following adjustment for relevant confounders, GLIM-defined cachexia was more strongly associated with reduced survival (aHR: 1.57 [95%CI: 1.25-1.96], p<0.001) than Fearon-defined cachexia (aHR: 1.41 [95%CI: 1.13-1.76], p=0.002). Median survival amongst patients with Fearon-defined cachexia only (363 days) was higher than the median of the overall cohort (257 days). Those who only met the GLIM criteria has shorter survival (median: 158 days), comparable to that of patients who met both (median 120 days, p=0.300). Neither weight loss (aHR: 1.00 [95%CI: 0.72-1.40], p=0.977) or low BMI (aHR: 1.05 [95%CI: 0.71-1.57], p=0.791) were associated with reduced survival, amongst GLIM-cachectic patients. However, an adverse effect was evident for patients who had low radiological muscularity (aHR: 1.88 [95%CI: 1.15-3.07], p=0.012).
Conclusion: Cancer cachexia is strongly associated with shortened survival in patients with oesophagogastric cancer. Classification using the GLIM criteria provides more effective prognostication and should be utilised in multidisciplinary patient care.

4-02
An exploration of the GLIM inflammation criteria to predict survival in patients with advanced cancer

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Introduction: Global Leadership Initiative on Malnutrition (GLIM) criteria provide a framework for assessing cachexia in cancer patients. However, the role of systemic inflammation in this framework needs further exploration.
Methods: This study analysed a cohort of 338 advanced cancer patients from 18 oncological care settings in UK and Ireland. Modified Glasgow Prognostic Score (mGPS), Neutrophil-to-Lymphocyte Ratio (NLR) and C-reactive protein (CRP) were used to assess systemic inflammation. Associations between these markers, Weight Loss (WL), Body Mass Index (BMI), Skeleton Muscle Index (SMI), and survival outcomes (OS) were evaluated using Chi-square and Kaplan-Meier survival analyses.
Results: CRP was significantly associated with ECOG-PS (p<0.01), and WL (p<0.05). mGPS was significantly associated with ECOG-PS (p<0.001), WL (p<0.001), and BMI (p<0.05). NLR was significantly associated with ECOG-PS (p<0.05), WL (p<0.001), and BMI (p<0.05). CRP (P<0.001), mGPS (p<0.001), NLR (p<0.001), WL (P<0.001), and SMI (p<0.05) were significantly associated with OS, but not for BMI (p=0.23). Combining CRP, mGPS, NLR, with WL, BMI, and SMI significantly improved survival predictions. WL was significantly associated with OS in patients with NLR<3 (p<0.05) but not in those with CRP less than or equal to 10 mg/L or mGPS=0. SMI was significantly associated with OS in patients with mGPS=0 (p<0.05)
Conclusion: Systemic inflammation, as assessed by mGPS and NLR, significantly improves the relationship between phenotypic criteria and OS. These findings support the GLIM framework's inclusion of systemic inflammation as a critical factor. Given its strong predictive value, systemic inflammation should be prioritized in routine clinical assessments of cancer patients, with mGPS having greater prognostic value within the GLIM framework.

4-03
Prevalence and prognostic value of GLIM phenotypic cachexia criteria in patients with cancer: Systematic review and meta-analysis

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Introduction: The Global Leadership Initiative on Malnutrition (GLIM) criteria provide a framework for evaluating cachexia in cancer patients, yet variability in diagnostic application hinders

standardization. The aim of the present study was to examine the prevalence and prognostic value of GLIM phenotypic criteria in patients with cachexia cancer.
Methods: This review adhered to a pre-defined protocol. A comprehensive search of PubMed and EMBASE databases was conducted using specific keywords up to June 12, 2024. Titles and abstracts were screened for relevance, and eligible full-text studies focused on the phenotypic criteria of the GLIM framework and their impact on OS in adult cancer patients. Studies with fewer than 100 patients or lacking OS data were excluded.
Results: Out of 477 studies, 82 met the inclusion criteria, encompassing 114,458 participants. Lung cancer was the most studied type, followed by gastrointestinal and head and neck cancers. Within the GLIM framework, the prevalence of weight loss (WL) >5%, BMI <18.5, BMI <20.0, and lower muscle mass (LMM) were 34.21%, 10.02%, 9.51%, and 41.89%, respectively. Among the 82 articles, WL, BMI, and LMM were reported in 62 (75.6%), 57 (69.5%), and 16 (19.5%) articles, respectively. Meta-analysis showed significant associations between phenotypic criteria and OS, with hazard ratios (HR) of 1.55 (1.24; 1.95), $p < 0.01$ for WL, 1.16 (1.07; 1.27), $p < 0.01$ for BMI, and 2.01 (1.31; 3.10), $p < 0.01$ for LMM. LMM had the most pronounced impact on OS, while BMI showed a less substantial effect.
Conclusion: Variations in cut-offs and assessment periods indicate a need for standardization. The limitations of BMI as a reliable marker are evident, as it can misrepresent cancer cachexia. The analysis also underscores the significant impact of WL and LMM on OS, despite LMM being underrepresented in the literature.

4-04

Prevalence and Prognostic Value of the Global Leadership Initiative on Malnutrition (GLIM) Etiologic Cachexia Criteria in Patients with Cancer: Systematic Review and Meta-Analysis.

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Background: Cancer cachexia significantly impacts survival in advanced cancer patients. The Global Leadership Initiative on Malnutrition (GLIM) offer a standardized approach to diagnosing malnutrition, including cachexia, but require further validation.
Methods: A systematic review and meta-analysis were conducted according to PRISMA-P guidelines. Searches in PubMed and EMBASE up to August 05, 2024, identified studies using GLIM etiologic criteria to assess overall survival (OS) in adult cancer patients. Data from eligible studies were extracted and analysed to determine the association between GLIM criteria and OS.
Results: The review included 38 studies with a total of 61,146 patients. The prevalence of reduced food intake was observed in 49.3% of patients, systemic inflammation in 48.4%, and disease burden in 59.6%. Significant associations were found between each GLIM criterion and OS: reduced food intake (HR 1.71, $p <0.001$), systemic inflammation (HR 1.68, $p <0.001$), and disease burden (HR 2.11, $p <0.001$). The tools most commonly used for these assessments were PG-SGA for reduced food intake, CRP, and mGPS for systemic inflammation, and TNM staging for disease burden. These results highlight the prognostic significance of the GLIM etiologic criteria in cancer patients.
Conclusion: The GLIM etiologic criteria, particularly systemic inflammation and disease burden, effectively predict overall survival in cancer patients. While reduced food intake is similarly prevalent and prognostic, its assessment often relies on subjective tools, limiting its reliability. Therefore, future research should focus on refining the assessment of inflammation, controlled for disease burden, and improving the standardization and objectivity of food intake assessment to enhance the clinical applicability of the GLIM criteria.

4-05

Impact of Modified GLIM Criteria on Mortality Outcomes in Cancer Patients Receiving Palliative Care

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Introduction: The European Society for Medical Oncology (ESMO) cancer cachexia guidelines (Arends et al., 2021) advocate for the application of the Global Leadership Initiative on Malnutrition (GLIM) criteria for diagnosing cachexia. Despite this recommendation, comprehensive validation of these criteria in clinical settings is lacking. This study assesses the relationship between mortality in cancer patients receiving palliative care and the application of modified GLIM criteria.
Methods: A retrospective analysis was conducted on a cohort of adult solid cancer patients managed by the palliative care team at our university hospital from October 2021 to June 2023. Patients were assessed using the GLIM criteria at their initial consultation. Those meeting at least one phenotypic criterion of GLIM and presenting with inflammation (CRP > 0.5 mg/dl) were categorized as cachexia positive (Cx(+)). Patients not meeting these criteria were categorized as cachexia negative (Cx(-)). The study analyzed survival outcomes using log-rank tests and Cox proportional hazards models.
Results: The cohort comprised 516 patients (56.8% male, median age 72 years; 57.4% were aged over 70). There were 312 Cx(+) and 204 Cx(-) patients. Kaplan-Meier survival analysis revealed a significantly reduced median survival in Cx(+) patients (80 days, 95% CI 63-98) compared to Cx(-) patients (280 days, 95% CI 215-384) (log-rank test, P \< 0.001). Multivariate Cox regression, adjusted for age, gender, performance status ≥3, presence of edema, and cancer type, identified Cx(+) status as an independent predictor of increased mortality risk (HR 1.90, 95% CI 1.48-2.44, P \< 0.001).
Conclusion: Modified GLIM criteria for cachexia diagnosis may be useful in predicting worse survival rates in cancer patients receiving palliative care, suggesting their potential utility as a diagnostic tool for cachexia. This indicates that further validation could enhance their application in clinical settings, potentially guiding improved management strategies for these patients.

4-06

Cross-Cultural Adaptation and Application of the miniCASCO Tool for Detecting Muscle Weakness in Cancer Patients

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Introduction: Cachexia is a metabolic syndrome characterized by irreversible loss of skeletal muscle mass (with or without fat loss) that nutritional support cannot reverse. It negatively impacts cancer treatment tolerance and prognosis. Estimates suggest cachexia contributes to 20-60% of cancer deaths. Existing methods for detecting cachexia lack progression classification. Inaccurate assessment can lead to iatrogenesis (patient harm) by overestimating exercise capacity in oncological patients with cachexia. The miniCASCO tool offers an early severity index to address this gap. Our study aims to adapt and apply miniCASCO for detecting and classifying cachexia in Chilean cancer patients.

Method: The study was approved by the Universidad Católica del Maule and Maule Health Service Scientific Ethics Committee (AE N° 007). Cross-cultural adaptation from Spanish to Chilean context involved linguistic harmonization, informant consultation, and tool application. The tool was then administered to 86 patients at the Hospital Regional de Talca. Data normality was assessed using the Shapiro-Wilk Test. Differences between groups were analyzed using Mann-Whitney and Kruskal-Wallis tests with GraphPad Prism 9.5.1 software for macOS (significance level $\alpha = 0.05$).
Results: The miniCASCO tool underwent modification in 36.96% of its item sections. The study population consisted of 35% male and 65% female patients. Within the case group, 12.5% presented with mild cachexia, 5% with moderate cachexia, and 10% with refractory cachexia. In total, 27.5% of patients were classified with some level of cachexia.
Discussion: This study represents the first application of the miniCASCO tool to identify oncological cachexia in Chilean patients. The adapted tool is demonstrably applicable within the local healthcare system.
Conclusion: The cross-cultural adaptation of the miniCASCO tool allowed us to identify, for the first time in Chile, 27.5% cachexia in patients with an oncological diagnosis, demonstrating its potential for use in the Chilean context.

4-07
Prevalence and prognosis of cachexia in patients with non-sarcopenic dysphagia: a retrospective cohort study

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Introduction: The aim is to examine the prevalence and prognosis of cachexia according to the Asian Working Group for Cachexia (AWGC) criteria in patients with non-sarcopenic dysphagia.
Methods: A retrospective cohort study was conducted using the Japanese sarcopenic dysphagia database. Registered patients with dysphagia who did not have sarcopenic dysphagia were included. Cachexia was diagnosed by the AWGC criteria. Sarcopenia was diagnosed by the Asian Working Group for Sarcopenia (AWGS) 2019 criteria. Malnutrition was diagnosed by the Global Leadership Initiative on Malnutrition (GLIM) criteria. Outcomes were death, swallowing function as assessed by the Food Intake LEVEL Scale (FILS), and activities of daily living as assessed by the Barthel Index (BI) at follow-up.
Results: A total of 175 patients who were not sarcopenic dysphagia were included in the study. The mean age was 77 (± 11) years; 103 (59%) were men, 30 (17%) had cachexia, 133 (76%) had sarcopenia, and 92 (53%) had malnutrition. Major causative diseases of dysphagia were stroke (105; 60%), Parkinsonism (15; 9%), dementia (12; 7%), cancer (8; 5%), and others (35, 20%). Of 30 patients with cachexia, 4 and 11 patients did not have sarcopenia and malnutrition, respectively. No statistically significant association was found between the presence or absence of cachexia and the presence or absence of sarcopenia or malnutrition. In univariate analysis, death was significantly more common in the cachexia group (5/30; 17% vs. 2/145; 1%, P=0.002). No significant differences were found in the presence or absence of cachexia in the follow-up median FILS (7 vs. 8, P=0.585) and the median BI (35 vs. 50, P=0.469).
Conclusions: Cachexia was found in 17% of patients with non-sarcopenic dysphagia. Some patients with cachexia did not have sarcopenia or malnutrition. Death may be significantly higher in cachexia.

4-08
Towards a fully automatic workflow for resolving the dynamics of muscle wasting associated with lung cancer cachexia using cone beam computed tomography

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Introduction: Cachexia affects more than half of stage III non-small cell lung cancer (NSCLC) patients, diminishing cancer treatment effects and increasing mortality. Cone-beam computed tomography (CBCT) images, routinely acquired during radiotherapy treatment, might contain valuable anatomical information for monitoring cachexia. For this purpose, we propose an automatic artificial intelligence (AI)-based workflow, consisting of CBCT to synthetic (sCT) conversion, followed by segmentation of the pectoralis muscles for longitudinal follow-up of muscle mass changes.
Methods: Data from 140 stage III NSCLC patients was used. Two deep learning models, CycleGAN and contrastive unpaired translation (CUT), were used for image-to-image translation, to generate sCT images from CBCT images. The no-new U-Net (nnU-Net) model was used for automatic pectoralis muscle segmentation. To evaluate tissue segmentation performance in the absence of ground truth labels, an uncertainty metric (UM) based on Monte Carlo dropout was developed and validated. The contribution of change in pectoralis muscle area (PMA) to overall survival (OS) was analysed by Kaplan-Meier and Cox regression analysis.
Results: Both CycleGAN and CUT restored the Hounsfield unit fidelity of the CBCT images and visually reduced streaking artefacts. The nnU-Net achieved a Dice Similarity Coefficient (DSC) of 0.94 for the sCT images, respectively, on an independent test set. The UM showed a high correlation with DSC with a correlation coefficient of -0.89 for the sCT dataset. PMA loss of more than 3% during radiotherapy was observed in 48% of the patients, which had a negative impact on OS (HR 1.74 [95%CI 0.95-3.19], P=0.072).
Conclusion: This work demonstrates a proof-of-concept for automatic AI-based monitoring of the pectoralis muscle area during radiotherapy treatment based on CBCT images, presenting an unprecedented time resolution of muscle wasting associated with cachexia progression. Ultimately, the proposed workflow could provide valuable information for early intervention of cachexia, ideally resulting in improved cancer treatment outcome.

4-09

Ubiquitous and Unseen: Cancer Cachexia at the End of Life

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Introduction: Cancer cachexia (CC) poses significant challenges for cancer care. It is characterised by tissue loss, anorexia and inflammation. The role CC plays in the cause of death in cancer remains poorly understood. Furthermore, there are little contemporary data on the prevalence of CC at the end of life. This study aims to estimate CC prevalence at end-of-life and explore its role in cancer-related mortality.
Methods: A retrospective analysis was conducted of all patients with cancer who died across a three-year period at a specialist inpatient hospice unit. Patient demographics, clinical and biochemical details and radiological data were extracted from electronic patient records. Data extracted had been generated within 90 days of death. Four definitions (The Global Leadership Initiative on Malnutrition [GLIM], modified Glasgow Prognostic Score, Fearon *et al*. & Evans *et al*.) of CC were applied across the cohort. Cachexia was determined to be the cause of death if there was no evidence that death was caused by tumour obstruction or replacement of an organ.
Results: There were 513 deaths during the period, with lung (n=122, 22%) and colorectal (n=65, 13%) cancer being the most prevalent primary tumour sites. Overall, 94% of patients with available data (n=460) met at least one definition of CC. Differences in prevalence were observed depending on which criterion was used (75 – 93%), with Fearon capturing the greatest number of patients. Cachexia was determined to be the cause of death in up to 71% (201/285) of patients.
Conclusion: This unique study demonstrates the high prevalence of CC at the end of life and its role in the immediate cause of death in cancer. These findings underscore the urgent need to understand the pathophysiology of CC and the mechanisms by which it leads to death, in order to develop therapeutic options and improve quality of life.

4-10

Fully automated CT-segmented fat density may better identify early signatures of wasting in pancreatic cancer.

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Introduction: Opportunistic analysis of routine CT scans has high potential benefit to patient care outcomes. This study sought to investigate the prognostic utility of CT-based muscle, fat, and other organ parameters in a cohort of adults with pancreatic cancer.
Methods: This retrospective study applied a validated, automated body composition segmentation algorithm to contrast-enhanced abdominal CT staging exams in patients with newly diagnosed with pancreatic cancer. At the L3 axial level, area and density was evaluated for muscle, visceral adipose tissue (VAT), subcutaneous adipose tissue (SAT), liver, spleen, and kidney. Time-to-event analyses for mortality were conducted to generate univariate hazard ratios (HR) comparing lowest quartile to the highest three quartiles, multivariate HR by median values, and Kaplan-Meier curves.
Results: A total of 456 patients (mean age 65.6±11.0, 45% female) were included, of which 235 died upon follow-up. Risk of death decreased for every one standard deviation increase in muscle, VAT, and SAT area (HR = 0.79, 0.80, and 0.83, respectively, p<0.05). Conversely, risk of death increased for every one standard deviation increase in VAT and SAT median density (HR = 1.23 and 1.26, respectively, p<0.001). Risk of death was increased (p<0.05) in patients in the lowest quartile for liver density (HR = 1.39) and highest quartile for VAT median density (HR = 1.48) and SAT median density (HR = 1.46). The combination of low muscle density and high VAT density yielded the greatest increase risk of death (HR = 1.88, p<0.001).
Conclusion: There is value in assessing opportunistic CT scans using fully automated segmentation and body composition algorithms as it provides timely and relevant prognostic information for patients with pancreatic cancer. The results from this work identify fat density alone or in combination with muscle density as early prognostic signatures of wasting unique to pancreatic cancer.

4-11

Characterization of muscle in patients with head and neck cancer cachexia

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Introduction: Cachexia, a multi-system condition characterized by loss of skeletal muscle mass that may not improve with nutritional support. Our objective was to analyze muscle tissue from patients with head and neck cancer undergoing surgery via Next Generation RNA Sequencing and correlate with weight loss, imaging, and clinical data.
Methods: After obtaining regulatory approval, consenting adults undergoing head and neck surgery were enrolled. Pre-operative imaging, medical history and peri-operative laboratory data were extracted from the electronic medical record for analysis. Excess quadricep muscle obtained for reconstructive purposes was frozen in liquid nitrogen and stored at -80C. Total RNA was extracted from samples and submitted for Next Generation Sequencing with subsequent analysis.
Results: 51 patients were included in the study. The cohort had a mean age of 66 years ranging from 34 to 90 years. ~90% (46/51 patients) of patients demonstrated objective weight loss before surgery. The incidence of cachexia in this population was 45% and was associated with BMI, lower preoperative weight, larger tumors, and higher modified Glasgow Prognostic Score. Patients with cachexia were more likely to have documentation of malnutrition and screen for high risk of malnutrition on the malnutrition screening tool. RNA Seq analysis was performed on muscle with RIN 6.5 from cachectic (n=7) and non-cachectic groups (n=), with 480 downregulated and 141 upregulated differentially expressed genes (FC>1.5-fold, FDR<0.05). Kegg pathway analysis demonstrated upregulation of myotonic dystrophy 1 up-regulated genes and down-regulation of integrin binding, vascular associated smooth muscle contraction, cell differentiation, regulation of lipolysis, and AMPK signaling pathway.
Conclusion: The results of this study indicate that 1) almost half of patients with head and neck cancer undergoing major surgery present with cachexia, 2) cachexia is associated with other documentation of malnutrition/inflammation, and 3) the gene expression profiling exhibits downregulation of pathways consistent with skeletal muscle wasting.

5-01

Norm-reference values of phase angle for low muscle quality in a Korean population

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Introduction: Phase angle of bioelectric impedance analysis (BIA) is an index derived by dividing the arctangent of reactance by resistance, aimed at correcting for the impact of body fluid conductivity on cell membrane electrical capacitance. This study endeavors to establish cutoff values for PhA as indicator of muscle quality in the Korean population.
Methods: The reference population consisted of 2,844 subjects aged 18 to 92 years. The T-score of PhA was computed as the number of standard deviations (SDs) from the peak PhA value in the young reference group. Individuals were classified as having a “low phase angle” if their T-score ranged from -1.0 to -2.5 and as having a “lower phase angle” if their T-score was less than -2.5.
Results: PhA in men was significantly higher than that in women. Peak PhA in men was in the group of aged 30~39years, while that in women was in aged 40~49 years. According to the PhA-derived T-score, 41.6% of men and 45.1% of women aged 60+ years were classified as low phase angle and 43.6% of men and 13.0% of women aged 60+ years were classified as lower phase angle.
Conclusion: The peak phase angle occurs in the age range of 30~39 years in men and 40~49 years in women. This study establishes age- and sex-specific cutoff values for phase angle (PhA) as an indicative measure of muscle quality in the Korean population. The findings reveal notable gender differences, with men exhibiting higher average PhA levels, and highlight the prevalence of low and lower phase angles in older individuals, emphasizing the potential utility of PhA as a diagnostic marker for sarcopenia in the aging population.

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5-02

Adoption of Routine Clinical Assessment of Sarcopenia and Sarcopenic Obesity in Prostate Cancer Patients on Androgen Deprivation Therapy

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Background: Prostate cancer (PC) remains a prevalent malignancy among men, with androgen deprivation therapy (ADT) being the mainstay of treatment for advanced disease. However, ADT is associated with significant adverse effects, including the development of sarcopenia and sarcopenic obesity (SO), which may impact upon quality of life (QoL), increasing disability and mortality. Although muscle assessment is suggested in expert consensus guidelines, it is not routinely performed in clinic. Therefore, the aims of this project were to trial out routine assessment of sarcopenia and SO and identify prevalence with a goal to improve patient care.
Methods: A registered NHS UK quality improvement project was undertaken at University College London Hospital between April-August 2024. Prevalence of sarcopenia and SO was assessed using bioelectrical impedance assessment (BIA) of body composition, total skeletal muscle index (TSMI) and fat mass (FM), along with measurements of calf circumference (CC), waist circumference (WC) and hand grip strength (HGS). Sarcopenia presence was determined using cut off points and criteria published by the European Working Group for Sarcopenia in Older Adults (EWGSOP) consensus groups in 2010 and 2019.
Results: 30 older men (73.17 +/- 6.90 years, BMI: 26.17 +/- 4.37 kg/m^2) with advanced PC undergoing ADT were screened. Mean HGS was 27.85 +/- 10.05 kg and 46.7% of patients had low HGS. Mean TSMI was 10.14 +/- 1.77 kg/m^2, and 71.4% had either moderate or severe muscle loss. 39.3% had confirmed sarcopenia diagnosis with both low HGS and TSMI. Presence of SO varied from 25-50% depending on methodology used.
Conclusions: Non-invasive assessment of patients was feasible and acceptable, and sarcopenia and SO was highly prevalent in patients, indicative of physical symptoms of androgen deprivation and frailty. Early identification of these conditions in routine clinical practice is essential for targeting interventions for improving QoL, reducing disability risk and improving outcomes. (300 words)

5-03

Classification algorithm for low appendicular lean mass in hospitalized older adults: A classification regression tree approach

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Introduction: Measuring muscle mass to assess muscle status in clinical practice can be challenging, especially in hospital settings. However, having tools like our classification algorithm can make this process more manageable, leading to improved patient care and resource utilization.
Methodology: We conducted a prospective study involving adults over 60 years old who were hospitalized between April and October 2022. We included clinically stable individuals without severe dependency, advanced cognitive impairment, cancer, or diagnosis of COVID-19. Body composition was measured using bioimpedance, and we obtained the values of appendicular lean mass (ALM) and appendicular lean mass index (ALM/high^2) (ALMI). Additionally, we considered functional, cognitive, and nutritional status, clinical history variables, and inflammatory biomarkers (IL-1, IL-6, TNF-α). To identify the best variables for classifying subjects with low appendicular mass, we developed a classification tree model using the cut-off points proposed by the European Working Group on Sarcopenia in Older People (EWGSOP 2) for ALM and ALMI.
Results: Of the 193 individuals included, 66 had low ALM, and 26 had a low ALMI. For ALM, classification trees were generated by sex. For females, the classification model includes the obesity and Frailty Phenotype (FP). For males, Body Mass Index (BMI) and IL-6 were significant in the classification. In the classification tree for both males and females, BMI was the variable that allowed classify low ALM. The classification tree for ALMI was generated for both sexes, considering the low number of women with low ALMI in our sample. In this model, the BMI, hospitalizations, and history of COVID-19 were the variables that helped to classify patients with low ALMI.
Conclusion: This study underscores the practicality of using BMI as a primary method to classify muscle mass in older adults in hospital settings where body composition assessment is limited. This

approach can be particularly useful in resource-constrained environments.

5-04

Mid-regional pro-adrenomedullin is associated with sarcopenia in geriatric patients

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Background: Primary sarcopenia is linked to declining health quality and loss of functional independence in elderly. While there is indirect evidence suggesting that adrenomedullin (ADM) could play a role in the processes leading to or protecting against sarcopenia, particularly through its effects on vascular health and inflammation, direct studies specifically linking ADM to sarcopenia are lacking. Mid-regional pro-adrenomedullin (MR-proADM) is a stable fragment of proADM that is released in a one-to-one ratio with active ADM. We investigated the potential of MR-proADM for use as a novel biomarker for sarcopenia.
Methods: We assessed MR-proADM in 117 geriatric patients (age 80 ± 5 years, 81% female) enrolled in the evaluator-blinded, randomized controlled trial "Sarcopenia and Physical fRailty IN older people: multi-componenT Treatment strategies" (SPRINTT). Body composition was assessed by dual-energy X-ray absorptiometry. Sarcopenia was defined as low appendicular lean mass <19.75kg in males and <15.02kg in females. Patients were divided into lower and higher MR-proADM levels based on the median.
Results: The prevalence of sarcopenia was 36%. Serum levels of MR-proADM were lower in sarcopenic patients (0.77±0.23 *vs.* 0.89±0.26 nmol/L; p=0.017) and were predictive of sarcopenia (Odds ratio (OR) 0.109, 95% CI 0.016-0.732, p=0.023). In a multivariate regression model adjusted for age and sex, sarcopenia (adjusted OR 0.278, 95% CI 0.107-0.719, p=0.008), hand grip strength (adjusted OR 3.340, 95% CI 1.270-8.784, p=0.014), and neutrophil count (adjusted OR 1.677, 95% CI 1.154-2.436, p=0.007) were significantly associated with lower MR-proADM levels.
Conclusion: Lower MR-proADM levels are significantly associated with sarcopenia in geriatric patients. Further validation of these results in a different cohort and using different variables (particularly inflammatory markers) could shed new light on the possible role of MR-proADM in the elderly population and its link to inflammation.

5-05

Associations of low lean mass by EWGSOP2, FNIH and EASO/ESPEN and MRI muscle composition with all-cause mortality across BMI classes

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Introduction: Appendicular lean mass (ALM) by extensively is used in sarcopenia assessment. Different body size normalisations are recommended by working groups and guidelines. The aim was to investigate prevalence of "low lean mass" (ALM, ALM/height^2, ALM/BMI, ALM/weight) as well as adverse muscle composition (AMC), low muscle volume z-score (MVz) and high muscle fat infiltration (MFI) by MRI, and their associations with all-cause mortality in UK Biobank participants with normal weight (BMI<25 kg/m^2), overweight (BMI 25-30 kg/m^2), and obesity (BMI>30 kg/m^2).
Methods: N=14,399/14,318/6,160 with normal weight/overweight/obesity were included. Published thresholds for "low lean mass" (EWGSOP2 [ALM, ALM/height^2], FNIH [ALM/BMI], and EASO/ESPEN [ALM/weight]) and MRI muscle composition were used. Cox regression with adjustment for sex, age, and BMI were used.
Results: Prevalence of "low lean mass" varied greatly across BMI classes: 22.4/5.2/0.8% for ALM in normal weight/overweight/obesity, 20.5/1.8/0.1% for ALM/height^2, 0.9/4.6/15.6% for ALM/BMI, and 0.1/1.0/8.7% for ALM/weight, while prevalence of low MVz were stable (25.9/25.0/25.0%). Higher MFI was associated with higher BMI leading to higher prevalence of AMC and high MFI in overweight/obesity: 6.4/12.7/19.4% and 11.4/28.1/54.1% respectively. For "low lean mass", significant associations with all-cause mortality were found for low ALM/height^2 in normal weight (HR [95% CI] 1.43 [1.02,2.01)], p=0.038), ALM/BMI in overweight (1.92 [1.26,2.93], p=0.002), and ALM/weight in overweight (2.52 [1.27,4.97], p=0.008). Associations with all-cause mortality were significant across all BMI classes (normal weight, overweight, obesity) for low MVz (1.50 [1.12,2.00]; p=0.007, 1.42 [1.08,1.88]; p=0.012, 2.10 [1.48,2.99], p<0.001), high MFI (1.78 [1.27,2.50]; p=0.001, 1.85 [1.40,2.44]; p<0.001, 1.72 [1.15,2.58]; p=0.008), and AMC (2.16 [1.47,3.17]; p<0.001, 1.68 [1.23,2.29]; p=0.001, 2.41 [1.68,3.45]; p<0.001).
Conclusions: Different body size normalisations of ALM for "low lean mass" identifies different sub-populations making interpretations of sarcopenia literature challenging. Associations with all-cause mortality were consistent across BMI classes for MRI muscle composition but not for "low lean mass" with DXA.

5-06

Building Capacity in Computed Tomography (CT)-based body composition analysis:
Development and implementation of an online education program

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Introduction: Computed tomography (CT)-defined reduced muscle mass is a well-established poor prognostic factor in patients with cancer, contributing to growing interest in CT-based body composition analysis. Broader clinical and research application of this method requires accessible education and adherence to rigorous precision standards. To address this gap, we developed and implemented an education program to build capacity and ensure accurate application of CT-based body composition analysis.
Methods: Led by an expert international faculty, a 3-day face-to-face (F2F) program (2018-19) was delivered prior to the launch of a self-directed online education program at Monash University (2024). The program comprises four modules on scientific theory and practical experience in CT evaluation of body composition concluding with an inter- and intra-rater precision assessment (coefficient of variation (%CV) <2% muscle, <3% adipose tissue). Program evaluation includes pre-post-surveys to assess confidence, knowledge gain, skill development, engagement/satisfaction and suggestions for improvements.
Results: Twenty-five participants (19 F2F; 6 online) completed evaluations: 17 dietitians, 3 researchers, 2 doctors, 2 students and

1 exercise physiologist. Over half had previous formal training in anatomy (n=16). Prior to the program, participants reported being 'not at all confident' (n=20) or 'somewhat confident' (n=5) in CT-based assessments. Post-program, confidence improved to 'mostly confident' (n=17) or 'completely confident' (n=6). All participants agreed the program met their expectations regarding acquisition of knowledge, new skills and expert presentations assisted their learning. All participants successfully demonstrated acceptable inter-observer precision (mean CV (%) ±SD: 1.35 ±0.37 skeletal muscle, 1.37 ±0.37 visceral adipose tissue, 1.64 ±0.56 subcutaneous adipose tissue).
Conclusions: The program successfully achieves participant proficiency in CT-based body composition analysis and adherence to precision standards. The accessibility of the online format and emphasis on precision standards are expected to facilitate advances in the understanding and management of reduced muscle mass in cancer care and support positive clinical impact.
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5-07

Bioimpedance phase angle and thigh muscular assessment are promising approaches to assessing 30-day mortality risk after hip fracture in older people.

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Introduction: In the acute phase of hip fracture, patients are bedridden, receiving saline infusions, and after surgery, will have a metal device to fix it. Therefore, the diagnosis of sarcopenia and muscle wasting is challenging and poorly studied as a predictor of mortality. **Objective:** The present study aimed to assess muscle thickness and quality with ultrasound, body composition with bioimpedance, and hand-grip strength with dynamometer and investigate the association of these parameters with 30-day mortality after a fracture.
Methods: This prospective cohort included people older than 60, with less than three days of neck, trans, and subtrochanteric femur fracture, who had undergone surgical treatment. The Nottingham Hip Fracture Score (NHFS) was used to assess the severity. Phillips Lumify ® ultrasound acquired rectus femoris and vastus lateralis images. Image J software ® was used to measure muscle thickness, pennation angle, fascicle length, and echogenicity. SECA mBCA 525 ® bioimpedance was used to measure phase angle, water, fat, and fatty-free mass). Hand grip strength was measured with a JAMAR ® dynamometer.
Results: 132 patients were included, 78% female, and a mean age of 81.5±8.95. According to NHFS, 51% were high-risk, and 14% died in 30 days. Fat-free mass and hand grip strength were not associated with mortality. ROC curve and Multiple logistic regression adjusted by NHFS showed, respectively, that Phase Angle (AUC=0.740) and OR=0.35 (95%CI=0.16-0.73) (P=0.006); rectus femoris thickness (AUC=0.670) and OR=0.06 (95%CI=0.00-0.089) (P=0.041); vastus lateralis thickness (AUC=0.660) and OR=0.12 (95%CI=0.01-0.98) (P=0.049); length of vastus lateralis (AUC=0.73) and OR=0.87 (95%CI=0.79-0.97) (P=0.014) were associated with 30-day mortality.
Conclusion: Raw data from bioimpedance, such as Phase angle and Muscular ultrasound assessment, are a promising approach to detecting risks and muscle wasting in older people with acute trauma, better than fatty-free mass and muscle strength, traditionally included in the sarcopenia diagnosis.
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5-08

Defining sarcopenia: New MRI cut-off values for low muscle mass

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Introduction: Sarcopenia is defined as a combination of low skeletal muscle mass and reduced muscle function. Magnetic resonance imaging (MRI) is a gold standard for the non-invasive quantification of muscle mass, making it a valuable tool for diagnosing low muscle mass in sarcopenia. However, no standardized cut-off values for low muscle mass using MRI have been established yet.
Methods: The skeletal muscle index (SMI=total muscle mass/height²) was used to establish the cut-off values. The total muscle mass was semi-automatic contoured from cervical vertebra 1 to the malleoli of the ankle. Four hundred fifty-two healthy Caucasians (212 men, 240 women, median age: 42 years, IQR: 30-56) were divided into five age categories. The 5th percentile (P5) was determined for each category. The prevalence of low muscle mass in people over 40 was determined based on the P5 cut-off value for SMI in the young participants (113 men and 104 women, aged 18-40).
Results: The cut-off values for SMI for the different age categories for men were: <30y: 8.6kg/m², 30-39y: 7.9kg/m², 40-49y: 7.7kg/m², 50-59y: 7.4kg/m², 60+y: 7.4kg/m². For women, the cut-off values were: <30y: 6.6kg/m², 30-39y: 5.6kg/m², 40-49y: 6.0kg/m², 50-59y: 5.4kg/m², 60+y: 5.3kg/m². The cut-off values for SMI based on the young participants were 8.2kg/m² for men and 6.0kg/m² for women. The prevalence of low muscle mass in the group aged 40-65 and aged 65+ was 5.1% and 35% for men and 6.7% and 16% for women.
Conclusion: This study established age-specific MRI-based cut-off values for SMI, providing a standardized method for diagnosing low muscle mass. These cut-off values may improve early detection of sarcopenia in clinical practice. This study supports the use of MRI as a gold standard in muscle mass quantification.

5-09

Exploring the link between sarcopenic obesity and hepatic steatosis in patients with NAFLD

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Introduction: Nonalcoholic fatty liver disease (NAFLD) affects approximately 25-30% of the general population in the United States. Over 80% of those with NAFLD have overweight or obesity, and 30-40% of these individuals progress to liver fibrosis and cirrhosis. Sarcopenic obesity (SO) refers to the coexistence of sarcopenia, characterized by progressive loss of muscle mass and strength and excess body fat. Evidence indicates a higher prevalence of sarcopenia among individuals with NAFLD.SO is a significant risk factor for developing hepatic steatosis and is linked to more severe liver fibrosis. We proposed to test the hypothesis that body composition parameters might be associated with hepatic steatosis, liver fibrosis, and type 2 diabetes mellitus (T2DM) in the NAFLD population.
Methods: This cross-sectional study was part of a larger randomized, placebo-controlled clinical trial. Data from 74

participants aged 22 to 80 years with a BMI between 20-55 kg/m² were included in the analysis. Multivariate linear regression was performed to investigate the association of skeletal muscle index (SMI) with the hepatic steatosis index (HSI). Multivariate logistic regression analysis was applied to evaluate the independent association between fat mass or appendicular/total lean mass and incident of liver fibrosis and T2DM in NAFLD patients.
Results: Preliminary analysis revealed that a higher SMI is negatively correlated with the HSI (coefficient: -0.526, p = 0.028). Furthermore, logistic regression results indicate that more visceral fat is associated with a higher risk of fibrosis (OR: 3.61, *p*=0.008). However, there was no association between the SMI and TD2M (OR: 1.18, *p*=0.888). Moving forward, we will investigate the relationship between sarcopenia and liver steatosis/fibrosis based on SMI cut-off points for male and female participants.
Conclusions: SO may be linked to NAFLD. Prospective studies are needed to clarify the causal relationship and understand if SO impacts NAFLD, which could inform effective management strategies.

5-10
Comparing predictive ability of sarcopenia definitions using muscle ultrasound for clinical outcomes among older inpatients

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Background: There is a lack of studies among older inpatients investigating sarcopenia based on muscle ultrasound. We aimed to investigate the predictive ability of sarcopenia based on rectus femoris (RF) ultrasound for key clinical outcomes in hospitalized older patients.
Methods: Data were analyzed from 215 inpatients aged 70 years or older, consecutively admitted to a geriatric rehabilitation hospital in Switzerland between October and December 2023. Sarcopenia was defined based on the European Working Group on Sarcopenia in Older People (EWGSOP2) comparing muscle mass measured by 1) Ultrasound RF thickness, 2) Ultrasound RF cross-sectional area (CSA), and 3) bioelectrical impedance analysis (BIA). As secondary analyses, cut-offs of the Sarcopenia Definitions and Outcomes Consortium (SDOC) were applied (definitions 4-6) to the three definitions. Predictive ability of all six sarcopenia definitions was assessed for non-home discharge, functional and mobility impairment upon discharge using multivariate logistic regression models.
Results: Prevalence of sarcopenia ranged from 19.1% using RF thickness (EWGSOP2), to 34.4% using RF CSA (SDOC). Overall, 49 patients (22.8%) had non-home discharge, 53 (24.7%) functional impairment, and 96 (49.7%) mobility impairment. Sarcopenia using all six definitions was predictive for non-home discharge (e.g. RF thickness (EWGSOP2) adjusted OR 5.7 (95% CI 2.6-12.5)). Ultrasonographic RF thickness and CSA showed a higher odds ratio to predict functional impairment (OR 5.2 (95% CI 2.4-11.5), OR 5.5 (95% CI 2.6-11.9)), compared to BIA (EWGSOP2) (OR 2.8 (95% CI 1.2-6.4)). Overall, RF CSA (SDOC) was the only sarcopenia definition not only predicting non-home discharge and functional impairment, but also being significantly associated with impaired mobility (OR 2.5 (95% CI 1.3-5.0)).
Conclusion: Predictive ability of sarcopenia definitions varied depending on the clinical outcomes and cut-offs applied. Muscle ultrasound applying the SDOC cut-offs was the most promising sarcopenia definition to predict clinical outcomes in older inpatients, highlighting the need for further study.

5-11
Predictors and clinical correlates of Frailty in heart failure

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Background: The combination of frailty and heart failure is associated with increased risk of hospitalization and mortality as with exacerbation of symptoms. Thus, the characterization of both syndromes by clinical parameters is of great interest.
Methods: In a retrospective analysis, we included 253 patients (22.1% female) with heart failure. Physical frailty was defined as a summary score on the short physical performance battery (SPPB) of 3 to 9 points. Iron deficiency (ID) was defined as ferritin <100µg/L or ferritin between 100 and 299µg/L with transferrin saturation (TSAT) <20%. Anaemia was defined as decreased haemoglobin (Hb) values <13g/dL in males and <12g/dL in females.
Results: Prevalence of patients with frailty, ID and anaemia were 68 (36.8%), 129 (51.0%) and 78 (30.8%), respectively, even though only 32 (12.6%) patients presented with the three comorbidities simultaneously. Frail patients were more symptomatic (NYHA class III-IV: 66.2 vs 22.6%, p<0.001), had higher plasma concentrations of NT-proBNP (1066 (300-2805) vs. 437(171-1342) pg/mL, p=0.003), and more advanced renal function (eGFR: 55.9(39.5-69.8) vs. 68.7(54.8-70) mL/min/1.73m^2, p<0.001) than non-frail patients. There was no difference in frail status with respect to sex or LVEF. Using univariate logistic regression analysis, predictors of frailty were age, peak VO2 and 6-minutes walking distance (6MWD), NT-proBNP, eGFR, FGF-23, anaemia and iron deficiency. Anaemia (OR: 4.1, 95%CI: (1.86-9.04), p<0.001) and 6MWD (OR: 0.004, 95%CI: (0,00-0.143) per log-unit increase, p=0.002) remained independent predictors of frailty in a multivariate model including all above-mentioned parameters. Osteoprotegerin remained a predictor of frailty in univariate and multivariate models adjusted for age and anaemia (OR: 1.201, 95%CI: (1.013-1.424), p=0.035).
Conclusion: In our cohort, physical frailty defined by SPPB score was strongly related to anaemia and reduced walking distance, irrespective of age, and severity of HF or renal function. Additionally, osteoprotegerin might be used as a biomarker for early detection of frailty.

5-12
Assessing the validity of serological biomarkers in estimating muscle mass: a retrospective cross-sectional NHANES analysis

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Introduction: A novel equation for estimating total body muscle mass was proposed by researchers who hypothesized that differences between creatinine and cystatin C based eGFR calculations are attributable to differences in total body muscle mass (Kim et al., 2016). The purpose of this study is to assess the validity

of their equation by applying it to a large, representative population sample from the National Health and Nutrition Examination Survey (NHANES).
Methods: This cross-sectional study utilized data from the NHANES 2001-2002 dataset, selecting participants with complete, valid data on total body weight, serum creatinine, serum cystatin C, gender, and DXA scan measurements. Participants with missing or imputed data were excluded from the study population. The estimates generated using the Kim equation were compared to the corresponding DXA-measured muscle mass values. Linear regression analyses were conducted to assess the relationship between the estimates and the DXA measurements, both overall and by gender.
Results: This study included 1989 participants between the ages of 12 and 85. A strong positive association was observed between the muscle mass estimated by the Kim equation and the DXA measurements (R^2=0.868, p<0.001). However, gender-specific analyses revealed inconsistencies between the male (R^2=0.808, p<0.001) and female (R^2=0.659, p<0.001) subgroups.
Conclusions: The novel equation for estimating total body muscle mass from creatinine and cystatin C levels demonstrates a strong positive association with actual muscle mass when applied to the large NHANES population sample. However, the lack of consistent R-squared values across subgroups suggests that further refinement and validation are necessary before a serologically based muscle mass estimation method can be considered for clinical use. Future assessment can focus on adjustment or addition of equation constants, as well as the effect of demographic or clinical factors such as age, BMI, and kidney function.

5-13
Developing an AI-Driven X-Ray Segmentation Model for Accurate Sarcopenia Diagnosis: Overcoming DEXA Limitations

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Introduction: Sarcopenia, characterized by loss of skeletal muscle mass and strength, significantly impacts elderly populations' health outcomes. While Dual-energy X-ray absorptiometry (DEXA) is widely regarded as the gold standard for muscle mass assessment, it presents notable limitations, particularly for individuals with implants, where accuracy may be compromised. Additionally, the high cost and limited accessibility of DEXA make it less feasible for routine use in primary care settings. This study aims to address these challenges by developing and validating a more accessible and cost-effective AI-driven auto-segmentation model for muscle mass assessment using long X-rays.
Methods: We developed an AI-based semantic segmentation model using 351 lower extremity X-ray images from the Real Hip Cohort. The model, trained with U-Net++ architectures, was evaluated using metrics like IoU and Dice Coefficient. Two expert annotators manually segmented the images to estimate muscle areas. Validation was conducted against 66 Dual-Energy X-ray Absorptiometry (DEXA) scans, employing Spearman's correlation and included an one-year follow-up DEXA analysis.
Result: The study included 157 patients, average age 77.1 years. The U-Net++ model excelled in muscle segmentation, achieving an IoU of 0.93 and a Dice coefficient of 0.95. Validation against 66 DEXA scans showed a Pearson correlation of 0.72 with the DEXA-derived skeletal muscle index. One-year follow-up indicated a 22.5% increase in the skeletal muscle index but revealed a 7.15% muscle volume loss in X-rays, contradicting DEXA results.
Conclusion: The AI-based semantic segmentation model using U-Net++ architecture demonstrated high accuracy in muscle mass quantification from X-ray images, with IoU of 0.91 and Dice Coefficient of 0.95. The model's estimates showed a strong correlation with DEXA skeletal muscle index (r = 0.664, p < 0.001). This X-ray segmentation method offers a promising tool for sarcopenia diagnosis, overcoming DEXA limitations and providing detailed muscle group analysis.

5-14
Skeletal muscle index optimal thresholding for prognosis in metastatic non-small-cell lung cancer

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ABSTRACT TOPIC – Diagnosis of sarcopenia

Introduction: Non-small-cell lung cancer (NSCLC) is deeply heterogeneous, hence precision oncology is cornerstone to treatment decision. Contrastingly, despite mounting evidence supporting sarcopenia as a prognostic biomarker, skeletal muscle index (SMI) analysis remains neglected. Discrepant sarcopenia definitions are a major caveat regarding this analysis. Herein, we assess SMI optimal thresholding for prognostic value in a Portuguese metastatic (m) NSCLC cohort.
Methods: Retrospective study including mNSCLC patients treated at Unidade Local de Saúde São José between January 2017 and December 2022. National Institute of Health ImageJ software was used to assess skeletal muscle area (SMA; cm2) in CT cross-sectional L3 vertebrae images, allowing for SMI measurement (SMA/square height; cm2/m2). SMI thresholding was obtained using receiver operating characteristic analyses. Based on relevance, sarcopenia would be defined both as according to Prado et al. (SMI <52.4cm2/m2 for men/ <38.5 cm2/m2 for women) and through SMI optimal thresholding. Statistical analysis was performed with SPSS v25. Follow-up data cutoff was 15th July 2024.
Results: One hundred ninety-seven patients were included. Mean age was 65 years-old (± 11.31). Adenocarcinomas were predominant (n=165); most NSCLC were metastatic ab initio (n=154). SMI was evaluable in 184 patients: optimal sex-specific SMI thresholds (<49.96cm2/m2 for men and <34.02cm2/m2 for women) led to 36 patients (19.56%) being reclassified as not sarcopenic vs prespecified literature threshold. Median Survival was 18.4 months (95% confidence interval [CI] 14.79–22.01). Optimal SMI thresholding was prognostic (12.75 months vs 21.13 months, hazard ratio 1.654 95%CI 1.20–2.29, p=0.002). Conversely, prespecified literature definition could not predict survival (17.9 months vs 20.11 months, p=0.588). Sarcopenia's survival impact was consistent across treatment subgroups.
Conclusions: As sarcopenia becomes a key prognostic biomarker, heterogeneous SMI cut points impact timely multimodal intervention, as highlighted herein. Noteworthy, body composition analysis is feasible in routine clinical practice without additional costs or logistics.

5-15

Exploring the Obesity Paradox: Body Composition and Outcomes in Older Women with Hip Fractures

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Introduction: The obesity paradox suggests that higher body weight may protect older adults from poor outcomes. However, it remains to be clarified whether this protection is due to obesity or muscle preservation.
Objective: To classify older women with hip fractures using the body composition chart (BCC) comparing variables and mortality. Methods: Observational study of older women with acute hip fractures. SECAmBCA525 bioimpedance showed the BCC according to fat mass index (FMI) and fatty-free mass index (FFMI), in Obesity (O): high FMI/high FFMI; Sarcopenic obesity (SO): high FMI/low FFMI; Low body mass (LM): low FMI/ low FFMI and High fat-free mass (HFF): high FFMI/ low FMI. Phillips Lumify ® ultrasound acquired rectus femoris thickness (RFt; cm) and fat thickness (Ft; cm). The Nottingham Hip Fracture Score (NHFS) measured severity. Mini Nutritional Assessment (MNA) defined undernutrition. ANOVA compared the groups, considering [a] ≠ of O; [b] ≠of SO; [c] ≠of HFF. Logistic regression evaluated 30-day mortality, adjusted by NHFS. Significance level was 5%.
Results: 118 women with 81±8.9 years were evaluated. Group O(33): MNA=24±4; RFt=0.77±0.21; Ft=1.34(1.02-1.48); extracellular water; liters (eW)=15(14-16). Group SO(25): MNA=23±3; RFt=0.66±0.26; Ft=0.82(0.59-1.18)[a], eW=13(11-13)[a,c]. Group LM(37): MNA=19±4[a,b]; RFt=0.54±0.19[a]; Ft=0.52(0.35-0.78)[a]; eW=13 (11-14)[a,c]. HFF(23): MNA=21±4[a]; RFt=0.58±0.21[a]; Ft=0.67 (0.39-0.96)[a] ; eW=15 (14-16). Mortality was different between groups LM=16%; HFF=17%; SO=4%; O=0%. LM and HFF combined increased 30-day mortality (OR=8.94; 95%CI=1.08-73.88; p=0.04).
Conclusion: Obesity protects older women from poor outcomes. O and SO presented similar RFt. Being careful with HFF is essential because a higher FFM might mean water retention, not muscle mass. In HFF group, lower muscle thickness and undernutrition were similar to LM and SO and worse than O. BCC might not be suitable to differentiate Obesity from Sarcopenic obesity and not appropriate to identify high muscle mass, but water retention in older women with hip fracture. Support FAPESP: 2022/15147-6 and 2022/15993-4.

6-01

chemR23 as a new therapeutic target for uraemic sarcopenia?

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People with chronic kidney disease (CKD) often experience poor muscle quality and elevations in skeletal muscle wasting and dysfunction contributing to a reduced quality of life and an increased risk of morbidity and mortality. The adipokine chemerin is associated with CKD progression and is involved in inflammatory-related signalling processes. With chronic inflammation recognised as a driving factor in uraemic sarcopenia, we aimed to investigate the potential role of chemerin as a uraemic toxin in CKD and identify the mechanisms of action to elucidate therapeutic opportunities in uraemic sarcopenia.
Chemerin levels from EDTA-plasma and urine samples were quantified via ELISA on basal samples from those across the kidney disease continuum. Chemerin levels were correlated with eGFR and measures of body composition, physical performance, muscle mass, and muscle quality. A sub-set of participants from each group underwent skeletal muscle biopsies and samples were processed for gene and protein analysis, or cells extracted for *in-vitro* experimentation.
Higher circulating chemerin was associated with lower eGFR ($p<0.001$, $r=-0.571$). Positive correlations with body fat % and BMI were noted in CKD patients. Higher circulatory chemerin was associated with poorer muscle quality ($r=0.396$, $p=0.003$). Molecular analysis detected the presence of 2 out of 3 receptors of interest for chemerin in skeletal muscle. *In-vitro* analysis showed that the exposure of CKD-derived muscle cells to chemerin induced a significant inflammatory response (IL-6 $p<0.001$; TNFα $p=0.0215$), which was halved using the ChemR23 receptor inhibitor αNETA (IL-6 $p<0.001$; TNFα $p<0.001$).
We report that chemerin is a uraemic toxin in those with CKD and may contribute to poorer muscle quality in these people. Chemerin can moderate indicators of inflammation within skeletal muscle via the activation of ChemR23 and as such proposes a new therapeutic target to alleviate the symptoms of uraemic sarcopenia.

6-02

Astaxanthin Mtigates Doxorubicin-Induced Muscle Atrophy by Inhibiting NF-κB-Mediated TRPC6 Upregulation

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Introduction: TRPC6 is crucial in muscle atrophy, as it mediates oxidative stress and inflammation through ROS and NF-κB activation. This study examines how astaxanthin, a strong antioxidant, protects against muscle atrophy by regulating TRPC6 activity and reducing oxidative damage.
Methods: Differentiated C2C12 were treated with 0.2 μM Dox for 48 hr to induce atrophy, with concurrent ATX administration. NF-κB, TRPC6 protein and mRNA levels were analyzed using Western blotting and qPCR.
Results: Dox treatment significantly increased TRPC6 expression and enhanced nuclear translocation of NF-κB subunit p65. Co-treatment with ATX significantly reduced ROS levels, inhibited NF-κB activation, and prevented TRPC6 upregulation, thereby mitigating muscle atrophy.
Conclusion: Dox induces muscle atrophy in C2C12 by upregulating TRPC6 through NF-κB activation, driven by increased ROS levels. ATX protects against muscle atrophy by reducing oxidative stress, inhibiting NF-κB activation, and preventing TRPC6 upregulation. These findings suggest ATX as a potential therapeutic target for preventing muscle atrophy via the NF-κB/TRPC6 pathway.
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6-03

Ferroptosis in facioscapulohumeral muscular dystrophy

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Introduction: Facioscapulohumeral muscular dystrophy (FSHD) is an autosomal dominant muscle disease, caused by aberrant expression of double homeobox protein 4 (DUX4) gene. We recently reported that abnormal accumulation of mitochondrial proteins and plasma membrane repair deficits in myocytes from individuals with FSHD as well as in a mouse model of the FSHD. In a scRNA-seq study, we discovered that genes involved in ferroptosis were mis-regulated in the FSHD myoblasts after mild membrane injury. We hypothesized that ferroptosis might be involved in the higher cell death rate observed in the injury study. In this study, we examined the iron level and lipid oxidation in the plasma membrane.
Methods: Immortalized human myoblasts from individuals with FSHD and their unaffected siblings (as control) were cultured in growth media and gently scraped off the culture plate before staining with either FerroOrange to determine the Iron level; or BODIPY FL dye to determine lipid oxidation. The time points include baseline, 6 hours and 24 hours after the injury.
Results: There were differences in genes involved in ferroptosis at the baseline. After the cell injury, we observed additional genes involved in ferroptosis were mis-regulated. Intracellular iron levels were higher in the FSHD myoblasts and there was higher lipid oxidation in the cell membrane. Treatment with Trolox had a protective effect.
Conclusion: We conclude that high free iron and membrane lipid oxidation may contributes to the cell death process in the FSHD myoblasts after mild membrane injury. The findings suggest that FSHD myocytes may be more susceptible to membrane injury via the ferroptosis pathway.

6-04

The effects of glucagon-like peptide-1 receptor agonists on skeletal muscle mitochondrial function: a systematic review

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Introduction: The advent of glucagon-like peptide-1 (GLP-1) receptor agonists (RAs) have the potential to revolutionize the management of obesity and T2DM, demonstrating significant efficacy in glucose lowering and weight loss. While GLP-1RAs have shown substantial weight loss benefits, up to 40% of the loss comprises lean mass, raising concerns about potential adverse effects on skeletal muscle function. Mitochondrial dysfunction, characterized by reduced mitochondrial size and activity, is prevalent in individuals with obesity and T2DM, underscoring the need to understand the implications of GLP-1RA therapy on mitochondrial health. This systematic review investigates the impact of GLP-1RA therapy on skeletal muscle mitochondrial function in individuals with obesity and T2DM or in related animal and cell models.
Methods: A comprehensive search of MEDLINE, Scopus, CINAHL, and clinicaltrials.gov was conducted. Inclusion criteria: studies examining mitochondrial function in the context of GLP-1RA therapy in clinical populations, animal models or *in-vitro* models with obesity and/or T2DM.
Results: The review included 8 pre-clinical studies that used rodent models and *in-vitro* cell lines, no human studies were identified. Mitochondrial density, area or morphology was reported in 3 studies with all demonstrating an increase in area and number. Mitochondrial content was reported in 1 study with increases of citrate synthase activity and Cox5B. Mitochondrial function was reported in 2 studies with 1 showing an increase in oxygen consumption rate following Exendin-4 while the other study demonstrated no difference. Mitochondrial biogenesis was reported in 2 studies with both demonstrating an upregulation of PGC-1α although 1 study also noted no difference in the regulation of PGC-1α in the soleus muscle.
Discussion: These findings indicate that GLP-1RA therapy may positively influence various aspects of mitochondrial function, including density, morphology, content, biogenesis, and metabolism. However, data is scarce and requires further research to understand these effects, particularly within human models.

6-05

Mitochondrial permeability transition causes skeletal muscle alterations common in Sarcopenia Cachexia and Wastind Disorders

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Introduction: In contrast to the established role of mitochondrial permeability transition (mPT) in cardiac ischemia-reperfusion injury and other tissue pathology, the role of mPT in skeletal muscle is less clear, notwithstanding some work in muscular dystrophies.
Methods: To address this gap, we used mouse single muscle fibers, isolated skeletal muscle mitochondria, and C2C12 cells to establish the consequences of mPT in skeletal muscle. We induced mPT using Bz423; inhibited mPT using Alisporivir, TR002, or Isox63; assessed mitochondrial ROS (mROS) generation using mitoSox, and inhibited mROS using mitoTEMPO. We assessed caspase 3 (Casp3) activation using a Casp3 FLICA assay, and inhibited Casp3 using Ac-ATS0101-KE. We assessed mitochondrial respiration in isolated mouse skeletal muscle mitochondria, and assessed co-localization of mitochondria in C2C12 myotubes using mitoTracker Green and LysoTracker Deep Red. We evaluated acetylcholine receptor cluster (AChR) morphology on single mouse muscle fibers. The Ca^{2+} threshold for mPT was determined in a Ca^{2+} retention Capacity (CRC) assay.
Results: Inducing mPT in single mouse muscle fibers increased mROS that was prevented by inhibitors of mPT and mROS. Similarly, Bz423 increased Casp3 activity that was prevented by inhibiting mPT or Casp3. Incubating single muscle fibers with Bz423 for 24 h reduced fiber diameter by ~20% and was prevented by inhibiting mPT, mROS, or Casp3. Inducing mPT with Bz423 caused a complex I-specific mitochondrial respiratory impairment and increased co-localization of lysosomes with mitochondria. Bz423 treatment also fragmented the AChR cluster at the muscle endplate that was prevented by inhibiting mPT or Casp3. The Ca^{2+} threshold for mPT was reduced by incubating in pancreatic tumor-conditioned media and in media containing LPS.
Conclusions: Inducing mPT in skeletal muscle generates muscle phenotypes common with aging and a variety of disease conditions and we suggest that mPT may be more likely in cancer cachexia and sepsis.

6-06

Effects of iron deficiency on bone health in patients with chronic heart failure:
Results from the Studies Investigating Co-morbidities Aggravating Heart Failure (SICA-HF)

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Introduction: Iron is crucially involved in the activation cascade of vitamin D. However, the association of iron deficiency (ID) with vitamin D levels and bone mineral density (BMD) is not well described. The definition of ID in heart failure (HF) is also still controversial. This study aims to investigate the association of established and emerging definitions of ID with vitamin D levels and BMD in patients with chronic HF.
Methods: A total of 212 patients with chronic HF (67±11 years, 80% male) were assessed for iron status, vitamin D levels, and BMD from the Studies Investigating Co-morbidities Aggravating HF (SICA-HF) database. ID was defined using different criteria: 1) serum ferritin <100 ng/mL or 100-299 ng/mL with transferrin saturation (TSAT) <20%) (current definition); 2) serum iron ≤13 µmol/L; 3) TSAT <20%. Patients were divided into higher and lower total-body BMD based on the sex-specific median (men = 1.23 g/cm^2, women = 1.13 g/cm^2).
Results: The prevalence of ID was 44.8%, 27.4%, and 31.6% for each definition. Patients with ID by lower serum iron levels or lower TSAT had significantly lower 1,25-dihydroxy vitamin D (1,25(OH)2 vitamin D) levels (30 [25-40] vs. 35 [28-42] pg/ml, p=0.04; 30 [25-39] vs. 35 [28-43] pg/ml, p=0.03) and interestingly, higher total-body BMD (1.25 ± 0.11 vs. 1.20 ± 0.13 g/cm^2, p=0.02; 1.25 ± 0.11 vs. 1.20 ± 0.13 g/cm^2, p=0.009) than those without ID. No such difference could be detected with the current ID definition. In a multivariate regression analysis, ID by lower serum iron or lower TSAT were significantly associated with higher total-body BMD (adjusted odds ratio (aOR) 3.46, p=0.005, and aOR 3.97, p=0.001, respectively).
Conclusion: In patients with chronic stable HF, the association of ID defined by different criteria with 1,25(OH)2 vitamin D levels and BMD was discordant.

6-07

AMPK in skeletal muscle as a therapeutic target for sarcopenic obesity

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Introduction: Sarcopenic obesity (SO) is characterized by muscle weakness and atrophy, accompanied by increased body fat as individuals age. Currently, there is no FDA-approved treatment for this condition. AMP-activated protein kinase (AMPK) is an energy sensor activated by exercise, and reduced levels of muscle AMPK have been previously reported with aging This study aims to understand the role of muscle AMPK in aged mice and investigate its potential as a therapeutic target for SO.
Methods: Wild-type (WT) and muscle-specific AMPKα2 transgenic (α2 D157A mutant, TG) mice were used for this study. Young (4-6-month), middle-aged (12-13-month), and old (20-24-month) male and female WT and TG mice were evaluated for body composition, grip strength, endurance (treadmill), and muscle mass. Muscle physiology was assessed in young and old mice, while the protein content of isolated mitochondria from muscles was evaluated in middle-aged mice.
Results: Compared to WT mice, male TG mice exhibited higher body weight and fat mass across all age groups and this difference was less in females. TG mice of both sexes showed lower endurance at younger ages (young and/or middle-aged), and lower grip strength and muscle mass at older ages (middle-aged and/or old) compared to WT. During muscle physiology tests, TG mice were more fatigable than WT in young and old mice of both sexes. In middle-aged mice, TG mice had lower protein content in isolated mitochondria, with this difference being more pronounced in males.
Conclusions: AMPK in skeletal muscles may play an important role in preventing SO with aging. AMPK inactivity in skeletal muscles is associated with obesity in male mice but not in females. In younger mice, AMPK is crucial for maintaining endurance, while it becomes more important for maintaining muscle mass and strength as they age.

6-08

Endurance exercise accelerates disease progression in desminopathy

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Introduction: Desminopathy is a progressive genetic muscle disease and the most common intermediate filament disease in humans. The factors contributing to the variability in symptom onset and disease progression are poorly understood. We hypothesized that mechanical stress plays a pivotal role in disease development. To investigate the effects of chronic exercise on desminopathy, we challenged a rat model harboring a R349P *DES* mutation with eccentric-biased exercise training.
Methods: R349P *DES* rats (DES) and their wild-type (WT) and heterozygous (HET) littermates were subjected to four weeks of downhill running. At the end of the four-week period, muscles were collected and analyzed histologically and biochemically.
Results: DES rats demonstrated significantly lower running capacity compared to wild-type and heterozygous littermates ($p < 0.0001$), which worsened over the course of the study ($p < 0.001$). Running performance in DES rats decreased by 50% after four weeks of downhill running. Desmin-positive aggregates, a histopathological hallmark of desminopathy, were approximately two-fold higher in DES muscles after downhill running compared to the sedentary group ($p = 0.04$). At the protein level, we found indicators of increased autophagy and proteasome activity with running in DES compared to WT.
Conclusions: Our results suggest an impairment in adaptation to chronic eccentric-biased exercise in DES muscle, leading to an exacerbation of the functional and histopathological phenotype.

6-09

Delayed skeletal muscle regeneration in an accelerated ageing mouse model

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Introduction: PolgD257A constitutive knock-in mice exhibit a premature aging phenotype between 8 to 12 months, characterized by anaemia, kyphosis, alopecia, lipodystrophy, and sarcopenia. The D257A mutation specifically impairs the DNA-proofreading activity, but not the DNA polymerase activity, of Polg, a nuclear gene encoding a DNA polymerase crucial for mitochondrial DNA repair. This impairment leads to increased mutations in mitochondrial DNA, resulting in primary mitochondrial myopathy. Additionally, PolgD257A mice display signs of immunosenescence and inflammaging by 11 months of age. In this study, we aimed to develop a model for delayed skeletal muscle regeneration associated with premature aging. This model can be used in future studies to investigate delayed regeneration due to mitochondrial dysfunction and aging, providing insights into the role of mitochondrial dysfunction in aging and its impact on muscle regeneration.
Methods: Male and female PolgD257A and wild-type mice, aged 3-months and 11-months, were histologically analysed to assess skeletal muscle regeneration, as well as satellite cell-autonomous and non-cell-autonomous effects. To study cell-autonomous effects, primary myoblasts were cultured ex vivo. For the regenerating environment effects, GFP+ myoblasts were transplanted into 11-month-old PolgD257A and wild-type mice.
Result: PolgD257A mice exhibit significantly delayed muscle regeneration at 11-months of age and moderately delayed regeneration at 3-months, compared to their age-matched controls. At both 11 and 3 months of age, PolgD257A mice show a reduction in satellite cells (SC) and Pax7+ myoblasts in both basal and regenerating muscles, respectively, when compared to age-matched wild-type mice. However, primary myoblasts from PolgD257A mice cultured ex vivo do not display any defects in proliferation or differentiation. Notably, there are fewer and smaller cross-sectional area wt-GFP+ myoblasts engrafted in the muscles of 11-month-old PolgD257A mice compared to wild-type mice. Additionally, PolgD257A mice show increased M2-macrophage infiltration and higher levels of senescence in regenerating muscles compared to wild-type mice.
Conclusion: Collectively, we characterized both satellite cell (SC) autonomous and non-cell autonomous factors in age-related defective skeletal muscle regeneration using a model of accelerated aging driven by mitochondrial dysfunction. Our findings indicate that non-cell autonomous factors play a significant role in the impaired muscle regeneration observed in PolgD257A mice, primarily due to the accumulation of senescent cells and other age-related factors.

6-10

Investigating muscle-derived SPMs as a potential treatment for muscle wasting

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Introduction: Sarcopenia is a common co-morbidity of ageing and various long-term conditions, with inflammation being noted as a cross-cutting mechanism. However, treatments such as NSAIDs have been seen to inhibit muscle growth, which doesn't aid in long-term states of inflammation. Specialised pro-resolving mediators (SPMs) regulate the end of the inflammatory process and have proven to have positive effects on muscle growth and repair in *vitro*. However, understanding the local production of SPMs remains unknown, which is the aim of this project.
Methods: All experiments were carried out on C2C12 mytotubes. Cells were exposed TNF-α at 0ng,10ng,100ng, and 200ng, with cells and cell supernatants being analysed at 3h,24h,48h and 72h. Samples were analysed for morphological change, gene expression of known SPM production indicators and inflammatory genes using qPCR. Extracellular SPM levels were analysed using solid-phase extraction followed by a bespoke LC-MS-MS assay.
Results: Reduction in the width of the myotubes was seen via morphological analysis (n=3) with increasing dose and exposure time ($p<0.0001$), as well as a reduction in myotube length over increasing time with high dose exposure ($p<0.0001$). mRNA analysis (n=2) showed an increase in detectable levels of both TNF ($P=0.0468$) and IL6 ($P=0.0121$) over both time and dose. Further, levels of
COX1 ($P=0.0022$), COX2 ($P=0.0159$), and Alox5ap ($P=0.0089$) over time and dose; however, this was noticed to drop between 48h and 72h. LC-MS-MS analysis detected the presence of LXB4 and LTB4 and prostaglandins PGE2, PGD2, and PG2a increasing in response to the inflammatory state.
Conclusion: We report here that skeletal muscle myotubes show elevated expression of markers implicated in SPM production and the detection of muscle-derived SPMs in a state of inflammatory-induced atrophy. This early data is the first step toward understanding the true role of SPMs in skeletal muscle so we can harness their resolution properties for good in those with Sarcopenia.

6-11

Targeting reactive lipid carbonyls to protect against muscle wasting

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Introduction: Lipid hydroperoxides (LOOH), a class of lipid reactive oxygen species, appears to promote disuse-induced skeletal muscle atrophy. Genetic (GPX4 overexpression or LPCAT3 deletion) or pharmacological (N-acetylcarnosine) suppression of LOOH is sufficient to ameliorate muscle atrophy, and to a greater extent muscle weakness, induced by physical inactivity. **Methods:** In this study, we tested the efficacy of genetic or pharmacologic suppression of LOOH on muscle wasting induced by aging and cancer cachexia induced by LLC allograft in mice. **Results:** We report that LOOH scavenging similarly protects against muscle wasting induced by aging and lung cancer cachexia, having more robust effects on sustaining force-generating capacity than muscle mass. The precise mechanism by which LOOH contributes to muscle dysfunction is unclear, but findings from N-acetylcarnosine treatment suggests that lipid carbonyls derived from LOOH likely drive muscle wasting. To explore the mechanism by which lipid carbonyls induce muscle wasting, we have recently developed a novel mass spectrometry discovery platform to study proteins that are post-translationally modified by these reactive lipid carbonyls (CAPDD or carbonylated proteomics by DNPH derivatization).
Conclusion: Lipid peroxidation promotes atrophy and weakness under various muscle wasting conditions. We hypothesize that lipid carbonyls from LOOH covalently modify proteins that are subsequently targeted for degradation.

6-12

Impact of deleting MuRF1 or MuRF2 on skeletal muscle function – male vs. female

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Introduction: MuRF1 and MuRF2 are important ubiquitin E3-ligases, and their induction induces skeletal muscle (SKM) atrophy. In addition, deleting MuRF1 attenuates the development of SKM atrophy in several muscle wasting conditions. So far no information is available on the impact of MuRF1 or MuRF2 deletion on muscle function in non-stressed animals with a specific focus on gender distribution.
Methods: C57Bl/6 mice (WT), MuRF-1 (KO1) and MuRF-2 (KO2) knockout animals (for each group 10 male, 10 female) were included at an age of 10 weeks. SKM force (Soleus muscle) was measured in an organ-bath-setting. Cross sectional area (CSA) of SKM was quantified after HE staining and protein expression was quantified by Western blot analysis.
Results: Analyzing maximal absolute and maximal specific force, a significant reduction was evident in male KO2 mice when compared to WT and KO1 mice (absolute force: WT: 20.47±0.85, KO1: 20.88±0.61, KO2: 17.10±0.61 g; $p<0.05$ KO2 vs. WT and KO1; specific force: WT: 29.45±1.46, KO1: 29.52±0.85, KO2: 24.06±1.16 N/cm^2; $p<0.05$ KO2 vs. WT and KO1). These differences were not detected in female animals. Functional changes were accompanied by a significant reduced muscle weight (0.470±0.009 vs. 0.509±0.010 mg/mm; $p<0.05$) and a reduced CSA (512±47 vs 672±62; $p<0.06$) in male KO2 animals when compared to WT. In addition a significant reduction ($p<0.05$) in protein expression of specific mitochondrial respiratory chain complexes was detected in male KO2 when compared to WT (complex-II 21% reduction; complex-IV 33% reduction, complex-V 19% reduction).
Conclusions: We may conclude that only male MuRF2 knockout animals show a significant functional impairment in SKM. These functional changes may be related to loss in muscle mass, atrophy induction and reduced expression of mitochondrial respiratory chain complexes. Further studies are necessary to explore why these changes are not occurring in female animals.

6-13

The role of hepatokines in MASLD associated muscle wasting

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Introduction: Metabolic dysfunction-associated steatotic liver disease (MASLD) is the leading cause of chronic liver disease worldwide, affecting over a third of the adult population. Muscle wasting, or sarcopenia, characterized by a loss of muscle mass and function, is common in MASLD patients, impacting their quality of life and prognosis. We aimed to identify liver-secreted proteins mediating liver-muscle crosstalk in MASLD as potential therapeutic targets to prevent muscle wasting.
Methods: MASLD-associated muscle wasting was investigated in two mouse models: the Gubra-Amylin NASH (GAN) diet-induced obese model and the methionine-choline deficient 60% high fat diet (MCD) model. MASH was confirmed by immunohistochemical analysis, while muscle mass and strength were assessed via Echo-MRI and grip strength test respectively. At the end of the experiments, livers were extracted, sliced, and cultured for 16h to obtain supernatant (SN) containing liver-secreted factors. C2C12 myotubes were treated with either SN or recombinant protein for 48h to assess myotube atrophy.
Results: Mice with MASLD also developed sarcopenia, showing a significant decrease in both muscle mass and strength. SN from liver slices of these MASLD models induced atrophy of C2C12 myotubes, demonstrating that liver-derived factors directly cause myotube atrophy. Candidate hepatokines inducing muscle wasting were identified by proteomics of the SN, combined with analysis of published liver transcriptomics and muscle proteomics data from our models. Recombinant proteins of candidate hepatokines induced myotube atrophy in C2C12 cells dose-dependently.
Conclusions: Our data show that liver-derived factors can induce muscle atrophy in the context of steatotic liver disease both in vivo and in vitro. We identified candidate hepatokines secreted in MASLD that cause muscle atrophy in vitro, suggesting that targeting liver-secreted proteins could help ameliorate muscle atrophy.

6-14

MyoMed-205 counteracts titin hyper-phosphorylation, muscle dysfunction and atrophy in an animal model of HFpEF

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Introduction: We recently reported a hyperphosphorylation of titin in peripheral skeletal muscle (SKM) of ZSF1-rats, associated with reduced muscle force, atrophy and dysregulation of Z-disc proteins. Aim of the present study was to investigate if MyoMed-205, a small molecule interfering with MuRF-1 targets, also modulates titin hyperphosphorylation and the expression of contraction regulating and atrophy related proteins in rats exhibiting heart failure with preserved ejection fraction (HFpEF).
Methods: Obese ZSF1-rats (20 weeks) received MyoMed-205 for 12 weeks ($HFpEF_{treated}$); age-matched untreated ZSF1-lean (healthy) and obese (HFpEF) rats served as controls. HFpEF development, was confirmed by echocardiography and SKM force was measured in an organ-bath-setting. To detect titin, and its degradation product T2, extensor digitorum longus (EDL) samples were resolved on a vertical agarose gel. Phosphorylation and total protein expression were detected by gel-stain (Invitrogen). Specific protein expression was quantified by Western blot analysis.
Results: MyoMed-205 treatment significantly improved maximal specific force (+10 %) and muscle weight ($p<0.01$) vs. untreated HFpEF-rats. Furthermore, we detected a higher titin expression (HFpEF: 1.0±0.07 vs. $HFpEF_{treated}$: 1.2±0.05, p=0.01, n=12), going along with reduced T2-levels (HFpEF: 1.08±0.06 vs. $HFpEF_{treated}$: 0.85±0.04, p=0.003, n=14), and a normalization of titin-phosphorylation after treatment (con: 1.0±0.05 vs. HFpEF: 1.13±0.05 vs. $HFpEF_{treated}$: 1.01±0.04, p=0.09, n=13). MyoMed-205 treatment also resulted in higher expression of troponin C (HFpEF: 0.54±0.1 vs. $HFpEF_{treated}$: 0.75±0.06, n=10) and reduced troponin I expression (HFpEF: 1.304±0.082 vs. $HFpEF_{treated}$: 0.96±0.11, p=0.05, n=10), proteins important for calcium-sensing and muscle contraction. Regarding atrophy markers, we detected a significant upregulation of MuRF-1 (con: 1.0±0.07 vs HFpEF: 1.25±0.07, p=0.02, n=15) in HFpEF, which could be reduced by treatment ($HFpEF_{treated}$: 1.1±0.05, p=0.09, n=15).
Conclusions: We may conclude that MyoMed-205 led to improved muscle force, by modulating titin-phosphorylation as well as calcium-handling proteins. The remaining question still is, if modulation of titin regulates muscle force or vice versa.

6-15

Angiotensin Type 2 Receptor Deficiency Exacerbates Physical Decline and Cardiac Muscle Wasting in Aged Mice

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Introduction: Frailty, sarcopenia, and cachexia are associated with poor endurance, muscle wasting, and declining cardiovascular performance in aging. The renin-angiotensin system (RAS) is a key hormonal system, and through its main receptors, plays a major role in regulating muscle and cardiac function. The angiotensin type II receptor (AT2R) is a less known receptor of the RAS, but has been suggested to play a protective role in aging. This study examines the impact of the AT2R on physical performance, frailty markers, and cardiac function in aged mice.
Methods: We studied 24-month-old wild-type (WT) mice alongside age- and sex-matched mice lacking the AT2 receptor (AT2KO). Physical performance was assessed through treadmill exhaustion tests, measuring total time on the treadmill belt (TOB), number of falls (NOF), and the number of gentle stimuli to return each mouse to the belt (NGS). Echocardiographic data evaluated left ventricular end-diastolic (LVEDD) and end-systolic diameters (LVESD), fractional shortening (FS%), ejection fraction (EF%), and left ventricular mass (LV mass).
Results: AT2KO mice exhibited higher body weights than WT mice (ANOVA, p=0.03; post-hoc p=0.04) and had reduced treadmill performance, with lower TOB values (Kruskal-Wallis, p=0.03; AT2KO vs. WT, p=0.008). These mice required more external stimuli to maintain running (p=0.003), indicating increased fatigue. Echocardiography showed impaired cardiac function in AT2KO mice, including a higher LVESD (p=0.027), thinner interventricular septal thickness (IVSD, p<0.001), and reduced ejection fraction (EF%, p=0.02). Notably, AT2KO mice had lower LV mass (p=0.003), suggesting compromised cardiac muscle integrity and cardiac muscle wasting.
Conclusions: These findings highlight the essential role of AT2R in maintaining physical ability, muscle performance, and cardiac function during aging. Targeting the AT2R pathway may offer therapeutic insights for mitigating sarcopenia, frailty, and cachexia in aging populations.

6-16

Radiation reduces fibro/adipogenic progenitor-derived follistatin-like 1 to impair myoblast differentiation

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Introduction: Five-year cancer survivorship is increasing; however, the long-term effects of treatments are detrimental to skeletal muscle. We have found that fibro-adipogenic progenitors (FAPs) contribute to radiation-induced muscle atrophy and fibrosis, in part, through alterations to their secretome that impairs muscle stem (satellite) cell (MuSC) fate. It is unknown; however, which specific FAP-secreted factors are responsible for the radiation-induced defect in MuSC differentiation and fusion. Thus, we aimed to identify factors in FAPs impacted by irradiation to elucidate their role in myogenesis.
Methods: Five-week old male C57BL/6J mice received three 8.2 Gy doses of fractionated radiation to one hindlimb (IR) with the contralateral limb serving as a shielded control (CTRL). Mice were sacrificed at 3- and 56-days post-irradiation for flow cytometry and scRNA-seq analyses. Secreted factors identified as being differentially expressed by preliminary scRNA-seq analysis were confirmed in *in vitro* irradiated FAPs, using CRISPR/Cas9-mediated knockdown and media supplementation with recombinant protein in conditioned media experiments.
Results: Flow cytometry indicated that radiation depleted the FAP population overall but increased the pro-fibrotic FAP subpopulation (p<0.05). *Fstl1* is enriched in scRNA-seq data of pro-myogenic FAPs (p<0.05). *Fstl1* transcript and protein expression was reduced at 24 hours post-irradiation *in vitro* (p<0.05). FSTL1 protein expression was reduced by irradiation in whole muscle (p<0.05). The irradiated FAP secretome inhibited *in vitro* myogenesis (p<0.05); however, this effect was rescued by adding FSTL1 to culture media (p<0.01). FAP-specific FSTL1 knockdown by CRISPR/Cas9 inhibited *in vitro* myogenesis (p<0.001).
Conclusion: FSTL1 is a pro-myogenic trophic factor secreted by skeletal muscle FAPs that regulates *in vitro* myogenesis. FSTL1 secretion is depleted by irradiation which may contribute to muscle atrophy and fibrosis observed in cancer survivors. Our study identifies restoring FSTL1 as a compelling candidate for future work on mitigating the skeletal muscle defects caused by cancer radiation treatments.

6-17

Impact of *Ilk1* and *Fermt2* AAV-mediated knockdown on sepsis-induced muscle weakness

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Introduction: Sepsis is characterized by the manifestation of muscle weakness, partly due to the loss of mechanical stimuli. Muscle cells sense and convert mechanical forces into biochemical signals through the interaction of adaptor and signaling proteins, facilitating muscle cell adaptation. We hypothesized that the mechanosensitive proteins integrin-linked kinase (*Ilk1* gene) and kindlin2 (*Fermt2* gene) are involved in sepsis-induced muscle weakness.
Methods: In a catheterized mouse model of cecal-ligation-and-puncture-induced, fluid-resuscitated and antibiotics-treated polymicrobial abdominal sepsis, we investigated the effect of adeno-associated-viral-vector (AAV)-mediated miRNA-based knockdown of *Ilk1* or *Fermt2* in tibialis anterior (TA) muscle of 26-weeks-old C57BL/6-mice. Healthy (HC) and septic (SC) controls received AAV-control-vectors. Two weeks post-AAV injection, sepsis was induced. After five days, *in situ* TA muscle force was measured, and animals were sacrificed (N=88). Muscle weight and mRNA levels of mechanosensitive components (*Ilk1*, *Fermt2*, *Itga7*, *Itgb1*, *Tln1*), markers of atrophy (*Trim63*, *Fbxo36*), regeneration (*Myf5*, *Pcna*, *Myog*), autophagy (*Atg5*, *Atg7*), and metabolism (*Slc2a4*, *Rac1*) were assessed.
Results: Five days of sepsis resulted in upregulated mechanosensitive genes compared to HC (p<0.0001 for all). In *Ilk1* and *Fermt2* knockdown mice, the upregulation of *Ilk1* and *Fermt2* respectively was negated without affecting other mechanosensitive genes. The sepsis-induced reduction of absolute TA force (p<0.0001 vs HC) and TA weight (p<0.0001 vs HC) was not affected by *Ilk1* or *Fermt2* knockdown. However, *Ilk1* knockdown further enhanced sepsis-induced upregulation of atrogene *Trim63* (p<0.05 vs SC). Sepsis upregulated markers of autophagy (p<0.0001 vs HC) and regeneration (p<0.0001 vs HC) but no differences were detected between septic groups. *Fermt2* knockdown further increased sepsis-induced upregulation of *Rac1* (p<0.05 vs SC), an actin cytoskeleton-regulating GTPase.
Conclusion: AAV-mediated knockdown reversed sepsis-induced upregulation of *Ilk1* and *Fermt2* but did not alter muscle force or

weight reduction. The potential involvement of *Fermt2* in sepsis-induced metabolic changes should be further scrutinized.

6-18

The co-existence of sarcopenia and cognitive impairment: prevalence and the association with healthy aging in the kora-age study

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Introduction: Sarcopenia has been frequently observed to co-exist with cognitive impairment, whereas the impact of this co-existence on healthy aging is unknown. We therefore investigated the prevalence of this co-existence and its association with future geriatric outcomes.
Methods: We derived data of 1055 participants aged 65-93 years (50% women) from the population-based cohort Cooperative Health Research in the Region Augsburg (KORA)-Age. At baseline (2008/9), sarcopenia was defined according to EWGSOP2, and cognitive impairment was derived from the modified telephone interview for cognitive status or a proxy-interview with relatives or caregivers when participants had severe physical/mental impairment. The co-existence was defined as having both probable sarcopenia (= low grip strength) and cognitive impairment. The geriatric outcomes activities of daily life (ADL)-disability and nursing care were assessed at 2012 and 2016 in telephone interviews. Mortality was assessed using death certificates until 2016. Logistic regression was implemented to calculate age and sex-adjusted associations of muscle mass/grip strength with cognitive impairment and of the co-existence with geriatric outcomes. Age and sex-adjusted Cox regression assessed the association of the co-existence with mortality.
Results: While grip strength was associated with cognitive impairment, muscle mass was not. A total of 8.1% of the baseline population had both cognitive impairment and probable sarcopenia. Of participants with probable sarcopenia, 49.4% had cognitive impairment, while of participants without sarcopenia only 19.7% had cognitive impairment. The co-existence of probable sarcopenia and cognitive impairment was associated with all-cause mortality [HR(95%CI): 2.37(1.72,3.26)], CVD mortality [2.11(1.33,3.33)] as well as with ADL-disability after three [OR(95%CI): 5.18(2.37,11.21)] and seven years [3.5(1.11,10.86)], and with requiring nursing care after three years [5.07(2.12,11.55)].
Conclusion: Muscle mass appeared irrelevant for cognitive impairment, while the co-existence of probable sarcopenia and cognitive impairment elevated the risk for premature death, inability to perform ADL, and requiring nursing care in the future.

6-19

A novel role for extracellular matrix dysregulation in the development of muscle wasting in individuals with chronic kidney disease

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Introduction: Reduced physical function and a loss of muscle, is a complication of chronic kidney disease (CKD) leading to a downward spiral of further muscle wasting, disuse, reduced quality of life and poor outcomes. As skeletal muscle is highly adaptive and easily remodelled, this muscle wasting is likely to be reversible or preventable. Interventions for muscle wasting in CKD are lacking due to an in-complete understanding of the underlying processes. The aim of this study was to perform untargeted transcriptomics on skeletal muscle from CKD and controls to identify new therapeutic targets for CKD related muscle wasting.
Methods: Vastus lateralis muscle biopsies were collected from 10 CKD patients stage 3b-4 and 10 aged and sex matched controls. Library preparation and untargeted RNA sequencing were performed by Novogene. Differential gene expression (DEG) analysis was performed using the DESeq2 package in R. Genes with |log2(FoldChange)|>=1, adjusted $p<0.05$ were considered differentially expressed. Functional enrichment analyses included Gene Ontology (GO) and Kyoto Encylopedia of Genes and Genomes (KEGG) pathway analysis to determine which DEGs were significantly enriched in which GO terms or metabolic pathways.
Results: Enrichment analysis showed all the traditionally accepted pathways involved in skeletal muscle wasting were upregulated within CKD skeletal muscle (i.e. upregulation of ubiquitin-mediated proteolysis). Pathways relating to extracellular matrix composition and regulation and wound healing dominated the downregulated processes. Genes downregulated included Collagens 1, 4, 5, 6, 15 and 16, and Matrix Metalloprotease 14, all of which are involved in extracellular matrix structure and function and ultimately in muscle repair and regeneration.
Discussion: This analysis of CKD skeletal muscle has identified dysregulation in extracellular matrix composition and regulation and in the process of wound healing within CKD skeletal muscle and may contribute to development of CKD related muscle wasting which could be a new therapeutic target.

6-20

BIO101, a drug candidate to counter-act age-related sarcopenia: towards Phase 3 program

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Introduction: Sarcopenia is a progressive generalized loss of muscle mass and function associated with negative outcomes such as falls, fractures, and mortality. Lean body mass preservation may reduce the negative outcomes especially in subjects with obesity. Biophytis targets the Renin Angiotensin System with 20-hydroxyecdysone (20E), a MAS receptor activator, in the SARA program investigating its efficacy in sarcopenia through SARA-PK phase 1, SARA-INT phase 2 and the confirmatory phase 3 studies.
Methods: SARA-INT trial showed promising results at 350mg bid versus placebo on gait speed (improvement in the 400 Meter Walking Test (400MWT) of 0.07 m/s (in the Full Analysis Set

population, ns) and 0.09 m/s (in the Per Protocol population, p=0.008).
SARA-INT along with SPRINTT and LIFE studies, led to select major mobility disability (MMD) as the Phase 3 program primary endpoint. Major mobility disability (the inability to complete 400MWT within 15 minutes, without sitting, help from another person or use of a walker) is the most proximal of hard outcome cascade. Phase 3 target sarcopenic population has low gait speed (≤ 0.8m/s), SPPB score (between 3 and 7) and handgrip strength (≤ 20 kg for female and ≤ 35.5 kg for male).
Results: Biophytis has received regulatory approval of the current interventional, randomized, double-blind, placebo-controlled phase 3 trial to assess the effects of BIO101 in 932 randomized subjects with primary endpoint time to onset of a MMD event (event driven trial with a target of 330 events). Hierarchized secondary endpoints include 4-m gait speed SPPB, Hand grip Strength and SarQol questionnaire. Exploratory endpoints include hard outcomes (e.g. falls, injurious falls, hospitalizations, deaths).
Conclusion: Biophytis approach with interventional phase 2 and phase 3 remains the way to evaluate the effect of BIO101 in sarcopenic patients and an appropriate path to approval of a drug in sarcopenia.

6-21
Pathological changes in skeletal muscle throughout colon cancer trajectory-multi center study

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Introduction: High-resolution imaging techniques, such as computed tomography (CT), have significantly advanced our understanding of body composition and its implications for human health. This technology revealed a high prevalence of sarcopenia (low muscle mass) and pathological fat accumulation within muscles (myosteatosis) in cancer patients. These conditions, indicative of disease-related muscle loss, are strongly associated with poor outcomes and reduced survival in cancer patients. However, there is limited data on these phenomena in Middle Eastern populations.
Methods: This study has three primary objectives. First, we aim to retrospectively characterize sarcopenia and myosteatosis in colon cancer patients, with and without chemotherapy, over time using sequential CT scans (n=400) from King Faisal Specialist Hospital and Research Center. Second, we seek to identify the mediators and pathways affecting skeletal muscle mass and adipose tissue in colon cancer patients at the biological level (n=34/group). Finally, we will compare these mediators and pathways in cancer patients with an obese control group (n=34) to better understand the specific mechanisms contributing to muscle loss and myosteatosis in cancer. Skeletal muscle biopsies from the anterior abdominal wall will be collected from cancer patients undergoing tumor resection and from control patients during bariatric surgery. Additionally, subcutaneous and visceral fat tissues and blood samples will be obtained to study the signaling pathways between these tissues. We will measure the proportions of adipocytes, myocytes, total fat, fatty acid composition, muscle stem cells, adipokines, myokines, and inflammatory markers. Muscle strength and physical function will be assessed using handgrip strength tests, a 30-second sit-to-stand test, and a physical performance test. Lifestyle factors that influence muscle mass, including sedentary behavior, will be assessed using the Global Physical Activity Questionnaire.
Conclusions: This research aims to uncover the causes of sarcopenia and myosteatosis in Saudi Arabian cancer patients, conditions linked to complications and higher mortality.

6-22
Loss of skeletal muscle mass is associated with poor shorter survival and immunosuppressive tumor microenvironment in advanced lung cancer

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Introduction: Severe skeletal muscle (SM) loss is associated with poor survival. Previous works showed the immune cell-driven pathways linked to muscle wasting. We aim to investigate the prognosis effect of SM and its relationship with tumor-infiltrating lymphocytes (TILs) in advanced lung cancer.
Methods: This multicohort involved 200 advanced lung cancer patients. SM index (SMI) at baseline and follow-up changes were assessed on computed tomography (CT) scans at the third lumbar vertebra. Associations between SMI and overall survival (OS) were evaluated using Cox regression analysis. Logistic regression analysis shows the association between peripheral circulating immune cell and SMI. Additionally, the relationship between TILs and SM status was evaluated by immunohistochemistry.
Results: SMI loss was associated with shorter OS (Whole cohort: HR=2.314, 95% CI=1.388-3.858, p=0.001; immunotherapy cohort: HR=3.028, 95%CI=1.113-8.236, p=0.03, non-immunotherapy cohort: HR=2.298, 95%CI:1.191-4.435, p=0.013). Low SMI was associated with peripheral blood CD3+ T cell (HR=1.24, 95%CI: 1.08-1.424, p=0.002), and CD3+CD8+ T cell (HR=0.862, 95%CI: 0.762- 0.974, p=0.018) in Logistic regression analysis, as well as SMI loss was associated with CD3+ T cells (HR=3.414, 95%CI: 1.301-8.961, p=0.013) and CD3+CD8+ T cell (HR=0.666, 95%CI: 0.459- 0.968, p=0.033). Patients with stable SMI had a significantly higher number of CD8+ TILs than patients with SMI loss (p=0.036) by multiplefluorescence staining.
Conclusions: SMI loss was an independent predictor for advanced lung. Furthermore, the association between SMI and T cells may play a pivotal role in predicting the oncology outcome.

6-23
Impact of miRs modulation and inflammatory response on body composition changes in patients with gastrointestinal cancer

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Introduction: Altered expression of microRNAs (miRs) might associated to muscle wasting (MW) conditions, including cancer cachexia (CC). Aims of the present study were to profile the expression of muscle-derived miRs and to investigate their relationship(s) with changes in body composition in gastrointestinal cancer patients (GICP).
Methods: Circulating muscle-specific miRs obtained from 37 diagnosed GICP and 15 controls (C) were assayed with RT-qPCR

and IL-6, IL-10 and IFNg were quantified with xMAP Intelliflex®. Diagnosis of cancer cachexia (CC) was made based on Fearon's definition. Body composition was quantified with CT scan and patients stratified according to lower (LMM) and higher (HMM) muscle mass, based on sex-specific internal cut-offs.
Results: We observed significant upregulation of miR-15b, -21 and -29b and significant downregulation of miR-133a, -206 and -486 in GICP vs C ($p<0.05$). IL-6 was higher in GICP vs C ($p=0.023$) and correlated negatively with miR-206 ($p=0.009$, $r=-0.499$), whereas IL-10 and IFNg correlated negatively with miR-133a ($p=0.025$, $r=-0.373$) and miR-21 ($p=0.012$, $r=-0.477$), respectively. MiR-206 ($p<0.001$) and -486 ($p=0.009$) were downregulated in GICP with CC ($n=18$) vs no CC ($n=19$), whereas miR-29b was upregulated in GICP with CC vs no CC ($p=0.005$). In GICP with CC, IL-6 correlated negatively with miR-206 ($p=0.031$, $r=-0.693$). MiR-29b was upregulated in GICP with LMM vs HMM ($p=0.049$). Interestingly, we observed upregulation of miR-133a ($p=0.037$) and -206 ($p=0.010$) and downregulation of miR-29b (0=0.021) in GICP with both CC and LMM vs no CC and HMM.
Conclusion: Altogether, our data confirm that both miRs and circulating levels of cytokines are significantly and differentially modulated in GICP. Studies are under way to clarify whether the described associations may govern the underlying regulatory mechanisms negatively impacting on muscle homeostasis and whether they might represent potential novel markers and/or targets for diagnostic and/or therapeutic strategies for CC-related MW.

6-24
Different miRs patterns associate with changes in body in composition in patients with systemic sclerosis

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Introduction: Systemic sclerosis (SSc) is an autoimmune disease characterized by sustained vascular inflammation and progressive fibrosis of skin and internal organs. Up to 22% of SSc patients may manifest skeletal muscle (SM) impairment, which predicts worse clinical outcomes, including increased mortality, but its pathogenesis is still largely unclear and could be associated with modulation of circulating miRNAs (miRs). Aims of the present study were i) to profile circulating miRs related to muscularity and fibrosis SSc and ii) to evaluate their association with changes in body in composition(s) and with the clinical course and type of the disease.
Methods: We obtained blood samples form 47 SSc patients and 21 C and assessed circulating levels of miRs by RT-qPCR. Muscularity (FFMI kg/m^2) and phase angle (PhA, °) were estimated by BIA.
Results: Levels of miR-15b ($p=0.024$), -21 ($p<0.001$), -29a ($p<0.001$), -29b ($p=0.007$) and -133a ($p<0.001$), were downregulated in SSc vs C, whereas miR-206 ($p<0.001$) and -486 ($p<0.001$) were significant overexpressed. MiR-15b was downregulated in SSc with low PhA (<4.7°) vs high ($p=0.019$) and showed a negative correlation with disease activity index ($p=0.012$, $r=-0.422$). In SSc with low FFMI (M <17, F<15 kg/m^2) miR-206 was downregulated vs high FFMI ($p=0.001$). When considering nailfold capillaroscopy (NVC) stages, miR-15b ($p=0.026$) and -29b ($p=0.033$) were lower in late compared to early NVC. According to the subset of autoantibodies profile, miR-133a was significant higher in SSc with Scl70 vs ACA ($p=0.002$) and was downregulated in SSc with diffuse vs limited skin involvement ($p=0.051$).
Conclusion: Our data show a modulation of specific miRs involved in muscularity and fibrosis in SSc patients. Further investigations are mandatory in order to deeper unravel of the underlying mechanisms of the SSc onset and progression and to develop novel diagnostic and therapeutic strategies for this devastating disease.

6-25
Aging and exercise differentially modulate mercs and contractile dynamics in skeletal muscle

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Introduction: Mitochondria and sarcoplasmic reticulum (SR) dysfunction contribute to sarcopenia, but early events triggering these impairments remain poorly understood. Physical couplings between these organelles, termed MERCs, are critical for numerous cellular processes. Therefore, the ultrastructure and proteome of these subcellular locations may be inversely modulated by aging and regular exercise impacting muscle function.
Methods: Our study included three groups of male C57BL6N mice: healthy young adults (HYA, 5 mo. of age), early age-related muscle dysfunction (eAMD, 21 mo. of age) and an additional cohort of eAMD that underwent 6-8 weeks of treadmill training (eAMD+Ex). Plantar flexor muscle function was assessed *in vivo* via percutaneous stimulation of the tibial nerve. High-resolution respirometry was used to interrogate oxidative capacity of permeabilized fibers using the O2k Oxygraph. TEM was employed to measure the morphology of individual mitochondria and MERCs. The proteome of mitochondrial-associated ER/SR membranes (MAMs) was also profiled.
Results: Compared to HYA, eAMD animals displayed minimal or no muscle atrophy, no change in maximal force, and yet ~20% lower rate of relaxation leading to ~40% greater fatigue ($p<0.05$). These trends were all reversed with exercise (eAMD+Ex). Mitochondrial respiration was unaffected by sedentary aging (eAMD), but H_2O_2 emission nearly doubled compared to HYA, and this was alleviated by exercise ($p<0.05$). MERC length was decreased by 20% in eAMD animals, recovered in eAMD+Ex, and strongly correlated with relaxation rate across groups ($r = 0.704$, $p<0.05$). Proteomic analyses of muscle MAM fractions revealed 191 proteins modified by aging or exercise. Twenty-eight of these proteins were inversely modulated in these conditions, suggesting they may be particularly relevant for muscle health.
Conclusions: Our results point to MERCs as molecular hubs modulating functional adaptions to regular exercise while also contributing to the onset of mitochondrial abnormalities and contractile dysfunction characteristic of sarcopenia.

6-26
ATAD2: A Novel Regulator of Muscle Cell Proliferation, Differentiation and Autophagy

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Introduction: Skeletal muscles represent about 50% of the body mass and need good maintenance. Autophagy is a dynamic pathway for the removal of non-functional organelles to facilitate recycling by the lysosomes. We recently identified a new gene, MYTHO, as a new regulator of autophagy, skeletal muscle mass, and integrity (Leduc-Gaudet & Franco-Romero et al., 2023). Co-immunoprecipitation revealed that MYTHO protein interacts with a cofactor for oncogenic transcription factors called ATAD2.
Methods: SiRNA-mediated Atad2 transient knockdown (KD) was performed in C2C12 cells for 48h before cells were switched to differentiation medium for 7 days.
Results: The expression of mRNA and protein levels of ATAD2 strongly decreased in differentiated C2C12 compared to undifferentiated cells. Immunofluorescence staining showed that ATAD2 is expressed mainly in nucleus of C2C12 and colocalizes with PAX7 in satellite cells in a single isolated muscle fiber. ATAD2 KD induced significantly C2C12 number, cell proliferation rate, cell viability, G and S cell cycle phases but significantly decreased p53-p21-RB axis mRNA expression concordant with significant increase of cyclin D1 and D2 gene expression. Interestingly, ATAD2 KD significantly increased expression of differentiation genes, MyoD1 and MyoG1, as well as Myh1 at day0 of differentiation with a significant increase of MHC positive cells number. On day5 of differentiation, ATAD2 KD myotubes appear elongated and atrophied compared to control with significant reduction in fusion index. Regarding autophagy, ATAD2 KD significantly increased protein level of LC3-BI and LC3B-BII, P62 and Beclin1 with no major change in mRNA expression of these genes suggesting that autophagy was induced in response to ATAD2 KD.
Conclusion: In summary, the absence of ATAD2 leads to a disorder in proliferation with premature cell differentiation and highly increased autophagy associated with an atrophied phenotype. We showed for the first time that the onco-enhancer, ATAD2, is a novel regulator of skeletal muscle cell proliferation, differentiation and autophagy.

6-27

Revisiting the cholesterol paradox in chronic heart failure: the potential role of skeletal muscle mass
Results from the Studies Investigating Co-morbidities Aggravating Heart Failure (SICA-HF)

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Introduction: Dyslipidaemia, a major risk factor for cardiovascular disease, has been demonstrated to be associated with lower mortality in patients with heart failure (HF). However, the pathophysiology of this counterintuitive "cholesterol paradox" has not been fully elucidated. This study aims to investigate the relationship between low-density lipoprotein cholesterol (LDL-C) levels and mortality in patients with chronic HF in the context of skeletal muscle mass.
Methods: A total of 241 patients with chronic HF (68±11 years, 80% male) were assessed for lipid profile and skeletal muscle mass from the Studies Investigating Co-morbidities Aggravating HF (SICA-HF) database. Patients were divided into higher and lower LDL-C levels based on the median (93 mg/dL) and into higher and lower appendicular skeletal muscle mass index (ASMI) based on the sex-specific median (men = 7.97 kg/m^2, women = 6.87 kg/m^2). The primary endpoint was defined as all-cause mortality.
Results: During a median follow-up of 6.3 years, 95 patients (39%) died. Overall, patients with higher LDL-C levels had significantly lower mortality than those with lower LDL-C levels (adjusted hazard ratio (aHR) 0.61, p=0.04). In the low ASMI group, higher LDL-C levels were significantly associated with lower mortality, but not in the higher ASMI group (37% vs 56%, p=0.01, and 28% vs 36%, p=0.28, by log-rank). There was a significant interaction between LDL-C levels and higher and lower ASMI groups on mortality (p=0.04 for interaction). In the low ASMI group, multivariate Cox regression analysis revealed that higher LDL-C levels were significantly associated with lower mortality (aHR 0.66 per 1SD increase, p=0.02).
Conclusion: In patients with chronic stable HF, higher LDL-C levels were significantly associated with lower mortality, especially in the lower ASMI group. Lower skeletal muscle mass may be involved in the pathogenesis of the "cholesterol paradox" in HF.

6-28

Ketone bodies in heart failure: metabolic changes and muscle health in cardiac patients

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Introduction: The heart requires substantial ATP to fulfil its functions, which is primarily sourced from fatty acid oxidative phosphorylation. In heart failure (HF), mitochondrial dysfunction prompts metabolic remodeling, causing a shift towards alternative energy pathways, including ketogenesis. Recent interest has focused on the role of ketone bodies (KB) in cardiac energetics and their predictive value in HF, but their associations with body composition and muscle strength remain underexplored.
Methods: We performed a retrospective analysis of 100 HF patients from the SICA-HF study with available blood total KB levels (measured as the sum of acetoacetate and β-hydroxybutyrate). Patients were grouped based on KB levels (< or ≥ median value of 103 µmol/l). Cachexia was defined as weight loss ≥5% over 1 year. Fat and lean mass were measured using dual-energy X-ray absorptiometry. Appendicular skeletal muscle mass index (ASMI) was calculated as appendicular skeletal muscle mass/height².
Results: Patients with higher KB levels exhibited worse NYHA class (53% vs. 22% with NYHA class III-IV, p=0,002) and higher NT-proBNP (1074 ng/l *vs.* 386, p=0.012). Interestingly, higher KB levels were also associated with lower fat mass (25.6±9.9 kg *vs.* 30.2±8.9, p=0.017) and reduced hand grip strength (33.2±10.4 *vs.* 39.5±11.1 kg, p=0.005). No differences were observed in terms of HF phenotype, prevalence of comorbidities or ASMI between the two groups. Univariate logistic regression confirmed these observations. In a multivariate model adjusted for NT-proBNP, ASMI, and presence of cachexia (among other variables) a lower hand grip strength remained independently associated with higher total ketone levels (adjusted OR 0.924, 95% CI 0.863-0.990, p=0.024).
Conclusions: Lower hand grip strength was seen in patients with HF and higher ketone body levels, regardless of muscle and/or

weight loss. The alterations in cardiac energetics observed in HF may significantly impact muscle health, warranting further investigation.

6-29
Effect of current smoking on fat-free mass in COPD patients

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Introduction: Patients with chronic obstructive pulmonary disease (COPD) exhibit changes in body composition, including reduced fat-free mass index (FFMI), sarcopenia, and decreased exercise capacity. The underlying mechanisms are complex and not fully understood. The effect of current smoking on FFMI in COPD patients is not clear. This study aimed to investigate whether current smoking is associated with decreased FFMI in patients referred to a pulmonary rehabilitation (PR) program.
Methods: We included consecutive COPD patients who completed a 4-week inpatient PR program at the University Clinic Golnik, Slovenia from 2017 to 2021. All patients were clinically stable at the start and underwent a series of predefined tests, including body composition analysis via bioelectrical impedance at the beginning of PR. Low FFMI was defined using ESPEN criteria (<17 kg/m² for males and <15 kg/m² for females). Multiple logistic regression was employed to identify predictors of low FFMI.
Results: The study included 139 patients (mean age 65±7.2 years, 34% women, mean FEV1 40±18% predicted, mean BMI 26.5±5.9 kg/m², mean 6MWD 341±109 m, mean pack-years of smoking 45.0 ± 27.8). At baseline, 44% had low FFMI. Among the patients, 27 (19%) were current smokers, while the remainder were former smokers. Multivariate logistic regression revealed that current smoking was significantly associated with a 5-fold increased risk of low FFMI (OR 5.06, 95% CI: 1.7-15.1, p=0.004). Other significant predictors included FEV1 (per %, OR 0.96, 95% CI: 0.93-0.99, p=0.005), age (OR 1.066, 95% CI: 1.001-1.135, p=0.046), and male gender (OR 0.15, 95% CI: 0.06-0.38, p<0.001). Long-term oxygen treatment, pack-year smoking history, and exercise capacity measured by the 6-minute walk test did not predict low FFMI.
Conclusions: The significant association between current smoking and low FFMI in COPD patients has important clinical implications and warrants further investigation.

6-30
Satellite cells during skeletal muscle regeneration in survivors of critical illness

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Introduction: Intensive care unit-acquired weakness (ICUAW) is a common complication of critical illness, associated with increased morbidity and mortality. During injury, satellite cells activate from a quiescent state, proliferate, differentiate, and fuse into new myotubes. In critically ill patients, dysfunction of these cells might impair muscle regeneration and contribute to muscle weakness.
Objectives: To determine whether and how satellite cell activation, differentiation, or function is affected in critically ill patients with ICUAW over time.
Methods: We enrolled 16 critically ill patients with an MRC score < 48 points (indicative of muscle weakness). Biopsies were performed at “day 1” (within 72 hours after ICU admission) and after 7 days. Satellite cells were isolated using the magnetic beads technique to obtain purified cell cultures. Proliferation rates were observed at 24, 36, 48, and 72 hours using a BrdU proliferation kit and fluorescence microscopy. The ability of cells to fuse into myotubes was determined by staining the cytoskeleton and nuclei, and calculated as the percentage of nuclei inside myotubes divided by the total number of nuclei. In both proliferating muscle cells and myotubes, an Extracellular Flux Analyzer measured the oxygen consumption rate (OCR) at baseline and after sequential addition of an ATP synthase inhibitor, uncoupler, and complex III inhibitor, determining proton leak, ATP production, maximal respiratory capacity, and non-mitochondrial respiration.
Results: Compared with metabolically healthy volunteers (n = 12), proliferation tended to decrease over time. The fusion index was slightly decreased and highly variable between individuals. The most significant result was decreased maximal respiratory capacity to 62% and 56% of control values in myotubes obtained from biopsies at day 1 and day 7, respectively.
Conclusions: Mitochondrial functions are affected in differentiated myotubes of critically ill patients with ICUAW from biopsies obtained during the first week of ICU stay.
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6-31
Vitamin D signaling is essential for maintaining skeletal muscle and adipose mass during weaning

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Introduction: Several studies have shown that vitamin D influences metabolism, and its deficiency leads to defective metabolic homeostasis. However, the exact mechanisms by which vitamin D affects systemic metabolism are unknown. We have previously shown that a lack of vitamin D signaling leads to glycogen storage disorder in the skeletal muscles, which causes energy deprivation and subsequent muscle wasting. Here, we address how the lack of vitamin D signaling affects adipose and liver metabolism.
Methods: We have analyzed the adipose tissue using histopathology to study adipose wasting, qRT-PCR, and western blot techniques to study gene expression changes and pathway changes. Adipose tissue explants were used to study the changes in adipose lipolysis. ELISA assays were employed to understand changes in the organokines and cytokines.
Results: We observed that weaning leads to systemic energy deprivation and cachexia in vdr-/- mice. Similar to skeletal muscles, the adipose tissue of mice lacking VDR exhibited severe atrophy. These changes are associated with metabolic rewiring of the adipose and liver evidenced by increased oxidative phenotypes of these tissues. Adipose tissue explants from vdr-/- show increased lipolysis. Further analysis showed that these changes were associated with the downregulation of the adipokine leptin and the upregulation of adiponectin. We further analyzed the metabolic changes in the liver to show that vdr-/- liver exhibits reduced energy levels. This is due to the inefficient utilization of carbohydrates, which is indicated by the reduced glycogen phosphorylase activity. Finally, we show that subjecting these mice to a milk-fat-based diet rescues adipose tissue weight and lowers liver glycogen levels.
Conclusions: Our data reveals that vitamin D signaling is essential for the adaptation of mammals to a carbohydrate-rich diet during weaning due to their inability to mobilize liver and skeletal muscle glycogen.

6-32
Histidyl dipeptides preserve skeletal muscle mass during heart failure

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Introduction: Muscle wasting is the serious comorbidity associated with heart failure leading to reduced physical function, increased mortality and poor quality of life. Recent report from our laboratory showed endogenous histidyl dipeptides carnosine and anserine are

decreased in the muscle of mice subjected to pressure overload model of heart failure by transaortic constriction (TAC). Histidyl dipeptides are synthesized by the enzyme carnosine synthase (CARNS) that can buffer intracellular pH and bind with reactive aldehydes. Whether these dipeptides are essential to maintain muscle mass under heart failure conditions has not been studied.
Methods: Wild type (WT) C57Bl/6J and skeletal muscle specific Carns transgenic mice (Tg) mice were subjected to sham and TAC surgeries for 12 weeks. Cardiac function, muscle mass, total cross-sectional area, muscle strength and plasticity, atrophic markers, expression of carnosine transporter were measured by echocardiography, immunohistochemistry, grip strength meter, atomic force microscopy, RT-qPCR, and western blots respectively. Levels of histidyl dipeptides was measured by LC-MS/MS.
Results: TAC induced heart failure decreased muscle weight, total cross-sectional area, muscle strength and plasticity in WT type mice. Decrease in muscle weight and cross-sectional area was associated with significant increase in atrophic marker *atrogin1,* lipid peroxidation products, such as acrolein, and inflammatory cytokine *TNF-α.* Overexpression of Carns in the muscle increased endogenous levels of histidyl dipeptides, preserved the muscle mass, strength and plasticity during heart failure. Furthermore, the expression of atrophic and inflammatory markers was decreased and levels of histidyl dipeptides were preserved in CarnsTg TAC mice.
Conclusion: Increasing endogenous histidyl dipeptide levels in skeletal muscle preserves removes toxic aldehydes, alleviate inflammatory and atrophic markers and consequently could preserve muscle mass and function, during heart failure.

7-01
Practical cancer nutrition, from guidelines to clinical practice: the mypath® project

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Background: Optimal nutritional care in patients with cancer remains underutilised. MyPath, an EU-funded implementation study, has developed a digital solution that integrates patient-centred care pathways into standard cancer care. Of these, the MyPath Nutrition Care Pathway (NCP) is an accessible, globally applicable method for addressing the nutritional needs of cancer patients.
Methods: During the MyPath project design phase (September 2022 - August 2024), an international multidisciplinary steering group developed the MyPath NCP based on evidence-led nutrition guidelines. A thorough appraisal of existing nutrition guidelines informed the final variables of the classification system. This included identifying items to be collected as digital Patient Reported Outcome Measures (PROMs) and defining the NCP components.
Results: The NCP offers a systematic assessment and classification framework to identify patients needing timely nutritional interventions and deliver tailored care. It focuses on three central pillars: 1) nutritional status, identifying decreased dietary intake and malnutrition, 2) health status, considering functional status, cancer prognosis, and prehabilitation needs, and 3) inflammatory status, using C-reactive protein levels. Based on this classification, the MyPath NCP suggests patient-specific nutritional care options, which clinicians will discuss and agree upon with patients. Continuous monitoring through digital PROMs and clinical consultations is essential for assessing compliance and efficacy, allowing for dynamic adjustments to meet the evolving nutritional needs of cancer patients.

An interactive overview of the MyPath Nutrition Care Pathway will be presented with key features highlighted.

7-02
Edentulism as a Risk Factor for Sarcopenia in Older Chileans. A Longitudinal Study

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Introduction: Besides aging, the impairment of chewing ability of edentulism and concomitant nutrition impairment, inflammation produced by periodontal diseases leads to an imbalance of protein synthesis and catabolism, both increasing the risk of sarcopenia
Objective
To determine the risk of sarcopenia associated with edentulism in older Chileans
Methods: Longitudinal study in 1278 community-dwelling people 60y and older (65.7%women, mean age 72.2±8.1y) living in Santiago/Chile, participants of ALEXANDROS cohort study. Edentulism was defined as self-reported loss of all or most teeth. Sarcopenia was identified using the EWGSOP 2010 algorithm validated for Chile. The participants were followed from 5 to 15 years to determine the incidence of sarcopenia according to tooth loss. Penalized regressions models were made to assess associations.
Results: At baseline, we analysed 1298(65.7%women) participants with oral health data, with a mean age of 72.2±8.1y, from the cohort study ALEXANDROS. Of the participants, 19.6% had sarcopenia and 74,2% (69.9% of men and 76.4% of women) manifested to have lost most or all teeth. At baseline the age, sex and nutritional state adjusted OR for sarcopenia and edentulism was 1.44%CI:1.06-1.95, p=0.02. After follow-up, the penalized regression model of sarcopenia associated with edentulism showed an OR of 1.65 (95%CI:1.01-2.71) adjusted by age, sex and nutritional state
Conclusion: Considering the rapid ageing of the population and the importance of sarcopenia as one of the main menaces of healthy aging, concomitantly with the high prevalence of edentulism in older Chileans, makes mandatory programs and policies to address early oral health problems in the population.

7-03

Differences on the prevalence of anorexia and clinical manifestations in patients with solid and hematological tumors who attend a tertiary care hospital from 2023 to 2024

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Introduction: Anorexia is present in 20-40% upon cancer diagnosis and its prevalence increases along the development of the disease, resulting in patients´poor quality of life and increased morbimortality.
Objective: To compare the prevalence of anorexia in patients with hematological and solid cancer at the time of diagnosis using three tools in adult patients attending a tertiary care hospital.
Secondary objectives: To compare the prevalence of anorexia in patients with digestive versus non-digestive solid tumors and the clinical manifestations associated.
Methodology: A cross-sectional, descriptive and comparative study was carried out from August 2023 to March 2024 in recently diagnosed outpatients. Two groups were studied: 1)Patients with solid tumors (ST); 2)Patients with hematological tumors (HT). The prevalence of anorexia was evaluated by means of the FAACT AC/S-12 questionnaire (anorexia: ≤ 30); the AQ, a simple tool of four questions related to symptoms (anorexia: a positive answer to any of these); and the VAS (anorexia: ≤ 50 mm).
Results: 241 cancer patients were included: 139 (57.6%) with ST and 102 (42.3%) with HT. Among the patients with ST, 80 were men (58.8%) and 59 women (56.1%); and with HT, 56 were men (41.1%) and 46 were women (43.8%). Patients with HT had a median age of 42.5 years (26.3 - 60 years) while patients with ST 60 years (49.5 - 70 years), ($p \leq 0.001$). Only the FAACT AC/S-12 detected significantly more anorexia patients with ST than in HT (47.4 vs 35.2%, respectively). Overall, ST (specially digestive cancers) produced more anorexia ($p<0.04$). Nausea/vomiting was the most common symptom in the ST patients and early satiety in the HT.
Conclusions: Anorexia was greater in the ST, mostly in digestive cancers. The FAACT AC/S-12 questionnaire identified more patients with anorexia. The most frequent symptoms in ST (nausea/vomiting) and HT (early satiety) may definitely contribute to anorexia.

7-04

Food acceptance in hospitalized cancer patients

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Introduction: Food acceptance of hospitalized patients and its contributing factors are crucial for optimal food intake and, therefore, to achieve a good nutritional status. For this reason a questionnaire including aspects related to food preparation and food service issues (staff/hospital resources) as well as eating habits was applied.
Methods: A modified questionnaire of Nutrition Day was tested and applied to hospitalized adult oncological, hemato-oncological patients and patients with other diseases at INCMNSZ. None of the patients had nutritional support. The questionnaire evaluated three main aspects: the organoleptic characteristics of meals/beverages, the meal presentation (tray, food packaging, staff service) and the patients´ eating habits. In general smell, consistency, temperature, taste, degree of cooking, as well as staff attitude towards the patient, hygiene and packaging were evaluated using the Likert Scale or LS (1 “very unpleasant” through 5 “very pleasant”) as well as the time allowed for food consumption (enough-not enough) with/out interruptions. Patient energy and protein intake was also estimated, and the attractiveness of menus (different colors, textures, tastes) was altogether reviewed by the dietitians.
Results: The questionnaire was applied to 63 patients (55% women). Taste was graded as LS 2 by 39.7% of the patients, especially by 58.3% of the hematological patients; meanwhile, beverages were graded as LS 4 by 41.3% of the patients. Overall food presentation was graded as LS 4 by 50.8%. However, patients expressed lack of variety and dietitians observed menus that tended to be monochromatic. Eighty percent of the patients consumed less than 25 Kcal/Kg and 66.67% less than 1 g of protein per kg of body weight.
Conclusions: Cancer may affect food consumption because chemotherapy and the disease itself produces dysgeusia/dysosmia and anorexia. Whilst the meal presentation was generally accepted, a lack of variety may have also contributed to the low energy and protein intake.

7-05

Dietary assessment of hospitalized cancer patients

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Introduction: Up to 70% of hospitalized patients consume less than 80% of their energy requirement, increasing the risk of malnutrition; specifically, 66% of patients undergoing chemotherapy consume less than 1 g protein/Kg. The benefits of adequate intake of both energy and protein have been demonstrated in numerous studies, showing lower rates of infections, morbimortality, and shorter hospital stays. Therefore, the aim of this study was to analyze the current dietary intake of hospitalized oncological and hemato-oncological patients and patients with other diseases at our institution.
Methods: This cross-sectional study estimated the total daily food portion eaten from the tray and compared its total nutritional value (energy, protein content) with the current clinical practice guidelines.
Results: A total of 49 patients were included (22 men, age 53.3±17.1 years; 27 women, age 52.7±17.5 years); 10 hemato-oncological patients, 20 oncological patients and 19 patients with other diseases; 80% of the surveyed patients consumed less than 25 Kcal/Kg, and 13.33% less than 10 Kcal/Kg; only 3.33% met their energy requirements. Additionally, 66.67% of the sample consumed less than 1 g of protein/Kg; 6.67% of the patients consumed 1.5 g protein/Kg body weight or even more. The hemato-oncological group had a mean energy and protein intake of 22.5±10.3 Kcal/Kg and 1.01 ± 0.45 g protein/Kg, respectively; the oncological group 17.4 ± 6.6 Kcal/Kg and 0.78 ± 0.42 g protein/Kg, respectively; and finally, patients with other diseases 20.2 ± 7 Kcal/Kg and 1.03 ± 0.66 g protein/Kg ($p = 0.43$, n.s. Kruskal-Wallis).
Conclusions: Our results match those published elsewhere in hospitalized patients: 66.6% do not meet their energy and protein requirements. However, no differences among the three patient groups could be observed. The implementation of monitoring food ingestion together with appropriate nutritional screening may facilitate timely decision-making with respect to nutritional support.

7-06

Effect of caffeine consumption in patients undergoing immunotherapy for melanoma and lung cancer

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Background: Cancer immunotheraphy refers to several approaches intended to activate the immune system to induce objective responses and disease stabilization. One pathway that tumors use is the overexpression of programmed cell death ligand 1 (PD-L1). However, the clinical response rate of immune checkpoint inhibitors (ICIs) is limited to a subset of patient population (15–30%), while majority of patients are resistant to PD1 blockade. Several studies have shown that blocking adenosine production and A2AR antagonism may improve the effectiveness of immunotherapy. Caffeine is an antagonist of A2AR. As such, the aim of this study was to assess the effect of caffeine consumption on the response to immunotherapy for non-small cell lung cancer (NSCLC) and melanoma.
Methods: In an observational cross-sectional study, surveys were conducted with 80 patients diagnosed with NSCLC and melanoma under immunotherapy, followed at the Oncology Day Hospital at Coimbra Hospital and University Centre (CHUC). Data on average daily caffeine consumption for several timespans, sex and age were recorded. By consulting the clinical process, the remaining data were obtained (date of diagnosis, staging, date of start of immunotherapy, immunotherapy regimen, previous treatments and adverse events). The evaluation of the response to immunotherapy was performed considering the results of chest CT scans at 3, 6 and 12 months after the start of immunotherapy.
Results: An association was observed between the average daily caffeine consumption during immunotherapy and the response to treatment at 3 months (p= 0.036), at 6 months (p=0.027) and at 12 months (p=0.016), in one-factor analysis. In the group of patients with NSCLC, there was a better response to treatment in patients with higher caffeine intakes during immunotherapy at 3 months (p=0.047), at 6 months (p=0.022) and at 12 months (p=0.028), in one-factor analysis. In the group of patients with melanoma no association was identified.
Conclusions: In this study, caffeine consumption appears to interfere with the response to immunotherapy, especially in patients with NSCLC undergoing immunotherapy with palliative intent. Caffeine consumption appears safe in both NSCLC and melanoma patients. These conclusions are favourable to the development of larger studies on this topic.

7-07

Malnutrition assessment in palliative cancer patients

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8-01

Co-designing the implementation process of an exercise intervention as part of a multimodal intervention for patients with renal cachexia

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Introduction: No evidence to date exists regarding the successful implementation of an exercise intervention for renal cachexia. Co-design is an effective approach in collaborating with service users, carers and healthcare professionals to identify methods of improving delivery of care.
Methods: Our objectives were: (1) To co-design a strategy to promote optimal recruitment and adherence to an exercise intervention for those with renal cachexia and (2) To test and refine initial programme theory in relation to the implementation of an exercise intervention with this group. Co-design workshops took place between November 2023 and November 2024. The first two workshops were held in-person in the United Kingdom while the subsequent one will be in Nov 2024 conducted virtually prior to the commencement of our funded multimodal intervention feasibility cRCT. Patient and public representatives from Northern Ireland and England representing Kidney Care UK, Northern Ireland Kidney Patients association and Northern Ireland Kidney Research Fund (n=8) took part in the workshops.
Results: Contexts, intervention factors, mechanisms and outcomes which influence the uptake of and adherence to an exercise intervention within this patient population were identified. These include: the exercise intervention adopting an individualised and flexible approach; ensuring the exercise programme is manageable for those on haemodialysis (fistula awareness, duration and timing); ensuring the structure of the exercise booklets are relatable and achievable (using household items not traditional exercise equipment and crediting everyday activities as part of exercise log); support during the intervention (weekly telephone calls and progress tracking); and invitation from consultant nephrologist or dietician of patients on haemodialysis considered most promising to encourage recruitment.
Conclusion: The workshops have contributed to the evolution of a programme framework to optimise implementation of an exercise intervention for renal cachexia management in practice. This has informed the implementation and evaluation design of a multimodal intervention for renal cachexia commencing 08.01.25.

8-02

Endurance training did not mitigate transcriptional changes in muscle apelin induced by systemic inflammation in rats with cardiac cachexia

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Apelin has emerged as a promising therapeutic target for muscle wasting. However, the underlying mechanisms are not fully understood. This study aims to investigate the impact of endurance training on rat skeletal muscle-derived apelin during cardiac cachexia.
Methods: 20 male Wistar rats (~250g) were randomized into four groups: control sedentary (C); control exercise (E), cachexia sedentary (MCT), and cachexia exercise (MCTE). Cardiac cachexia was induced by monocrotaline (MCT; 60 mg/kg) while control animals received saline. The exercise protocol consisted of running on a treadmill five days/week at 60% of maximal capacity for 4 weeks. At the end of the experiment, endurance capacity was

assessed by an incremental treadmill test, and blood and tibialis anterior muscle (TA) were collected for morphological and biochemical analysis.
Results: Cachectic animals showed reduced endurance capacity (C 17.7±4.3, E 22.3±3.0, MCT 11.7±2.7, MCTE: 9.0± 2.6 min, $F_{(1,15)}$=44.09, p<0.0001) and muscle fiber cross-sectional area (C 3150±486, E 3466±946, MCT 1764±122, MCTE 1860±432 μm^2, $F_{(1,13)}$=29.42, p=0.0001) compared to controls. Additionally, we observed higher plasma concentration of pro-inflammatory cytokines (TNF-α: C 1082.6±0.1, E 1016.8±0.1, MCT 1434.5±0.3, MCTE 1373±0.2 pg/mL, $F_{(1,15)}$=16.85, p=0.0009; IL-6: C 255±17.9, E 244±15.6, MCT: 329±49.3, MCTE 344±60.2 pg/mL, $F_{(1,16)}$=22.73, p=0.0002), and reduced apelin gene expression (*APLN*) in TA muscle (C 1.1±0.4, E 0.9±0.3, MCT 0.5±0.2, MCTE 0.6±0.3 fold-change; $F_{(1,16)}$=9.310, p=0.0076) compared to controls. No differences were found between the cachexia and control groups regarding cytokine muscle concentrations, and plasma and muscle apelin-13 concentrations. Moreover, we found associations between *APLN*/plasma TNF-α (r^2=0.42, p=0.0026) and *APLN*/right ventricle mass (r^2=0.36, p=0.0052) while, in TA muscle, apelin-13 was correlated with IL-1β (r=-0.49, p=0.0273). Endurance training did not impact the variables analyzed.
Conclusion: Cardiac cachexia-induced systemic inflammation promotes an early stage of apelin dysfunction, characterized by transcriptional changes in muscle apelin; which was not mitigated by 4 weeks of endurance training.

8-03
Impact of aerobic training on inflammatory and autophagic markers in rats with heart failure

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Heart failure (HF) is a complex clinical syndrome with systemic effects, including low-grade chronic inflammation, skeletal muscle dysfunction, and atrophy. Autophagy is a critical process in the regulation of muscle mass and function, which has been shown to regulate and be regulated by proinflammatory cytokines. *We aimed to investigate the impact of aerobic training on inflammatory and autophagic markers in rat skeletal muscle during the onset and progression of HF.*
Methods: Twenty-four 8-week-old male Wistar rats were randomly assigned into 4 groups: Control Sedentary (CSed), Control Exercise (CEx), HF Sedentary (HFSed), HF Exercise (HFEx). Rats in HFSed and HFEx received a single injection of monocrotaline (MCT, 60mg/Kg) for the induction of HF while control groups were injected with saline. Trained groups (CEx and HFEx) were subjected to 30min/day treadmill running sessions, 5 days/wk for 4 weeks, at 60% intensity determined by a maximal endurance test. At the end of the experiment, the tibialis anterior (TA) muscle was collected and frozen for future analyses. Statistics: Two-way ANOVA at a significance level of p<.05.
Results: HF led to a decrease in TA muscle mass in HF rats compared to their respective controls (CSed 735.68±42.55g, CEx 733.48±56.71, HFSed 586.32±121.2, HFEx 599.50±85.84mg; p<.05). Autophagic activity was significantly increased in HFSed compared to its sedentary counterpart (LC3 II/I ratio: CSed 1.06±0.38, CEx 1.87±1.69, HFSed 4.67±2.94, HFEx 2.68±1.56a.u.; p<.05). IL-6 and IL-1β pro inflammatory cytokines gene expression showed no differences among the groups, while TNF-a gene expression was surprisingly significantly decreased in HF groups relative to controls (CSed 1.27±.46, CEx .79±.17, HFSed .26±.05, HFEx .77±.74; p<.05).
Conclusion: HF caused skeletal muscle wasting via increased autophagic activity in a mechanism independent of proinflammatory cytokines. Furthermore, endurance training did not appear to be a preventative measure against skeletal muscle wasting during the progression of HF.

8-04
Effects of wearable electrical muscle stimulation on lower muscles during walking-workout

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Introduction: Sarcopenia, characterized by a decrease in muscle mass and impaired physical function. To address sarcopenia, exercises that activate Type II muscle fibers are essential. An wearable electrical muscle stimulation (EMS), which contracts muscles by electrically stimulating both muscles and nerves, has shown potential for inducing hypertrophy in Type II muscle fibers but has demonstrated limited effectiveness in improving muscle function. This study aimed to investigate the improvement in muscle function by applying EMS and light walking exercise simultaneously to the quadriceps muscle, a major site of muscle atrophy as sarcopenia.
Methods: Fifteen adults aged 20-52 participated in the study, engaging EMS on the right quadriceps nerve at a high frequency (50-70Hz) with in briskly walking for 4 weeks. Bioelectrical Impedance Analysis (BIA) and isokinetic measurements were conducted pre and post-intervention to assess changes in lower limb muscle function.
Results: After training, the combined use of walking exercise and EMS (EMS-EX group) showed no differences in body weight, body mass index, percentage of body fat, skeletal muscle mass from the only walking exercise (EX-CON group), respectively. However, The EMS-EX group showed a significantly increase in muscle strength, muscle power, and muscle endurance compared to the EX-CON group.
Conclusion: The significant increase in muscle strength observed in the leg that underwent both EMS and walking exercise compared to the leg that underwent only walking for 4 weeks may suggests that this outcome is attributed to an increase in strength as well as muscle structure. The larger improvements in muscle strength in the leg that underwent both EMS and walking can emphasize the effectiveness of this combined approach in enhancing muscle function in patients with sarcopenia.

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8-06
Intermittent hypoxic-hyperoxic training during inpatient rehabilitation improves exercise capacity and functional outcome in patients with long COVID: Results of a controlled clinical pilot trial

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Introduction: COVID-19 is causing long-term lung damage that will lead to increasing numbers of patients disabled by reduced lung

function. Intermittent hypoxia-hyperoxia training (IHHT) is a non-pharmacological therapeutic modality which has been suggested to improve exercise performance via controlled respiratory conditioning. to positively influence the recovery process in post-COVID syndrome. The purpose of present study is to further investigate the therapeutic effects of IHHT on the recovery process during inpatient rehabilitation in post-COVID syndrome.
Methods: A prospective, controlled, open-treatment, non-randomized pilot trial was conducted on 145 patients with COVID19 (mean age 53±11years, female: 74%), who were admitted to an inpatient rehabilitation program. Patients were assigned to receive IHHT in addition to the standardized rehabilitation program (IHHT group) or standard rehabilitation alone (control group). The IHHT group received supervised sessions of intermittent hypoxic (10–12% O_2) and hyperoxic (30-35% O_2) breathing training 3 times per week throughout the rehabilitation period. Primary endpoint was improved walking distance in a six-minute walk test (6MWT) between study groups. Secondary endpoints were change in stair climbing power, dyspnoea (Borg dyspnoea Scale), fatigue assessment scale (FAS) and change in health related quality of life (HRQoL) assessed by patient global assessment (PGA), EQ5D analogue scale and the MEDIAN Corona Recovery Score (MCRS). Further assessments included maximum handgrip strength, nine hole peg test, timed up-and-go, respiratory function and functional ambulation category (FAC), lab analyses and safety of the intervention.
Results: The IHHT group compared to controls demonstrated a significant higher increase in 6MWT (all data pre-post difference per group: 91.7±50.1m vs 32.6±54m, ANCOVA p<0.001), improved stair climbing power (-1.91±2.23 sec vs. -0.51±1.93 sec, p<0.001), improved fatigue assessment (FAS: -8.9 vs 3.6, P<0.001) as well as improved HRQoL by EQ5-D analog scale (31.3 vs 2.9, P<0.001), and by MCRS (-10.3 vs -2, P<0.001) comparing to control group.
The IHHT group exhibited a significant decrease in blood pressure, heart rate and increase in haemoglobin levels compared to baseline (p<0.01), whereas these changes were not significant in the control group. No adverse events were observed.
Conclusion: Treatment with IHHT in addition to a multidisciplinary rehabilitation program improves functional capacity, symptomatic status and quality of life in patients with disabling long COVID illness respiratory. IHHT has been demonstrated to be safe, well tolerated and feasible to be integrated in an inpatient rehabilitation program to improve outcome in long COVID.

9-01

Neuromuscular electrical stimulation (NMES) for sarcopenia in people with long-term conditions: a protocol for a systematic review and meta-analysis

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Introduction: Sarcopenia, characterized by progressive loss of muscle mass and strength, is exacerbated in patients with long-term conditions. This leads to poor functional capacity, reduced quality of life (QoL), and high mortality. Effective methods to reverse sarcopenia are crucial for preserving autonomy, reducing hospitalization and death rates. While exercise is an established treatment for sarcopenia, it is often not feasible for patients with advanced diseases due to poor physical fitness. Neuromuscular electrical stimulation (NMES) is a promising alternative. This systematic review aims to evaluate the effectiveness of NMES on muscle strength, muscle mass, physical function, and QoL in patients with long-term conditions.
Methods: Studies were identified through searches of MEDLINE, EMBASE, CINAHL, Cochrane CENTRAL, Web of Science, Scopus. Randomized controlled trials (RCTs) comparing NMES as a sole intervention to usual care in adults with long-term conditions were included. Two reviewers independently extracted data on study design, participants, interventions, and outcomes using Covidence. The risk of bias was assessed with the NHLBI's tool. Mean differences (MD) or standardized mean differences (SMD) were calculated for outcomes with sufficient data, while findings from individual studies were described for other outcomes.
Results: 21 studies involving a total of 572 participants met the inclusion criteria across chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD), chronic heart failure (CHF) and cancer. It is hypothesized that NMES will significantly improve quadriceps muscle strength, muscle mass, physical function, and QoL compared to usual care in patients with long-term conditions.
Conclusions: This systematic review aims to provide comprehensive evidence on the efficacy of NMES in reversing sarcopenia in patients with long-term conditions. By identifying optimal NMES parameters and standardizing intervention protocols, this review seeks to facilitate better comparison and application of NMES in clinical practice, ultimately improving patient outcomes and reducing morbidity and mortality rates in this population.

9-02

A synbiotic improves muscle strength, mass and performance in older Australians: preliminary results from a randomized, controlled trial

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Introduction: The etiology of sarcopenia is complex and multifactorial yet recent evidence suggests one contributing factor may be age-related alterations in gut microbiota. Synbiotic administration appears effective in modifying gut microbial composition, however it remains unclear if these changes translate into functional improvements. We examined the effects of synbiotic (SYN) supplementation compared with placebo (PLA) on muscle strength, lean body mass and physical performance in older adults.
Methods: A randomized, double-blinded controlled trial was performed among 70 community-dwelling, older (60-85 years) adults. Participants were randomly allocated (1:1) to receive either SYN or PLA daily for 16 weeks. Outcomes including handgrip strength (HGS), Short Physical Performance Battery (SPPB), timed up and go (TUG) and body composition (dual-energy X-ray absorptiometry) were assessed at baseline and after 16 weeks.
Results: Sixty-four participants (72.7 ± 5.6 years; 61% female) completed the trial. Compared with PLA, SYN supplementation for 16 weeks resulted in significantly increased HGS (p = .024) and total SPPB score (p = .006), and significantly improved times for gait speed (p < .001) and TUG (p = .001). No significant between-group changes in body composition were observed (p > .05). Absolute and relative fat mass decreased in the SYN group (Δ -0.24 kg and Δ -0.26%, respectively) and increased in the PLA group (Δ 0.03 kg and Δ 0.09%, respectively), however, these were not significant (p > .05). A larger increase in lean body mass was observed in the SYN vs. PLA group (Δ 0.14 kg vs. Δ 0.04 kg, p = .697).
Conclusions: Sixteen weeks of synbiotic supplementation improved muscle strength and physical performance in community-dwelling older adults compared with placebo. These improvements were not accompanied by significant changes in body composition.

9-03

Can astaxanthin supplementation improve human body composition and muscle function

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Introduction: Astaxanthin (Ax), a carotenoid derived from Haematococcus lacustris, exhibits potent antioxidant capabilities, counteracting cell damage caused by oxidative stress through free radical scavenging and cellular protection. Thus, Ax may serve as a potential adjunct therapy for enhancing muscle mass and function through its antioxidant activity. This pilot study aimed to assess the impact of Ax supplementation on body composition and muscle function.
Methods: Fourteen sedentary adults, aged 21 to 52, received a daily dose of 12 mg Ax for four weeks. Skeletal muscle mass and percentage of body fat (PBF) were assessed using bioelectrical impedance analysis before and after supplementation, along with scaled maximal isokinetic knee extension and flexion strength at 60°/s and 180°/s to evaluate muscle strength, power, and endurance.
Results: Fourteen participants completed the study, and after four weeks of Ax supplementation, there was a significant increase in skeletal muscle mass. Body weight remained unchanged. At 60°/s, the maximum torque of knee flexor muscles significantly increased, and at 180°/s, both knee flexor and extensor maximum muscle torque for muscle power significantly increased, respectively. Moreover, the total work of knee flexor and extensor muscles at 180°/s for muscle endurance exhibited a significant increase.
Conclusion: Supplementation with 12 mg/day of astaxanthin from Haematococcus lacustris in sedentary adults for four weeks demonstrated a significant improvement in body composition, including increased skeletal muscle mass and decreased body fat percentage, as well as enhanced muscle strength, power, and endurance. These findings suggest that Astaxanthin may serve as a promising adjunct therapy for addressing aspects of sarcopenia. However, further research with larger sample sizes, longer duration, and randomized controlled trials is warranted to validate and generalize these preliminary findings.
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9-05

Combined GDF8 and activin A blockade in healthy volunteers: safety, efficacy, and pharmacokinetics

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Introduction: Preclinical studies have shown that GDF8 (myostatin) and activin A are negative regulators of muscle mass, with combined blockade of these ligands leading to hypertrophy. Trevogrumab is an investigational monoclonal antibody (mAb) that binds to and blocks GDF8 signaling; the investigational mAb garetosmab binds to and blocks signaling of activins A, AB, and AC. The safety and efficacy of trevogrumab and garetosmab on body composition in healthy participants was evaluated.
Methods: Part 1 of this double-blind, placebo-controlled, phase 1 trial randomized postmenopausal women to a single intravenous administration of trevogrumab 6 mg/kg (n=6); garetosmab 10 mg/kg (n=6); trevogrumab 6 mg/kg + ascending garetosmab doses (1 mg/kg, n=6; 3 mg/kg, n=6; and 10 mg/kg, n=12); or placebo (PBO; n=12).
Results: All participants receiving treatment had mild-to-moderate treatment-emergent adverse events; no clinically significant safety concerns were identified in any active treatment groups. At week 8, single-dose treatment with the individual mAbs resulted in numeric increases in muscle volume and lean body mass measures and numeric decreases in fat mass measures versus placebo; only combination treatment showed consistent nominally significant differences in all measures of muscle gain/fat loss. At week 8, thigh muscle volume increased by 3.5%, 6.2%, and 7.7% for the combination trevogrumab 6 mg/kg + garetosmab 1-, 3-, and 10-mg/kg groups versus placebo, with similar trends in total lean mass and appendicular lean body mass. Increases in total GDF8 and total activin A in serum coincided with observed effects on muscle and fat.
Conclusion: In healthy participants, trevogrumab and garetosmab were generally well tolerated. Combination treatment led to greater-than-additive increases in muscle mass, with reductions in fat. Results suggest that GDF8 and activin A are key negative regulators of muscle mass in humans and that combination blockade may be a promising therapeutic approach in muscle atrophy and obesity settings.
Conflict of Interest: DGT, SD, SA, PP, KM, JM, RP, and GAH are employees and stockholders of Regeneron Pharmaceuticals, Inc. CW is an employee of and shareholder in New Zealand Clinical Research.
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9-06

CT-Derived Psoas Muscle Measurements are Associated with Increased Mortality in Venovenous Extracorporeal Membrane Oxygenation

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Introduction: Venovenous Extracorporeal Membrane Oxygenation (VV-ECMO) is an intensive care therapeutic modality used for individuals in respiratory failure who are failing conventional endotracheal intubation and mechanical ventilation. Sarcopenia has been previously associated with a longer time spent on VV-ECMO and an increased risk of 1-year mortality. This analysis explores the association of computed tomography (CT)-derived psoas area and density with mortality in patients undergoing VV-ECMO.
Methods: Individuals ≥ 18 years old at a single center who underwent VV-ECMO between 09/2017 - 01/2022 were included in the screening (n=158). Individuals who received an abdominal CT scan within 30-days of VV-ECMO cannulation were included in analysis (n=106). CT scans were assessed from which Psoas Area Index (PAI) and mean Hounsfield units (mHU) were calculated. All statistics performed using GraphPad Prism v10.2.3.
Results: Calculated PAI values ranged from 1.64 to 11.48 (cm^2/m^2). In univariate logistic regression, each unit increase in PAI was associated with a 36% increase in odds of discharge alive (OR = 1.357; 95% CI = 1.131 - 1.663). Application of a receiver operating characteristic curve (ROC) produced an area under the curve (AUC) of 0.6821 (p-value < 0.001) indicating an independent ability of PAI to predict discharging alive. Measured mHU values ranged from -0.52 to 63.60. Each unit increase in muscle density was associated with a 5% increase in odds of discharging alive (OR = 1.051; 95% CI = 1.024 - 1.082). With ROC the AUC of mHU demonstrated an area of 0.6826 (p-value < 0.001).

Conclusion: CT freehand ROI measures psoas sarcopenia measured immediately prior to VV-ECMO cannulation is associated with mortality while on VV-ECMO. This represents a feasible, real-time measurement for clinicians to explore and utilize in individuals undergoing VV-ECMO.

9-08

menac - a randomised, open-label trial of a multimodal intervention (exercise, nutrition and anti-inflammatory medication) plus standard care versus standard care alone to attenuate cachexia in patients with incurable lung or pancreatic cancer undergoing systemic anti-cancer therapy

clinicaltrials.gov id: nct02330926

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Introduction: Combining interventions for cancer cachexia is proposed as an effective strategy. Building on a promising pilot study, we conducted the MENAC (Multimodal Exercise Nutrition Anti-inflammatory Cachexia) trial to comprehensively evaluate this.

Methods: MENAC was a multicentre, randomised phase 3 trial in 4 countries. Patients with stage III or IV lung or pancreatic cancer receiving SACT with non-curative intent were randomly assigned (1: 1) to a multimodal intervention consisting of nutritional counselling plus fish oil containing oral nutritional supplements, physical exercise (endurance and strength) and non-steroidal anti-inflammatory drugs (NSAIDs) versus standard care. Randomisation was stratified by country, cancer type and stage.

Our primary objective was to body weight. Secondary Objectives assessed muscle mass (measured by CT L3 technique) and physical activity (assessed through step count using ActivPAL activity meter) between arms. Exploratory endpoints included treatment response (RECIST), survival, and Quality of Life. Assessments were conducted at base line (pre-randomisation), at endpoint (after 6 weeks) and follow -up (12 weeks).

Results: From May 2015 to February 2022, 212 patients were enrolled (105 to multimodal treatment, 107 standard care). Over 6 weeks, weight stabilised in patients assigned to multimodal treatment compared with those assigned to standard care (mean weight change [SD] 0.05 kg [3.8] *vs* – 0.99 kg [3.2], respectively) with a mean difference in weight change of -1.04, 95 % CI -2.02 to -0.06, p = 0.04. There was no difference in muscle mass (mean change [SD] -6.5cm^2[10.1] *vs* -6.3cm^2 [11.9], p = 0.93) or in step count (mean change [SD] -377.7 [2075] *vs* -458 [1858], p = 0.89). There were 28 and 24 reported SAEs in the intervention and control arm respectively, no SUSARs were reported. Data on exploratory endpoints and 12 week follow up will be presented.

Conclusion: A multimodal cachexia intervention stabilised weight compared to standard care at six weeks. There was no difference in physical activity or muscle mass between trial arms.

9-09

Efficacy and safety of anamorelin in pancreatic cancer patients with cachexia: a prospective observational study

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Introduction: Anamorelin, a ghrelin agonist, has demonstrated efficacy in treating cachexia in non-small cell lung cancer (NSCLC) patients. However, its effectiveness in pancreatic cancer patients with cachexia remains underexplored. This study aimed to evaluate anamorelin's efficacy and safety in this patient population.

Methods: This prospective observational study included 24 pancreatic cancer patients with cachexia. Seventeen patients who continued anamorelin treatment for over a month were included in the efficacy analysis. The primary endpoint was the change in lean body mass (LBM) from baseline. Secondary endpoints included the anamorelin response ratio and the incidence of adverse events. Responders were defined as patients who maintained or increased their LBM during treatment.

Results: Among the 17 patients analyzed, the average LBM increased by 0.9 kg at one month and 1.4 kg at two months post-treatment. Quality of life, as assessed by the QOL-ACD questionnaire regarding appetite, significantly improved, and more patients reported weight gain. Ten patients (58.8%) were classified as responders, showing substantially more significant hand-grip strength increases than non-responders. A lower baseline BMI (<20.4) was significantly associated with a higher likelihood of being a responder (AUC 0.886, p=0.008 in ROC analysis). No significant differences between responders and non-responders were observed in IGF-1, plasma cytokines (IL-6, TNF-α, IL-1β), ghrelin, or leptin levels. Hyperglycemia was the most common adverse event, occurring in 34.8% of patients. Low baseline insulin secretion (measured by the glucagon test) was significantly associated with grade ≥2 hyperglycemia (cut-off value: ΔC-peptide 1.03, AUC 0.967, p=0.0032).

Conclusion: Anamorelin appears to be as effective in treating cachexia in pancreatic cancer patients as in NSCLC patients, particularly in those with a low BMI. However, the risk of hyperglycemia, especially in patients with reduced insulin secretion, should be carefully considered. BMI and insulin secretion capacity should be evaluated when prescribing anamorelin to pancreatic cancer patients.

9-10

Efficacy and safety of ponsegromab, a first-in-class, monoclonal antibody inhibitor of growth differentiation factor 15, in patients with cancer cachexia: a randomized, placebo-controlled, phase 2 study

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Introduction: Cancer cachexia can lead to weight loss, muscle wasting, and reduced quality of life. Ponsegromab is a humanized monoclonal antibody targeting growth differentiation factor 15 (GDF-15), a circulating cytokine implicated in cachexia. Here, we report the results of a phase 2, randomized, double-blind trial of ponsegromab vs placebo in patients with cancer cachexia.

Methods: Patients with cancer cachexia and elevated serum GDF-15 (≥1500 pg/mL) were randomized 1:1:1:1 to subcutaneous ponsegromab (100, 200, 400 mg) or matching placebo every 4 weeks for 12 weeks. The primary endpoint was a change in weight from baseline to 12 weeks. Other endpoints included change in appetite and cachexia symptoms (Functional Assessment of Anorexia/Cachexia Treatment [FAACT] Anorexia Cachexia Subscale [FAACT-ACS] and 5-item Anorexia Symptom Scale [FAACT-5IASS]), non-sedentary physical activity, and lumbar skeletal muscle index (LSMI).

Results: Overall, 187 patients (39.6% non-small cell lung, 31.6% pancreatic, and 28.9% colorectal cancer; 73.3% stage 4) were randomized. Ponsegromab resulted in significant dose-responsive increases in weight, with placebo-adjusted modeled median (95% credible interval) increases of 1.22 kg (0.37, 2.25) [100 mg], 1.92 kg (0.92, 2.97) [200 mg] and 2.81 kg (1.55, 4.08) [400 mg] at 12 weeks. Placebo-adjusted weight gain was observed at week 8 in all ponsegromab groups. In the 400 mg ponsegromab group, placebo-adjusted modeled median (95% credible interval) improvements in FAACT-ACS (4.50 [1.29 to 7.77]); FAACT-5IASS, (2.39 [0.61 to 4.15]); non-sedentary physical activity (71.70 [37.01 to 107.21] minutes), and LSMI (2.04 [0.27 to 3.83] cm^2/m^2) were also observed compared with placebo. All-causality and treatment-related adverse events occurred in 70.4% and 7.7% of ponsegromab-treated patients and 80.0% and 8.9% of placebo-treated patients, respectively.

Conclusion: Ponsegromab improved weight, symptoms, overall activity, and skeletal muscle mass in patients with cancer cachexia and elevated GDF-15, confirming GDF-15 as a primary driver of cancer cachexia.

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9-11

BIO101: a drug candidate to reduce GLP1-RA-induced muscle mass or function loss in patients with obesity.

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Introduction: GLP-1 receptor agonists (GLP-1RAs), also named incretins, effectively reduce body weight, however up to 40% of the total lost weight is lean body mass, which includes loss of skeletal muscle mass. Similar levels of weight loss with bariatric surgery are associated with clinically significant reductions in muscle mass and strength. Combining skeletal muscle-targeted drug candidates with GLP-1RAs may preserve skeletal muscle mass and function. BIO101 (20-hydroxyecdysone; 20E), an oral MAS receptor activator, could be a promising treatment to prevent the loss of muscle mass or strength in patients with obesity or overweight treated with GLP-1RAs.

Methods: Preclinical studies of 20E-treated myoblasts and high fat diet (HFD) obese mice were completed to characterize the metabolic, muscular and weight loss properties of 20E. In addition, a 12-week double-blind placebo-controlled study (6-week hypocaloric intervention phase followed by 6-week weight loss maintenance phase) with 37.5mg 20E was conducted in 58 participants with overweight or obesity (BMI ≥ 27 kg/m^2 and ≤ 38 kg/m^2) aged 20-65 years.

Results: Preclinically, 20E has pro-differentiating effects *in vitro* in murine and human myocytes, increasing myotube diameter. *In vivo*, 20E improved muscle function and physical capacity. In HFD mice, 20E significantly prevented increase in adipose tissue by limiting adipocyte size, adipokines and inflammatory markers (leptin, MCP-1), insulin resistance (osteopontin) and decreased genes involved in lipid storage (lipoprotein lipase).

In patients with overweight or obesity, 37.5mg 20E significantly decreased android fat mass (p=0.039). From biopsies, a statistically significant reduction in adipocyte diameter was also observed over the entire trial period. Compared to placebo, a trend for improvement

in handgrip strength occurred in the subpopulation who lost more than 5% of their initial weight during the weight loss phase.
Conclusions: Supported by these data, a phase 2 Proof-of-Concept study combining BIO101 treatment with a GLP-1 RA will be shortly initiated.

10-01
Exon 2 is the key pro-myogenic mediator of the lncRNA CYTOR

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Introduction: Fast twitch, type II muscle fibers are particularly prone to degradation in skeletal muscle pathologies, such as sarcopenia and muscular dystrophies. So far, there are no medical strategies targeting those fibers. We previously showed that endogenous activation of the exercise-induced long noncoding RNA CYTOR promotes fast-twitch myogenesis. In the present study, we aimed to identify a putative pro-myogenic element of human CYTOR and to optimize CYTOR RNA delivery.
Methods : Primary human skeletal muscle cells were obtained from DMD patients (from lonza) (SkMC, #CC-2561).
Cells were homogenized, and RNA isolated using the RNeasy Mini kit (Qiagen, 74106).
Reverse transcription was performed with the High-Capacity RNA-to-cDNA Kit (4387406 Thermofisher scientific). Lentiviruses were produced by cotransfecting HEK293T cells with lenti plasmids expressing GFP or CYTOR EXON1, EXON2 or full length (see plasmid list in Table S3), the packaging plasmid psPAX2 (addgene #12260) and the envelope plasmid pMD2G (addgene #12259), in a ratio of 4:3:1, respectively. Plasmids were obtained from Vectorbuilder.
For experimental conditions in which there were two independent factors and multiple comparisons, a factorial ANOVA with subsequent post hoc analysis was performed.
Results : In human primary myoblasts we show that exogenous, vector-based $CYTOR^{Exon2}$ delivery recapitulates the effect of full-length CYTOR by enhancing fast-twitch myogenic differentiation. Chemically modified $CYTOR^{Exon2}$ $RNA^{\Psi U}$ (N1-me-PseudoU, 7-methyl guanosine 5'Cap, polyA tail) enhanced RNA stability and reduced the inflammatory response to RNA delivery. Finally, we demonstrate that viral- or optimized RNA-mediated $CYTOR^{Exon2}$ delivery enhances the commitment towards myogenic maturation in human primary myoblasts, induced myogenic progenitor cells and mouse embryonic stem cells.
Conclusions: Our findings identify CYTOR Exon 2 as the pro-myogenic element of CYTOR.

10-02
Early adolescent genotoxic stress leads to a reduction in skeletal muscle stem cells and persistent damage of the niche.

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Introduction: Genotoxic stress is a consequence of cancer treatments such as radiation whose persistence contributes to accelerated aging of tissues and organs. Immediately following radiation of growing adolescent skeletal muscle extensive DNA damage is observed, the integrity of muscle stem cells is reduced, and regenerative capacity is inhibited. Most of this damage subsides within weeks.
Methods and results: Single cell RNA sequencing analysis and assessment of fate reveal most muscle stem cells that are lost with adolescent radiation are non-quiescent. Furthermore, weeks after early adolescent radiation remaining muscle stem cells demonstrate little if any signs of DNA damage. In contrast, persistent signs of genotoxic stress are observed in components of the muscle stem cell niche.
This is associated with an increase in macrophage content and the expression of TGFbeta superfamily members and regulators, which based on Cell Chat analysis have the potential to impact multiple cellular processes during skeletal muscle growth and regeneration.
Conclusion: Collectively, these observations indicate the persistence of genotoxic stress after early adolescent radiation occurs primarily in niche as opposed to muscle stem cells.

10-03
Molecular characterization of cachexia in a novel model for the study of head and neck cancer

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Introduction: Up to 50% of patients with head and neck cancer (HNC) exhibit the symptoms of cachexia. Nevertheless, the mechanism(s) responsible for the onset of such comorbidity in HNC patients are not well understood, partly due to limited availability of animal models. Here, we characterized molecular and functional features of cachexia in a novel preclinical model for the study of HNC.
Methods: Murine C2C12 myotubes were exposed to 50% conditioned media (CM) from B0092 oral squamous cell carcinomas to determine the effects on myotube size and protein expression. 10-week-old C57BL/6J male mice were implanted with $5x10^5$ B0092 cells (s.c.) and the consequences on muscle and bone were assessed by means of Western blotting, qPCR, histological analysis, DEXA and microCT. The B0092 effects on gene signature associated with muscle wasting were investigated by performing RNA sequencing in skeletal muscle.
Results: The C2C12 cultures treated with B0092 CM exhibited significant myotube atrophy as compared to untreated controls (-32%, $p<0.001$), also consistent with increased p-STAT3/STAT3 (+2.6-fold, $p<0.0001$) and reduced p-AKT/AKT ratios (-70%, $p<0.0001$), thereby suggesting heightened catabolism and decreased anabolism, respectively. *In vivo*, growth of B0092 tumors caused progressive skeletal muscle atrophy, loss of muscle strength (-36%, $p<0.001$ *vs.* C), reduced bone mineral density (-8%, $p<0.01$ by DEXA), and decreased trabecular bone (Conn.Dn: -34%, $p<0.05$; Tb.N: -12%, $p<0.01$ by microCT). Interestingly, the muscle atrophic response was in line with overexpression of the muscle-specific ubiquitin ligases *Trim63* (+1.96-fold, $p<0.05$ *vs.* C) and *Fbxo32* (+1.97-fold, $p<0.05$ *vs.* C). Lastly, the RNA-seq analysis revealed extreme dysfunction of mitochondria, as well as upregulation of proteasome- and translation-related pathways, both of which are canonically observed in various cachexia models.
Conclusion: Our data suggests that the B0092-bearing mouse can be a useful tool to uncover novel molecular pathways and potential therapeutic targets for the treatment of HNC cachexia.

10-04

Potential anti-cachexia properties of novel dual-MEK inhibitor IMM-1-104

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Introduction: While cancer cachexia is responsible for a significant proportion of cancer morbidity and mortality, affecting a majority of advanced cancer patients[1], it lacks approved therapies. We previously demonstrated potential anti-cachexia effects of novel dual-MEK inhibitor (MEKi) IMM-1-104 in a cancer cachexia mouse model at a dose producing significant tumor growth inhibition.[2]
Methods: IMM-1-104 and selumetinib, a first-generation MEKi with reported clinical improvements in lean muscle mass[3], were dosed BID for 18 days in the Colon-26 (C26) mouse model. Tumor growth inhibition (TGI) and body weight were assessed, and transcriptomic effects in tumor and muscle were measured by RNA sequencing.
Results: In the C26 model, IMM-1-104 dosed at 25mpk BID reduced tumor-associated loss of body weight, normalized expression of transcripts for E3 ubiquitin ligases Murf-1 and Atrogin-1 while counteracting pathological expression of inflammatory and proteasomal pathways in muscle, and reversed a signature of thermostimulatory behavior[4] in tumor. Dosing at 25mpk did not produce significant reduction in tumor growth.
Conclusions: We previously reported similar body weight and transcriptomic effects for 100mpk IMM-1-104, a dose that strongly reduced tumor growth. The data reported here, by contrast allow separating the tumor-reducing effect of IMM-1-104 from its potential anti-cachexia properties. We observed similar cachexia-relevant transcriptomic effects, along with reduction in tumor-associated body weight loss, with 25mpk as with 100mpk IMM-1-104. These effects were comparable with those of selumetinib, a compound reported to have clinical anti-cachexia activity. Clinical evaluation of IMM-1-104 as a tumor-reducing agent in RAS-driven solid tumors is underway in a Phase 1/2a trial [NCT05585320]. The findings reported here support further evaluation for effects against cancer cachexia.

1 Mariean et al, Cancer, 2023.
2 Kolitz et al, SCWD, 2022.
3 Prado et al, British J Cancer, 2012.
4 Ung et al, AACR, 2018.

10-05

Musclin restrains muscle atrophy and NMJ degeneration in mouse models of ALS

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Introduction: Amyotrophic Lateral Sclerosis (ALS) is among the most devastating neuromuscular diseases, significantly affecting patients' and families' quality of life, with emotional effects on society and high health care costs. Sadly, ALS is still incurable. Emerging evidence shows similarities between muscle atrophy in cancer and ALS: muscle denervation occurs in cancer-induced atrophy (cachexia) and common players like the VCP/p97 complex act in both. Since we found beneficial effects of exercise-induced myokine musclin in cancer cachexia, we aim to see if this treatment could benefit ALS, by preserving muscle mass and restoring the NMJ in a retrograde mechanism.
Methods: We have applied for the first time the novel MyoRep technology, which we recently patented. This sophisticated tool enables us to follow muscle wasting over time through in vivo imaging in ALS mice without sacrificing them. Through MyoRep technology, we compared muscle atrophy of slow-progressing SOD1-G93A C57 mice with fast-progressing SOD1-G93A 129Sv mice and then, we evaluated the local effect of musclin on atrophy by means of AAV9 in the fast model.
Results: Bioluminescence imaging of tibialis anterior (TA) injected with MyoRep-encoding AAV9 shows that atrophy starts in vivo in SOD1-G93A 129Sv mice at 11 weeks of age, when the disease and muscle mass loss has not started yet. Musclin expression was reduced in atrophied gastrocnemius in the two models of ALS and its overexpression by intramuscular injection of AAV9 in TA of SOD1-G93A 129Sv mice protects them from muscle atrophy, denervation and restrains the acetylcholine receptor γ expression. We also found that decreased protein content of musclin in Vastus Lateralis muscle might be linked to faster disease progression in ALS patients.
Conclusion: We found that MyoRep detects early muscle atrophy in two separate models of ALS and that musclin could be an effective treatment for ALS against denervation and muscle atrophy.

10-07

ASCA101 as innovative multi-target therapeutic drug for cancer cachexia

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Purpose: Cancer cachexia, contributing to approximately 20% of cancer-related deaths, is a multifactorial syndrome characterized by metabolic imbalance, muscle dysfunction, and systemic inflammation. Despite this, there are still no effective treatments for cancer cachexia, highlighting the need for the development of therapeutic agents with various approaches.
Methods: Differentiated C2C12 myotube cells were treated with CT-26 cancer cell growth medium to induce in vitro cachexia condition. For in vivo efficacy, CT-26 cells were injected into Balb/c mice, with ASCA101 administered to each experimental group. Body weight, behavioral tests, serum cytokine levels, and CAS were monitored.
Results: In C2C12 myotubes, ASCA101 treatment reduced the expression of PDK4, a key regulator of glycolysis, and induced an increase of calpain 3 expression and a decrease of GDF15, both of which are associated with muscle atrophy. Additionally, ASCA101 induced the expression of MyHC and Myogenin, along with an increase in myotube size. ASCA101 administration in the cachexia mouse model led to increased body weight, enhanced muscle cross-sectional area, and improved muscle function. As a result of administering ASCA101 in a Phase 1 clinical trial targeting more than 12 patients with terminal cancer, 7 out of 14 patients showed an average weight gain of 2.2kg (3.3% from baseline), and 5 of these patients showed an increase in muscle mass of 1.7kg (7.5% from baseline).
Conclusions: ASCA101 attenuated muscle loss by modulating glycolysis and regulating factors contributing to cachexia, furthermore, it has been proven to induce weight and muscle mass gains in terminal cancer patients. To date, no other candidate drug has shown efficacy in both aspects, suggesting the significant potential of ASCA101 as a therapeutic agent for cachexia patients. Given these promising results, we plan to proceed with a Phase 2 clinical trial for cachexia.

10-08

GDF-15 neutralizing antibody visugromab overcomes cancer cachexia

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Introduction: Growth and differentiation factor 15 (GDF-15), a divergent member of the TGF-β superfamily, is overexpressed in

cancer cells and leads to serum elevation in cancer patients. GDF-15 has been shown to induce cachexia in patients via the brainstem-restricted receptor GFRAL. Visugromab is a GDF-15 blocking antibody currently under evaluation in patients with advanced cancers r/r to aPD -(L)1 therapy (GDFATHER; NCT04725474) in combination with nivolumab.
Methods: Visugromab-based neutralization of GDF-15 binding to and activation of GFRAL was assessed by enzyme-linked immunosorbent assay (ELISA) and homogeneous time resolved fluorescence (HTRF) cell line system-based functional assays *in vitro*. *In vivo* visugromab-mediated neutralization of cancer-induced cachexia was assessed in SK-MEL-5, SK-MEL-5 GDF-15KO and MKN45 tumor-bearing xenograft models. Visugromabs anti-cachexia properties were further evaluated in a subgroup of non-small cell squamous lung cancer (NSCLC), urothelial cancer (UC) and hepatocellular carcinoma (HCC) patients with elevated GDF-15 serum levels as part of an ongoing combined ph1/2a trial (GDFATHER; NCT04725474).
Results: Visugromab binds specifically to GDF-15 in a dose-dependent manner and blocks GDF-15-induced GFRAL/Erk1/2 phosphorylation. SK-MEL-5 and MKN45 bearing xenografts showed alleviation of cachexia parameters as body weight and food consumption upon treatment with visugromab. In the ph1/2a trial visugromab treatment (in combination with nivolumab) increased body weight significantly in patients with cachexia-inducing GDF-15 serum levels (GDF-15 >1.5ng/mL at baseline) at week 10.
Conclusions: Visugromab effectively neutralizes GDF-15, preventing GFRAL signaling-induced cachexia. In preclinical models, visugromab can block cancer-induced cachexia associated symptoms. Visugromab-induced GDF-15 blockade resembled body weight maintenance as in GDF-15KO tumor bearers, reflecting the key role of GDF-15 in cancer induced cachexia. Clinical data from a ph1/2a trial of visugromab+nivolumab show a significant body weight gain already at week 10 in patients with advanced cancer and elevated serum GDF-15 concentrations. Collectively, this provides compelling evidence for visugromab as anti-cachexia treatment option in cancer patients.

10-09
Repurposed relics: selective β – blockers as a treatment for cancer-associated cachexia

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Introduction: Cachexia, a significant cancer consequence, involves irreversible weight loss, muscle and fat depletion, and metabolic changes. Notably, 20% of cancer-related deaths are attributed to cachexia rather than the cancer itself. Currently, no particular treatments are available and there is an urgent need to address this problem. Chronic activation of the sympathetic nervous system (SNS) in cancer along with psychological stress can promote the progression of tumors. Based on the potential role of SNS in cancer, repurposing of β – blockers in the treatment of cancer cachexia might be beneficial.
Methods: We employed an in vitro model using 3T3-L1 adipocytes exposed to B16F10 tumor-conditioned medium (B16F10-CM). For the in vivo study, we injected B16F10 cells subcutaneously into 8-week-old male C57BL/6J mice and subsequently administered selective β-blockers (propranolol, metoprolol, and pindolol) orally. Body weight, grip strength, food intake, serum adipokines, inflammatory markers, muscle and adipose tissue weights, carbohydrate and lipid markers, histopathology, and gene expression were evaluated.
Results: We observed an increase in lipolysis in 3T3-L1 cells treated with B16F10-CM, which was inhibited by selective β-blockers. In vivo, studies on B16F10-CM tumor-bearing mice showed that selective β-blockers effectively maintained skeletal and adipose tissue mass and improved body weight. Additionally, selective β-blockers significantly restored grip strength compared to non-tumor-bearing mice. These β-blockers also improved carbohydrate and lipid metabolism, along with serum adipokine levels. Furthermore, they restored inflammatory cytokines (IL-6 and TNF-α) to levels comparable to non-tumor-bearing mice. Histopathological analysis confirmed that selective β-blockers preserved the architecture of skeletal muscle and adipose tissues. Treatment with selective β-blockers significantly decreased the gene expression levels of TRIM63, atrogin-1, HSL, PPAR-γ, IL-6, and TNF-α compared to tumor-bearing mice.
Conclusion: Selective β-blockers effectively alleviate cachectic syndrome, suggesting their potential as a treatment for cancer-associated cachexia. Further investigation is warranted to validate their use in this context.

10-10
Dual Targeting of Y5 and Ghrelin Receptors: A New Strategy for Treating Cancer Cachexia

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Introduction: Cachexia is a complex metabolic syndrome frequently occurring in cancer patients. Cancer cachexia is characterized by progressive loss of body weight in both lean and fat mass which increases mortality and resistance to chemotherapy. Despite recent progress in cancer cachexia research, there is currently no effective treatments of the condition on the market. Here, we present a multimodal treatment causing protection of body weight by targeting the Y5- and ghrelin receptors (GHSR) simultaneously to ameliorate cancer cachexia induced weight loss.
Methods: In vivo efficacy was tested in healthy mice for 28 days, following daily subcutaneous (s.c.) injections of PEP-300 (300 nmol/kg), a long acting NPY analog with specific affinity to the Y5 receptor, and PEP-064 (1000 nmol/kg), a long-acting ghrelin analogue. The treatment was applied in the classical Colon carcinoma 26 (C26) cancer cachexia mouse model. Lastly, whole brain c-fos activity was analyzed using iDISCO 3D imaging comparing a single dose (s.c.) of the combined treatment with vehicle treated animals.
Results: Combinatory Y5- and ghrelin agonism, induced significant hyperphagia (food intake increased by 31%) and body weight gain of 39% in healthy mice in 28 days of treatment. Furthermore, the treatment ameliorated cancer cachexia-induced weight loss (weight gain of 9.2% at terminal endpoint vs. -4.8 % body weight loss in tumor bearing vehicle controls) in the C26 mouse model of cancer cachexia by inducing hyperphagia (accumulated food intake increased by 21%). Lastly, we identified the activated brain areas of the combination treatment such as VMH, ARC and LH as well as the Tubular Nucleus of the hypothalamus which is an underexplored center of appetite regulation.
Conclusion: Simultaneous Y5R and GHSR agonism modulates energy homeostasis in the CNS and ameliorates cancer induced weight loss in the C26 cancer cachexia model.

10-12

Pharmacological inhibition of USP-19 attenuates cancer cachexia-induced muscle atrophy

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Introduction: Cancer cachexia is a multifactorial metabolic syndrome characterized by energy-wasting, increased systemic inflammation, and metabolic dysfunctions, leading to muscle and fat tissue deterioration. Cachexia is observed in 50-80% of advanced cancer patients, yet no approved pharmacotherapies are available to treat cachexia effectively[#1]. The ubiquitin-proteasome system (UPS) is a critical mediator of intracellular protein degradation that contributes to the development of cachexia and is driven by pro-inflammatory cytokines, oxidative stress, and other host and tumor-derived signaling molecules. Ubiquitin Specific Protease 19 (USP-19) is a deubiquitinating enzyme that plays an important role in various biological processes, including protein degradation, DNA repair, and cell cycle regulation. Previous studies have shown that USP-19 transcript levels are increased during various muscle wasting conditions[#2]. Researchers at Almac have previously shown that USP-19 inhibition prevents muscle wasting, observed in limb-casted and denervated mouse models. Here, we show the effect of inhibiting USP-19 using a potent inhibitor on weight and muscle loss during cancer cachexia.
Methods: Researchers at Almac developed potent inhibitors targeting USP-19. We evaluated their efficacy in mitigating muscle and weight loss using the Lewis Lung Carcinoma (LLC) and C26 mouse models of cachexia. Complementary analyses, including RNAseq and proteomics, were conducted, supported by *in vitro* mechanistic studies using C2C12 and L6 myotubes.
Results: Pharmacological inhibition of USP-19 by ADC-846 rescued around 60% of the LLC-induced weight loss and delayed cachexia onset in the C26 cachexia model. USP-19 inhibition restored the decreased levels of total plasma proteins observed during cachexia development, improved muscle strength, and ameliorated cachexia-induced muscle and adipose tissue wasting.
Conclusion: These data indicate that pharmacological inhibition of USP-19 may be beneficial in combatting muscle-wasting conditions. Further research is crucial to identify the specific targets of USP-19 and elucidate the molecular mechanisms by which USP-19 inhibition modulates signaling pathways involved in cachexia.

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10-13

Bimagrumab Prevents Semaglutide-Induced Muscle Mass Loss in Diet-Induced Obese Mice

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Introduction: Semaglutide (GLP-1 receptor agonist) effectively reduces body weight but also decreases muscle mass in obese individuals. Because maintained muscle mass is important for healthy metabolism, it is important to identify medications that can counteract or minimize this undesirable effect of weight-lowering drugs. The present study aimed to evaluate if bimagrumab (therapeutic antibody targeting activin type II receptors which are negative regulators of muscle growth), could prevent semaglutide-induced muscle loss in diet-induced obese (DIO) mice.
Methods: Male C57BL/6J mice were fed a high-fat diet (60 kcal-% fat) for 26 weeks. DIO mice were randomized to treatment based on body weight and whole-body fat mass, and administered (SC) vehicle, semaglutide (30 nmol/kg, QD), bimagrumab (20 mg/kg, QW) or semaglutide + bimagrumab (30 nmol/kg, QD + 20 mg/kg, QW) for 4 weeks (n=10 per group). Chow-fed mice served as lean controls. Endpoints included body weight, food intake, whole-body fat/lean mass (echoMRI), grip strength, muscle weight, plasma biomarkers (including urinary D3-creatin/creatinine) and quantitative muscle histology.
Results: Semaglutide reduced food intake, body weight, fat and lean mass in DIO mice. Bimagrumab increased lean mass per se and prevented loss of muscle mass while maintaining significant weight loss and reduced adiposity in semaglutide-treated DIO mice.
Conclusions: Bimagrumab prevents semaglutide-induced muscle loss in DIO mice. Bimagrumab may serve as reference compound in DIO mouse studies aiming to profile potential drug candidates with therapeutic potential to prevent anti-obesity drug-induced sarcopenia.

10-14

Loss of hindlimb muscle mass does not explain the loss of lean mass in semaglutide-treated mice

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Introduction: Glucagon-like peptide-1 receptor agonist (GLP-1RA, such as semaglutide) successfully induces loss of fat mass that is also associated with loss of lean mass. This loss of lean mass is increasingly recognized as a potential concern due to its impact on physical function and metabolic health. In this study, we investigated the effect of clinically equivalent dose of semaglutide (3 nmol/kg) treatment on skeletal muscle mass and function in mice.
Methods: Male C57BL/6J mice were fed a high-fat diet for 12 weeks, followed by daily subcutaneous injections of either semaglutide (3 nmol/kg) or PBS for 1 or 3 weeks. Body composition was assessed by nuclear magnetic resonance before and after treatment. Individual masses of hindlimb skeletal muscle tissues and force-generating capacity of the extensor digitorum longus (EDL) and soleus muscles were evaluated at the end of treatment.
Results: Treatment with semaglutide significantly decreased body weight, accompanied by a reduction in lean mass of 8.6% after 1 week and 9.9% after 3 weeks. The loss of lean mass was not fully accounted for by reductions in individual skeletal muscle mass which were reduced by 3.8-7.9% at 1 week and 1.4-9.0% at 3 weeks. In contrast, the liver and heart showed the most pronounced reductions in mass, with decreases of 30.3% and 16.1% at 1 week and 45.6% and 15.5% at 3 weeks. Semaglutide did not significantly reduce EDL mass, but their force-generating capacity was transiently reduced by 21.2% at 1 week which was recovered at 3 weeks.

Conclusions: Our results demonstrated that the loss of lean mass was not entirely accounted for by the loss of individual limb muscle masses but in other organs, including heart. These findings highlight the necessity to more carefully understand the origin of GLP-1RA-induced loss of lean mass in humans.

FACULTY

Swarnali **Acharyya**, USA
Rapid Fire 2, S

Volker **Adams**, Germany
Poster Session 1.6, V1

Julian **Alcazar**, Spain
Poster Session 1.6, K1

Stefan **Anker**, Germany
C, C1, G4, Symposium Friday, Lunch Symposium Saturday, U

Hidenori **Arai**, Japan
K, Highlights Session

Didier **Attaix**, France
B4

Vickie **Baracos**, Canada
P3, T, Highlights Session

David **Barry**, Australia
U3

John **Batsis**, USA
L, Q4

Faisal **Beg**, Canada
Poster Session 2.3, Poster Session 3.3, P2

Mauricio **Berriel Diaz**, Germany
Rapid Fire 1, V4

Zaver **Bhujwalla**, USA
R, S3

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A1, Poster Session 1.2, I, Poster Session 4.1, V

Miguel **Borda**, Norway
Q3

Danna **Breen**,
Lunch Symposium Saturday

Samuel **Breit**, Australia
R, S4, W

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Poster Session 2.5, T3

Justin **Brown**, USA
E4

Javed **Butler**, USA
G1

James **Carson**, USA
D

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B, Poster Session 1.4, Poster Session 2.4, K2

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I4

Sai **V Chitti**, Australia
D2

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A4

Andrew **Coats**, Australia
G, Symposium Friday, Q1, U

Paola **Costelli**, Italy
I, Poster Session 3.5, Poster Session 4.3

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Lunch Symposium Saturday, Poster Session 3.5, Poster Session 4.3, U7, Highlights Session

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J, N2

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Poster Session 3.4, N, Q, Poster Session 4.2

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K3, Rapid Fire 3, Q2

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Poster Session 1.4, Poster Session 2.4, K

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L1, U, W2

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A3, Rapid Fire 1

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I3, Poster Session 3.1

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Lunch Symposium Saturday

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V2

Denis **Guttridge**, USA
D, Poster Session 1.1, Poster Session 2.1

Steven **Heymsfield**, USA
E, T

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Symposium Friday

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W4

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B1, Poster Session 3.4, Poster Session 4.2

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A, Poster Session 1.2, S1, Poster Session 4.1

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Highlights Session

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Poster Session 3.1, V

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M4

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F3, H

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H1

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Brian **Kwee**, USA
T2

Mitja **Lainscak**, Slovenia
H, J, U1

Henning **Langer**, Germany
G2

Barry **Laird**, UK
U2, U5, W

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M1, R

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Poster Session 2.1, W1

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T1

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J4

Reshma **Merchant**, Singapore
Rapid Fire 3, Q

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H2, Poster Session 2.2,
Poster Session 3.2

Ishan **Roy**, USA
Poster Session 1.3, L4

Jorge **Ruas**, USA
B3

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O4

Joerg **Schefold**, Switzerland
M, M3, O

Richard **Skipworth**, UK
Symposium Friday, H4,
Poster Session 2.3,
Poster Session 3.3, P, U6

Adrian **Slee**, UK
Poster Session 1.5, H3

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G3

Florian **Strasser**, Switzerland
C3, Poster Session 2.2, J1,
Poster Session 3.2, R,
Highlights Session

Erin **Talbert**, USA
A, Highlights Session

Carolina **Trabulo**, Portugal
F2

Brandon **VanderVeen**, USA
I2

Wouter **van de Worp**, The Netherlands
P4

Rob **Van Maanen**, France
U4

Stephan **von Haehling**, Germany
C, C4, F, L2

Hidetaka **Wakabayashi**, Japan
W3

Shizhen Emily **Wang**, USA
D1

Eileen **White**, USA
E1, R

Simon **S Wing**, Canada
B

Tobias **Winkler**, Germany
Poster Session 2.5, M, T4

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D3, Rapid Fire 2

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C2, O

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