15th INTERNATIONAL CONFERENCE ON CACHEXIA, SARCOPENIA & MUSCLE WASTING

LISBON
24-26
JUNE 2022

FINAL PROGRAMME & ABSTRACTS

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SCWD
SOCIETY ON SARCOPENIA, CACHEXIA & WASTING DISORDERS

Organization

Society on Sarcopenia, Cachexia and Wasting Disorders (SCWD)
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Maurizio Muscaritoli, Italy
Florian Strasser, Switzerland
Stephan von Haehling, Germany
Hidetaka Wakabayashi, Japan

Conference Location

Friday 24 & Saturday 25 June:
Faculdade de Medicina da Universidade de Lisboa (FMUL)
Av. Prof. Egas Moniz MB, 1649-028 Lisbon
(behind the Hospital Santa Maria)
Sunday 26 June:
SANA Malhoa Hotel
Av. José Malhoa 8, 1099-089 Lisbon

Shuttle Service (departure every 30 minutes)

Friday, June 24
8.00-10.00 hrs
From SANA Malhoa Hotel (Av. José Malhoa 8, Lisboa, 1099-089) to
Faculdade de Medicina da Universidade de Lisboa (FMUL)

17.15 hrs – 18.30 hrs
From FMUL to SANA Malhoa Hotel

Saturday, June 25
8.00 hrs – 10.00 hrs
From SANA Malhoa Hotel to FMUL

18.20 hrs – 19.30 hrs
From FMUL to SANA Malhoa Hotel

Opening Hours of the On-site Registration Desk

Friday, 24 June 2022
8:30-17:30 hrs

Saturday, 25 June 2022
8:00-18:30 hrs

Sunday, 26 June 2022
8:30-15:00 hrs

Poster Exhibition

Friday, 24 June 2022
9:00-18:00 hrs

Saturday, 25 June 2022
7:30-19:00 hrs

Poster Sessions

Friday, 24 June 2022
13:50-14:40 hrs
15:35-16:25 hrs

Saturday, 25 June 2022
10:50-11:40 hrs
14:40-15:30 hrs

Coffee Breaks

Friday, 24 June 2022
11:00-11:15 hrs
13:45-14:45 hrs
15:30-16:30 hrs

Saturday, 25 June 2022
9:45-10:00 hrs
10:45-11:45 hrs
14:35-15:35 hrs
16:20-16:35 hrs
17:20-17:35 hrs

Sunday, 26 June 2022
9:50-10:00 hrs
13:50-14:00 hrs

10:00 – 11:00 **HALL A**

Opening session

(talk 1 and 2: 20 minutes + 5 minutes discussion, talk 3: 8 minutes +2 minutes discussion)

Chairs: Stefan Anker (Germany)
Fausto Pinto (Portugal)

1. 10:00 – 10:20
"Prometheus" basic science key note lecture
Targeting the ubiquitin proteasome system to fight muscle atrophy: update 2022
Volker Adams (Germany)

2. 10:25 – 10:45
"Hippocrates" clinical science key note lecture
From sarcopenia to frailty
John Morley (USA)

3. 10:50 – 10:58
JCSM & SCWD lecture
Stephan von Haehling (Germany)

11:00 – 11:15

Coffee Break

A
11:15 – 12:00 **HALL A**

Sarcopenia of aging and chronic diseases

(each talk 9 minutes + 2 minutes discussion)

Chairs: Paola Costelli (Italy)
Kamyar Kalantar-Zadeh (USA)

1. 11:15 – 11:24
MOTS-c: a new player in aging-related loss of muscle mass and function
Changhan David Lee (USA)

2. 11:26 – 11:35
Metabolic and molecular consequences of sarcopenia in alcoholic liver disease
Srinivasan Dasarathy (USA)

3. 11:37 – 11:46
Bone and muscle crosstalk: biological and clinical implications
Gustavo Duque (Australia)

4. 11:48 – 11:57
Results of the SPRINTT trial
Francesco Landi (Italy)

B
11:15 – 12:00 **HALL B**

Clinical Session
Novel aspects of adipose tissue function in wasting

(each talk 9 minutes + 2 minutes discussion

Chairs: Stephan Herzig (Germany)
Robert Mak (USA)

1. 11:15 – 11:24
Immune-sympathetic neuron communication guides adipose tissue browning in cancer-associated cachexia
Martina Schweiger (Austria)

2. 11:26 – 11:35
Angiocrine signals promote adipose tissue wasting in cancer cachexia
Andreas Fischer (Germany)

3. 11:37 – 11:46
Brown adipose tissue activation is not related to hypermetabolism in emphysematous COPD patients
Annemie Schols (The Netherlands)

4. 11:48 – 11:57
MRI-determined psoas muscle fat infiltration correlates with severity of weight loss during cancer cachexia
Dimitrios Karampinos (Germany)

12:10 – 12:55

Lunch Break

C
13:00 – 13:45 **HALL A**

Recent guidelines and consensus developments

(each talk: 12 minutes + 3 minutes discussion)

Chairs: Kamyar Kalantar-Zadeh (USA)
Stephan von Haehling (Germany)

1. 13:00 – 13:12
Appetite is key in geriatric syndromes: a pre-release of SCWD International Guidelines on Anorexia of Aging
Ivan Aprahamian (Brazil)

2. 13:15 – 13:27
Development of the cachexia consensus in Asia
Hidenori Arai (Japan)

3. 13:30 – 13:42
Recent guidelines on cancer cachexia: ESPEN, ESMO and ASCO
Alessandro Laviano (Italy)

D
13:00 – 13:45 **HALL B**

Clinical Session

Mechanisms of muscle loss due to cancer and chemotherapy and early interventions to help counteract negative effects

(each talk: 9 minutes + 2 minutes discussion)

Chairs: Fabio Penna (Italy)
Vera Mazurak (Canada)

1. 13:00 – 13:09
Doxorubicin-induced skeletal muscle atrophy, underlying molecular pathways and potential protective effects of exercise: evidence from pre-clinical and clinical data
Anouk Hiensch (The Netherlands)

2. 13:11 – 13:20
Exercise and nutrition-based Rehabilitation programme (EneRgy) in people with cancer
Barry Laird (UK)

3. 13:22 – 13:31
Resistance training during chemotherapy for non-metastatic colon cancer: the FORCE study: effects on body composition and physical function
Bette Caan (USA)

4. 13:33 – 13:42
Effects of exercise in patients after curative treatment for esophageal cancer: body composition and adequacy of energy and protein intake (the PERFECT study)
Anne May (The Netherlands)

13:45 – 14:45

Coffee Break + Poster Sessions

13:50 – 14:40 **POSTER AREA**

Poster Viewing 1

(each presentation: 2 minutes + 2 minutes discussion)

Poster session 1.1
Cancer cachexia I (posters 4-14 to 4-23 + 5-04)
Chairs: Andrea Bonetto, Andreas Fischer

Poster session 1.2
Diagnosis of cachexia and sarcopenia I (posters 1-25 to 1-34)
Chairs: Wolfram Doehner, Peter Martin

Poster session 1.3
Cachexia – mechanisms I (posters 3-09 to 3-18)
Chairs: Alessio Molfino, Marco Sandri

Poster session 1.4
Therapeutic development I (posters 6-01 to 6-10)
Chairs: Andrew Judge, Jochen Springer

13:50 – 14:40 **HALL A**

Rapid Fire Abstracts Session 1

(each presentation: 3 minutes + 2 minutes discussion)

Chairs: Denis Guttridge (USA)
Julia von Maltzahn (Germany)

13:50 – 13:53
Body composition assessment by artificial intelligence from routine CT scans in colorectal cancer, introducing BodySegAI (1-04)
Dena Helene Alavi (Norway)

13:55 – 13:58
Towards artificial intelligence: point-of-care musculoskeletal ultrasound correlates with body composition, muscle strength and physical performance in children with acute lymphoblastic leukemia (1-12)
Emma J Verwaaijen (The Netherlands)

14:00 – 14:03
Two years of aging – initial results on changes in muscle composition in the UK Biobank imaging study (1-26)
Dahlqvist Leinhard (Sweden)

14:05 – 14:08
Long-haul COVID-19 is related to lower pectoralis muscle mass at hospital admission for treatment of acute infection (2-07)
Marilia Seelaender (Brazil)

14:10 – 14:13
Chronic activation of ALK5/TGFbRI signaling in adult mouse skeletal muscle induces severe muscle wasting with concomitant impaired mitochondrial integrity (2-12)
Laetitia Mazelin (France)

14:15 – 14:18
The effect of severe burns on skeletal muscle protein balance in female rats 10 and 40 days post-burn (2-14)
Dorien Dombrecht (Belgium)

14:20 – 14:23
Sex differences in skeletal muscle-ageing trajectory: same processes, but with different magnitudes (2-19)
Jelle de Jong (The Netherlands)

14:25 – 14:28
Mechanosignaling through YAP/TAZ drives fibroadipogenic progenitors activation and promotes paraspinal muscle fibrosis in degenerative scoliosis (2-21)
Abdukahar Kiram (China)

E
14:45 – 15:30 **HALL A**

Basic Science Session
New basic findings in muscle wasting

(each talk: 9 minutes + 2 minutes discussion)

Chairs: Gustavo Nader (USA)
Andrew Judge (USA)

1. 14:45 – 14:54
Activation of Akt-mTORC1 signaling reverts cancer-dependent muscle wasting
Bert Blaauw (Italy)

2. 14:56 – 15:05
New insights into the role of GCN2-eIF2alpha signaling in the regulation of autophagy
Anne-Catherine Maurin (France)

3. 15:07 – 15:16
Interventions for improving mitochondrial function to counteract cancer and chemotherapy-induced cachexia
Fabio Penna (Italy)

4. 15:18 – 15:27
Fighting muscle loss: lessons from hibernation in brown bear
Etienne Lefai (France)

F
14:45 – 15:30 **HALL B**

Clinical Session
A focus on muscle health: assessment approaches and targeted nutrition interventions

(each talk: 9 minutes + 2 minutes discussion)

Chairs: Anne May (The Netherlands)
Maurizio Muscaritoli (Italy)

1. 14:45 – 14:54
Measuring muscle in oncology research and interventions
Elizabeth Cespedes Feliciano (USA)

2. 14:56 – 15:05
Artificial Intelligence approaches to improve speed, dimensionality and entry into clinical workflows
Faisal Beg (Canada)

3. 15:07 – 15:16
Surrogate markers of muscle mass and quality
M. Cristina Gonzalez (Brazil)

4. 15:18 – 15:27
A mechanistic perspective of specialized nutrition for muscle health
Philip Atherton (UK)

15:30 – 16:30

Coffee Break + Poster Sessions

15:35 – 16:25 **POSTER AREA**

Poster Viewing 2

(each presentation: 2 minutes + 2 minutes discussion)

Poster session 2.1
Muscle wasting & sarcopenia – mechanisms I (posters 2-20 to 2-29)
Chairs: Achim Krüger, Changhan David Lee

Poster session 2.2
Cancer cachexia II (posters 4-24 to 4-36)
Chairs: Andrea Bonetto, Andreas Fischer

Poster session 2.3
Physical activity & training (posters 7-01 to 7-09)
Chairs: Anne May, Ashley Smuder

Poster session 2.4
Diagnosis of cachexia and sarcopenia II (posters 1-01 to 1-12 + 1-26)
Chairs: Wolfram Doehner, Peter Martin

15:35 – 16:25 **HALL A**

Rapid Fire Abstracts Session 2

(each presentation: 3 minutes + 2 minute discussion)

Chairs: Laure Bindels (Belgium)
Gustavo Duque (Australia)

15:35 – 15:38
The relationship between cachexia and inflammatory biomarkers in patients with cancer; initial findings from the REVOLUTION cachexia characterisation study (4-04)
Robert Paval (UK)

15:40 – 15:33
Identifying cancer patients with cachexia at scale by leveraging self-supervised natural language processing and predictive models on unstructured data in patients' electronic health records (4-08)
Richard Skipworth; Barry Laird (UK)

15:45 – 15:48
Examining the negative impact of weight loss and cachexia in Chimeric Antigen Receptor (CAR) T-cell therapy (4-09)
Brittany Cucchiaro (UK)

15:50 – 15:53
Evaluation of weight gain and overall survival of patients with advanced non-small-cell lung cancer (NSCLC) treated with first-line platinum-based chemotherapy (4-11)
Eric Roeland (USA)

15:55 – 15:58
Assessment of muscle and lean mass in colon cancer patients on chemotherapy: correlations of d3-creatine, dual energy x-ray absorptiometry and computed tomography (4-16)
Elisabeth M Cespedes Feliciano (USA)

16:00 – 16:03
NAD+ repletion with niacin counteracts cancer cachexia (4-19)
Marc Beltrà Bach (Italy)

16:05 – 16:08
Respiratory Muscle Pathology in Esophageal Adenocarcinoma Patients (4-31)
Miles Cameron (USA)

16:10 – 16:13
Ketogenic diet slows down tumor growth but induces primary adrenal insufficiency that accelerates onset of cachexia in C26 and KPC murine models (3-05)
Miriam Ferrer Gonzalez (USA)

16:15 – 16:18
Colon cancer treatment with FOLFIRI exacerbates muscle fiber atrophy and induces a catabolic transcriptional program in skeletal muscle (3-08)
Vickie Baracos (Canada)

G
16:30 – 17:15 **HALL A**

Basic Science Session
Ammonia and the muscle – multiple diseases, one mechanism

(each talk: 9 minutes + 2 minutes discussion)

Chairs: Andreas Fischer (Germany)
Yi-Ping Li (USA)

1. 16:30 – 16:39
Mechanisms of ammonia induced sarcopenia – a common mediator in multiple diseases
Srinivasan Dasarathy (USA)

2. 16:41 – 16:50
Amino acid perturbations in hyperammonemia
Milan Holecek (Czech Republic)

3. 16:52 – 17:01
Multiomics based approaches to identify novel cellular and tissue responses
Nicole Welch (USA)

4. 17:03 – 17:12
The significance of myosteatosis in surgical cancer patients
Steven Olde Damink (The Netherlands)

H
16:30 – 17:15 **HALL B**

Clinical Session
Special diets – the power of food

(each talk: 9 minutes + 2 minutes discussion)

Chairs: Wolfram Doehner (Germany)
Paula Ravasco (Portugal)
Cristiana Vitale (UK)

1. 16:30 – 16:39
What determines / Which parameters determine optimal protein metabolism in the old?
Dominique Dardevet (France)

2. 16:41 – 16:50
Manipulating the microbiome to counteract frailty
Patrizia Brigidi (Italy)

3. 16:52 – 17:01
Nutrition and anorexia of ageing
Reshma Merchant (Singapore)

4. 17:03 – 17:12
Combining power food and fasting in cachexia: no go or wise go?
Florian Strasser (Switzerland)

J
09:00 – 09:45 **HALL A**

Clinical Session
Liver alterations as drivers of cancer cachexia

(each talk: 9 minutes + 2 minutes discussion)

Chairs: Andrea Bonetto (USA)
M. Cristina Gonzalez (Brazil)

1. 09:00 – 09:09
Hepatic and intestinal microbial disturbances as therapeutic targets in cancer cachexia
Laure Bindels (Belgium)

2. 09:11 – 09:20
A cachexia score based on liver alterations predicts prognosis of gastrointestinal cancer patients
Achim Krüger (Germany)

3. 09:22 – 09:31
Inflammation and impairment of hepatic metabolism and function in cachectic cancer patients
Marilia Seelaender (Brazil)

4. 09:33 – 09:42
Transcriptional reprogramming of hepatocyte function in cancer cachexia
Sören Fisker Schmidt (Denmark)

K
10:00 – 10:45 **HALL A**

Basic Science Session
Hot topics in basic research: role of muscle stem and progenitor cells during aging, disease and regeneration

(each talk: 9 minutes + 2 minutes discussion)

Chairs: Joe Chakkalakal (USA)
Nicholas Greene (USA)

1. 10:00 – 10:09
Muscle stem cells in age and disease
Julia von Maltzahn (Germany)

2. 10:11 – 10:20
Neurofibromatosis type 1 associated myopathy is due to metabolic reprogramming of muscle stem cells in a mouse model
Sigmar Stricker (Germany)

3. 10:22 – 10:31
Fibro-adipogenic progenitors coordinate muscle regeneration
Georgios Kotsaris (Germany)

4. 10:33 – 10:42
Muscle stem cells drive post-sepsis skeletal muscle recovery and regeneration
Jason Doles (USA)

L
10:00 – 10:45 **HALL B**

Clinical Session
Inter-organ crosstalks in cancer cachexia

(each talk: 9 minutes + 2 minutes discussion)

Chairs: Frank Misselwitz (Germany)
Gustavo Nader (USA)

1. 10:00 – 10:09
Abnormal liver-bone-muscle axis in cancer cachexia
Andrea Bonetto (USA)

2. 10:11 – 10:20
Impact of exercise and chemotherapy on the respiratory neuromuscular system
Ashley Smuder (USA)

3. 10:22 – 10:31
Cancer-induced muscle and bone deficits
Hanna Taipaleenmäki (Germany)

4. 10:33 – 10:42
A prospective study of hand-grip strength to predict mortality in patients with cancer with and without cachexia
Markus Anker (Germany)

10:45 – 11:45

Coffee Break + Poster Sessions

10:50 – 11:40 **POSTER AREA**

Poster Viewing 3

(each presentation: 2 minutes + 2 minutes discussion)

Poster session 3.1
Muscle wasting and sarcopenia – mechanisms II (posters 2-01 to 2-09)
Chairs: Denis Guttridge, Milan Holecek

Poster session 3.2
Nutrition & appetite (posters 5-01 to 5-09)
Chairs: Philip Atherton, Adrian Slee

Poster session 3.3
Diagnosis of cachexia and sarcopenia III (posters 1-14 to 1-24)
Chairs: Dimitrios Karampinos, Martina Schweiger

10:50 – 11:25 **HALL A**

Rapid Fire Abstracts Session 3

(each presentation: 3 minutes + 2 minutes discussion)

Chairs: Anouk Hiensch (The Netherlands)
Richard Skipworth (UK)

10:50 – 10:53
Muscle Wasting in Early-stage Cancer is Associated with Disorganized Extracellular Matrix Distinct from Fibrosis (4-25)
Erin E Talbert (USA)

10:55 – 10:58
Study of the histological and inflammatory rearrangements of the subcutaneous adipose tissue among gastrointestinal cancer patients with cachexia (4-32)
Alessio Molfino (Italy)

11:00 – 11:03
Targeted dietary intervention attenuates experimental lung cancer cachexia (5-04)
Wouter van de Worp (The Netherlands)

11:05 – 11:08
Leptin, Adiponectin, and Mortality Risk in a Prospective Hemodialysis Cohort (5-07)
Connie Rhee (USA)

11:10 – 11:13
Deletion of FNDC5/Irisin protects against cancer induced cachexia syndrome (6-09)
Fabrizio Pin (USA)

11:15 – 11:18
Effects of Bioarginine C supplementation on functional parameters in adults with Long Covid: a randomised clinical trial (6-15)
Matteo Tosato (Italy)

11:20 – 11:23
Metoprolol attenuates stimulated lipolysis in adipose tissue from cachectic patients with pancreatic cancer (6-08)
Lenka Rossmeislova (Czech Republic)

M
11:45 – 12:30 **HALL A**

Basic Science Session
Cachexia as an heterogeneous disease: underlying mechanisms

(each talk: 9 minutes + 2 minutes discussion)

Chairs: Marilia Seelaender (Brazil)
Jochen Springer (Germany)

1. 11:45 – 11:54
Sex-dependent response of adipose tissue and lipid metabolism in cancer cachexia
Vera Mazurak (Canada)

2. 11:56 – 12:05
Tumor microenvironment evolution and its relevance to cachexia
Mariam Jamal-Hanjani (UK)

3. 12:07 – 12:16
Sex variation in cachexia
Silvia Busquets (Spain)

4. 12:18 – 12:27
Tumor-specific ribosomal deficits in muscle wasting
Gustavo Nader (USA)

N
11:45 – 12:30 **HALL B**

Clinical Session
State of the art nutrition for outcome driven cancer treatments

(each talk: 9 minutes + 2 minutes discussion)

Chairs: Gustavo Duque (Australia)
Barry Laird (UK)

1. 11:45 – 11:54
Integrated evaluation of body composition in the oncology setting: paradigm change
David da Silva Dias (Portugal)

2. 11:56 – 12:05
Nutrition options in 2022: what is on the market?
Paula Ravasco (Portugal)

3. 12:07 – 12:16
Nutrition in ambulatory cytotoxic treatment: new data on the role of the clinical pharmacist
Leila Costa (Portugal)

4. 12:18 – 12:27
Head and neck cancer and sarcopenia – a high risk cancer and higher risk treatments
Maartje van Beers (The Netherlands)

12:40 – 13:40 **HALL A**

Lunch Session:
Cachexia – Unmet needs and opportunities for novel therapy

Chairs: ~~TBD~~
~~TBD~~

12:40-13:00
Circulating GDF15 and its relationship with cachexia in non-small cell lung cancer
Mariam Jamal-Hanjani (UK)

13:00-13:10
Discussion

13:10-13:30
GDF-15 is a key regulator of cancer cachexia and beyond
Bei Zhang (USA)

13:30-13:40
Discussion

O
13:50 – 14:35 **HALL A**

Basic Science Session
Novel cachexia mediators – proteins and beyond

(each talk: 9 minutes + 2 minutes discussion)

Chairs: Denis Guttridge (USA)
Maria Rohm (Germany)

1. 13:50 – 13:59
Early neutrophilia marked by aerobic glycolysis sustains host metabolism and delays cancer cachexia
Tobias Janowitz (USA)

2. 14:01 – 14:10
Tumor-derived cachexia mediators and biomarkers
Mauricio Berriel Diaz (Germany)

3. 14:12 – 14:21
Tumor-derived extracellular vesicles
Paola Costelli (Italy)

4. 14:23 – 14:32
KLF10: a novel mediator of cancer-associated skeletal muscle wasting
Jason Doles (USA)

P
13:50 – 14:35 **HALL B**

Clinical Session
Cancer progression and cachexia

(each talk: 9 minutes + 2 minutes discussion)

Chairs: Vickie Baracos (Canada)
Ashley Smuder (USA)

1. 13:50 – 13:59
Exercise and tumor control: expanding the field of exercise oncology to cancer progression and cachexia
Lee Jones (USA)

2. 14:01 – 14:10
Cardiac wasting in cancer
Alessia Lena (Germany)

3. 14:12 – 14:21
A review of the evidence for multi-modal interventions in cachexia management
Joanne Reid (UK)

4. 14:23 – 14:32
ACTAs for cancer cachexia
Andrew Coats (Australia)

14:35 – 15:35

Coffee Break + Poster Sessions

14:40 – 15:35 **POSTER AREA**

Poster Viewing 4

(each presentation: 2 minutes + 2 minutes discussion)

Poster session 4.1
Therapeutic development II (posters 6-11 to 6-19)
Chairs: Yi-Ping Li, Anne-Catherine Maurin

Poster session 4.2
Cachexia – mechanisms II (posters 3-02 to 3-08)
Chairs: Silvia Busquets, Marco Sandri

Poster session 4.3
Cancer cachexia III (posters 4-01 to 4-12 + 4-31)
Chairs: Sören Fisker Schmidt, Fabio Penna

Poster session 4.4
Muscle wasting & sarcopenia – mechanisms III (posters 2-11 to 2-19)
Chairs: Rodney Infante, Sigmar Stricker

Q
15:35 – 16:20 **HALL A**

Basic Science Session
Mechanisms of energy and anabolic crisis in cancer cachexia – new therapeutic targets?

(each talk: 9 minutes + 2 minutes discussion)

Chairs: Paola Costelli (Italy)
Tobias Janowitz (USA)

1. 15:35 – 15:44
MyomiRNA, systemic and local inflammation and muscle wasting
Maurizio Muscaritoli (Italy)

2. 15:46 – 15:55
The transcriptional repressor FoxP1 in cancer-induced skeletal muscle wasting and weakness
Sarah Judge (USA)

3. 15:57 – 16:06
Beyond good and evil: Discovering novel anabolic targets to overcome cancer related-muscle wasting
Marcelo Pereira (UK)

4. 16:08 – 16:17
Skeletal muscle mitochondrial dysfunction and lipid accumulation in breast cancer
Emidio Pistilli (USA)

R
15:35 – 16:30 **HALL B**

Clinical Session

Designing trials for cancer cachexia

(each talk: 9 minutes + 2 minutes discussion)

Chairs: Teresa Zimmers (USA)
Bette Caan (USA)
Andrew Coats (Australia)

1. 15:35 – 15:44
Muscle mass criterion for cachexia: measuring muscle mass in clinical trials
Vickie Baracos (Canada)

2. 15:46 – 15:55
Selecting populations for clinical trials
Eric Roeland (USA)

3. 15:57 – 16:06
Endpoints for cancer cachexia clinical trials
Stefan Anker (Germany)

4. 16:08 – 16:17
Use of biomarkers to assess treatment effect in cancer cachexia
Jose Garcia (USA)

5. 16:19 – 16:28
Regulatory perspective on cancer cachexia trials
Giuseppe Rosano (UK)

16:20 – 16:35

Coffee Break

S
16:35 – 17:20 **HALL A**

Basic Science Session
Cachexia & muscle wasting – pathophysiology update

(each talk: 9 minutes + 2 minutes discussion)

Chairs: Marco Sandri (Italy)
Denis Guttridge (USA)

1. 16:35 – 16:44
T cells and cachexia
Laura Antonio-Herrera (Austria)

2. 16:46 – 16:55
Aging exacerbates neuromuscular junction disruption after injury that stimulates inflammation
Joe Chakkalakal (USA)

3. 16:57 – 17:06
Macrophages and muscle regeneration
Emanuele Berardi (Belgium)

4. 17:08 – 17:17
Endothelial dysfunction in cachexia
Young-Mee Kim (USA)

T
16:35 – 17:20 **HALL B**

Young investigators awards session

(each talk: 7 minutes + 2 minutes discussion)

Judges: Hidenori Arai (Japan)
Vickie Baracos (Canada)
Bette Caan (USA)
Jose Garcia (USA)
Paula Ravasco (Portugal)
Jochen Springer (Germany)

16:35 – 16:42
MicroRNA-22 as a potential diagnostic tool in males with sarcopenic heart failure: Results from the Studies Investigating Co-morbidities Aggravating Heart Failure (SICA-HF) (1-29)
Mirela Vatic (Germany)

16:44 – 16:51
Tumor metabolic activity is associated with myosteatosis and reduced survival in patients with non-small cell lung cancer (4-15)
Yan Sun (The Netherlands)

16:53 – 17:00
OPA1 overexpression may protect against cancer-induced muscle wasting (4-22)
Stavroula Tsitkanou (USA)

17:02 – 17:09
Intramuscular lipid alterations in human pancreatic cancer cachexia (4-34)
Min Deng (The Netherlands)

17:11-17:18
Leucine-rich diet improves cachexia index and alters tumour thermogenic capacity in Lewis Lung tumour-bearing aged mice (5-03)
Natalia Angelo da Silva Miyaguti (Brazil)

17:20 – 17:35

Coffee Break

U
17:35 – 18:20 **HALL A**

Basic Science Session
Host-specific and tumor-specific molecular mechanisms of biological variability in cancer cachexia

(each talk: 9 minutes + 2 minutes discussion)

Chairs: Mauricio Berriel Diaz (Germany)
Puneeth Iyengar (USA)

1. 17:35 – 17:44
Host factors: sexual dimorphism in murine models of cancer cachexia
Nicholas Greene (USA)

2. 17:46 – 17:55
Host factors: aging and host genotype in cancer cachexia
Maria Rohm (Germany)

3. 17:57 – 18:06
Tumor factors: tumor molecular and cellular heterogeneity mediates cancer cachexia phenotype
Teresa Zimmers (USA)

4. 18:08 – 18:17
Identification of molecules that contribute to NSCLC cancer cachexia
Rodney Infante (USA)

V
17:35 – 18:20 **HALL B**

Clinical Session
Cachexia in chronic kidney disease: recent advances

(each talk: 9 minutes + 2 minutes discussion)

Chairs: Philip Atherton (UK)
Stephan von Haehling (Germany)

1. 17:35 – 17:44
Impact of protein intake on CKD cachexia and sarcopenia
Kam Kalantar-Zadeh (USA)

2. 17:46 – 17:55
Physical activity and nutrition in CKD
Angela Wang (Hong Kong)

3. 17:57 – 18:06
Inflammation and adipose tissue browning in CKD cachexia
Robert Mak (USA)

4. 18:08 – 18:17
Activin Signaling and GDF-15 in CKD Cachexia
Connie Rhee (USA)

W
09:00 – 9:50 **HALL A**

Covid-19 and cachexia: common players and perspectives

(each talk: 9 minutes + 3 minutes discussion)

Chairs: Hidenori Arai (Japan)
Annemie Schols (The Netherlands)

1. 09:00 – 09:09
The role of adipose tissue in Covid-19 cytokine storm: learning from cachexia
Marilia Seelaender (Brazil)

2. 09:12 – 09:21
Nutrition: a matter of life or death
Alessandro Laviano (Italy)

3. 09:24 – 09:33
Body composition and muscle quality in Covid-19 patients
Martine Sealy (The Netherlands)

4. 09:36 – 09:45
Frailty and rehabilitation in Covid-19 patients
Francesco Landi (Italy)

9:50 – 10:00

Coffee Break

X
10:00 – 10:50 **HALL A**

Multi-modal interventions for cachexia

(each talk: 9 minutes + 3 minutes discussion)

Chairs: Joanne Reid (UK)
Martine Sealy (The Netherlands)

1. 10:00 – 10:09
Evolution and outcomes from a multi-disciplinary cachexia clinic
Peter Martin (Australia)

2. 10:12 – 12:21
Clarifying the role of palliative rehabilitation in cachexia management
Cathy Payne (Belgium)

3. 10:24 – 10:33
The importance of exercise and nutrition in an integrated response to cachexia management
Adrian Slee (UK)

4. 10:36 – 10:45
Patient experience of a multi-professional cachexia clinic
Vanessa Vaughan (Australia)

10:50 – 11:00

Break

Y
11:00 – 11:50 **HALL A**

Mechanisms of cancer cachexia – transition from basic research to clinical investigation

(each talk: 9 minutes + 3 minutes discussion)

Chairs: Steven Olde Damink (The Netherlands)
Teresa Zimmers (USA)

1. 11:00 – 11:09
MEF2c-dependent downregulation of myocilin mediates cancer-induced muscle wasting and associates with cachexia in patients with cancer
Andrew R Judge (USA)

2. 11:12 – 11:21
Activation of p38β MAPK in skeletal muscle correlates with weight loss in cancer patients
Yi-Ping Li (USA)

3. 11:24 – 11:33
Association between growth differentiation factor-15 (GDF-15) serum levels, anorexia and low muscle mass among cancer patients
Alessio Molfino (Italy)

4. 11:36 – 11:45
Adipose depot gene expression and intelectin-1 in the metabolic response to cancer and cachexia
Richard J.E. Skipworth (UK)

12:00 – 12:45 **HALL A**

Lunch Session:
BIO101 in development for the treatment of sarcopenia

Chair: Francesco Landi (Italy)

Speaker: Waly Dioh
Cendrine Tourette

Supported by an educational grant from Biophytis

13:00 – 13:50 **HALL A**

Late Breaking Trials Session

(each talk: 9 minutes + 4 minutes discussion)

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

1. 13:00 – 13:09
From ROMANA to SCALA program: The journey of Anamorelin – the ghrelin receptor agonist – towards treating the malignancy associated weight loss and anorexia in adult patients with non-small cell lung cancer (NSCLC)
Daniela Domnica Rotaru (Italy)

2. 13:13 – 13:22
Use of chirally pure S-enantiomers in the treatment of cancer cachexia: clinical development of S-pindolol benzoate in cancer cachexia in patients with advanced non-small cell lung and colo-rectal cancer
Frank Misselwitz (Germany)

3. 13:26 – 13:35
Efficacy of empagliflozin in heart failure with preserved ejection fraction according to frailty status – insights from EMPEROR-Preserved trial
Andrew Coats (Australia)

4. 13:39 – 13:48
TBD

13:50 – 14:00

Coffee Break

Z
14:00 – 14:50 **HALL A**

Targeting cachexia treatment: GDF15 and beyond

(each talk: 9 minutes + 3 minutes discussion)

Chairs: Maurizio Muscaritoli (Italy)
Jochen Springer (Germany)

1. 14:00 – 14:09
GDF15 neutralization as a transformative therapeutic approach
Bei Zhang (USA)

2. 14:12 – 14:21
Activation of the hypothalamic–pituitary–adrenal axis by exogenous and endogenous GDF15
Danna Breen (USA)

3. 14:24 – 14:33
MC4R antagonism for appetite and body weight regulation – from human genetics to aged rat model
Zhidan Wu (USA)

4. 14:36 – 14:45
Beyond cachexia: the inhibition of antitumoral immune responses by cachexia-inducing tumor-derived factor GDF-15
Christine Schuberth-Wagner (Germany)

14:50 – 15:00

Break

15:00 – 15:50 **HALL A**

Highlights Session

Chairs: Vickie Baracos (Canada)
Andrew Coats (Australia)

Basic Science
Maria Rohm (Germany)

Clinical & Biomarkers
Stephan von Haehling (Germany)

Sarcopenia
Maurizio Muscaritoli (Italy)

Treatment
Frank Misselwitz (Germany)

Poster Award
Young Investigator Award
Farewell

ABSTRACTS OF ORAL PRESENTATIONS

Opening Session *(20 minutes + 5 minutes discussion)*

"Prometheus" basic science key note lecture:
Targeting the ubiquitin proteasome system to fight muscle atrophy: update 2022

Volker Adams
Laboratory of molecular and experimental cardiology, Heart Center Dresden, TU Dresden, Germany

Skeletal muscle is the largest and one of the most dynamic organs in the human body, representing 30–40% of total body mass and containing up to 75% of the organism's protein reserves. Skeletal muscle is essential for life, supporting movement, respiration, thermoregulation, and metabolic homeostasis. Skeletal muscle wasting (also referred to as atrophy) is a characteristic of several catabolic conditions, including aging (i.e., sarcopenia), starvation, and immobilization, but also many acute and chronic illnesses such as cancer, heart failure, sepsis, and diabetes. Our current lack of direct treatments to rescue muscle wasting across millions of patients is a key concern, with exercise training the only established intervention [1]. The most important proteolytic pathway recognized to mediate muscle atrophy is the ubiquitin proteasome system (UPS). This enzyme complex degrades structural and regulatory proteins selectively targeted following the covalent attachment of polyubiquitin chains to lysine residues. One major rate-limiting step considered in the UPS is the attachment of ubiquitin to target proteins via specific E3 ubiquitin ligases, which have attracted particular attention given their potential for therapeutic modulation not only for muscle atrophy but also in the regulation of inflammation and immunity. Two key atrogenes identified are the muscle-specific E3 ubiquitin-ligases MuRF1and muscle atrophy F-box (MAFBx; also termed atrogin-1). Evidence is now conclusive that knockdown of either gene can attenuate muscle wasting in various catabolic conditions including denervation, hindlimb suspension, fasting, chronic kidney disease, pulmonary hypertension and lung disease. Data in the current literature provide a strong rational to develop effective drugs capable to suppress MuRF1. Is this possible and what evidence is available that these drugs are able to inhibit the development of muscle atrophy in different disease leading to muscle wasting? Our group was one of the first describing the search for specific small molecules to target the interaction between MuRF1 and its target protein titin. Using these molecules in experimental models of pulmonary hypertension [2], chronic heart failure [3], tumor cachexia [4], and heart failure with preserved ejection fraction [5] we could demonstrate the attenuation of muscle wasting. During the presentation we will discuss these results and highlight important molecular pathways involved.

[1] Bowen TS et al. Skeletal muscle wasting in cachexia and sarcopenia: Molecular pathophysiology and impact of exercise training. J Cachexia Sarcopenia Muscle 2015, 6,197–207.
[2] Bowen TS et al. Small-molecule inhibition of MuRF1 attenuates skeletal muscle atrophy and dysfunction in cardiac cachexia. J Cachexia Sarcopenia Muscle. 2017 Dec;8(6):939-953.
[3] Adams V et al. Small-molecule-mediated chemical knock-down of MuRF1/MuRF2 and attenuation of diaphragm dysfunction in chronic heart failure. J Cachexia Sarcopenia Muscle. 2019 Oct;10(5):1102-1115
[4] Adams V et al. Small-Molecule Chemical Knockdown of MuRF1 in Melanoma Bearing Mice Attenuates Tumor Cachexia Associated Myopathy. Cells. 2020 Oct 11;9(10):2272.
[5] Adams V et al. Targeting MuRF1 by small molecules in a HFpEF rat model improves myocardial diastolic function and skeletal muscle contractility. J Cachexia Sarcopenia Muscle. 2022

Opening Session *(20 minutes + 5 minutes discussion)*

"Hippocrates" clinical science key note lecture:
From sarcopenia to frailty

John E Morley
Saint Louis University, USA

Sarcopenia is the loss of muscle mass and strength. It has multiple causes. While a number of drugs are available to treat it, exercise is the best treatment. Physical frailty is a major cause of disability and mortality. It can be rapidly identified with FRAIL. Sarcopenia is a key cause of physical frailty. Other modalities to treat physical frailty will be discussed.

References:
1. Editorial: Exercise, Aging and Frailty: Guidelines for Increasing Function. Merchant RA, Morley JE, Izquierdo M. J Nutr Health Aging. 2021;25(4):405-409. doi: 10.1007/s12603-021-1590-x
2. Editorial: Sarcopenia: 2020. Morley JE. J Nutr Health Aging. 2021;25(3):278-280. doi: 10.1007/s12603-020-1583-1.

Opening Session *(8 minutes + 2 minutes discussion)*

JCSM & SCWD lecture

Stephan von Haehling, Germany

A1 *(9 minutes + 2 minutes discussion)*

MOTS-c: a new player in aging-related loss of muscle mass and function

Changhan David Lee
Leonard Davis School of Gerontology, University of Southern California
USC Norris Comprehensive Cancer Center, USC Research Center for Liver Diseases, Angeles, CA, USA

Mitochondria are chief metabolic organelles with strong implications in aging. In addition to their prominent role in bioenergetics, mitochondria also coordinate broad physiological functions by communicating to other cellular compartments or distal cells, using multiple factors including peptides that are encoded within their own independent genome. MOTS-c is a mitochondrial-encoded peptide that regulates metabolic homeostasis, in part, by translocating to the nucleus to regulate adaptive nuclear gene expression in response to cellular stress in an AMPK-dependent manner[1,2]. We found that MOTS-c is an exercise-induced mitochondrial-encoded peptide that significantly enhanced physical performance when administered to young (2 mo.), middle-aged (12 mo.), and old (22 mo.) mice[3,4]. In humans, we found that endogenous MOTS-c levels significantly increased in response to exercise in skeletal muscle (5-fold) and in circulation (1.5-fold). Systemic MOTS-c treatment in mice significantly enhanced the performance on a treadmill of all age groups (~2-fold). MOTS-c regulated (i) nuclear genes, including those related to metabolism and protein homeostasis, (ii) glucose and amino acid metabolism in skeletal muscle, and (iii) myoblast adaptation to metabolic stress. We identified a strong signature of proteostasis in MOTS-c treated muscle cells and tissues upon metabolic stress. RNA-seq analyses from both mouse skeletal muscle and myoblasts revealed heat shock factor 1 (HSF1) as a putative transcriptional factor that could regulate gene expression upon MOTS-c treatment. Indeed, siRNA-mediated HSF1 knockdown reversed MOTS-c-dependent stress resistance against glucose restriction/serum deprivation in myoblasts. MOTS-c is a first-in-class mitochondrial-encoded regulator of aging with translational potential as a mitochondrial-encoded drug target for age-related disabilities and diseases, such as sarcopenia.

References:

1 Lee, C. *et al.* The mitochondrial-derived peptide MOTS-c promotes metabolic homeostasis and reduces obesity and insulin resistance. *Cell metabolism* **21**, 443-454, doi:10.1016/j.cmet.2015.02.009 (2015).
2 Kim, K. H., Son, J. M., Benayoun, B. A. & Lee, C. The Mitochondrial-Encoded Peptide MOTS-c Translocates to the Nucleus to Regulate Nuclear Gene Expression in Response to Metabolic Stress. *Cell metabolism* **28**, 516-524 e517, doi:10.1016/j.cmet.2018.06.008 (2018).
3 Reynolds, J. C. *et al.* MOTS-c is an exercise-induced mitochondrial-encoded regulator of age-dependent physical decline and muscle homeostasis. *Nature communications* **12**, doi:10.1038/s41467-020-20790-0 (2021).
4 Kang, G. M. *et al.* Mitohormesis in Hypothalamic POMC Neurons Mediates Regular Exercise-Induced High-Turnover Metabolism. *Cell metabolism* **33**, 334-349.e336, doi:10.1016/j.cmet.2021.01.003 (2021).

A2 *(9 minutes + 2 minutes discussion)*

Metabolic and molecular consequences of sarcopenia in alcoholic liver disease (ALD)

Srinivasan Dasarathy
Cleveland Clinic Lerner Research Institute, Cleveland, OH, USA

Alcohol use is one of the most frequent causes of liver diseases and is associated with more progressive and severe sarcopenia than in other causes of liver disease despite abstinence. The mechanisms of sarcopenia in ALD have been studies by us using an integrated bioinformatics-molecular-metabolic approaches to dissect potential causes of sarcopenia in a comprehensive array of models including murine C2C12 and human inducible pluripotent stem cell derived myotubes, gastrocnemius muscle from mouse models of ALD and human patients with alcoholic cirrhosis. We show the high translational relevance and therapeutic approaches to sarcopenia in alcohol related liver disease using multiomics analyses mitochondrial and antioxidant pathways enrichment across layers and models (Kumar et al Free Radical Biology in Medicine. We identified that ethanol and its metabolite, acetaldehyde, cause dysregulated proteostasis with decreased protein synthesis and increased autophagy flux. Mechanisms of these include a PI3Kγ-protein phosphatase 2A axis via mitochondrial free radical generation (Davuluri et al Hepatology 2021; pMID 32799332). We dissected the mechanisms of mitochondrial dysfunction using loss and gain of function studies using substrate, uncoupler, inhibitor, titration protocols and showed defects in inhibition of complexes I, III and IV with ethanol and ALD. Hyperammonemia in ALD and in response to ethanol have been reported by us and others due to impaired hepatic ureagenesis. Using a combination of biotin-streptavidin pulldown of different constructs of the inducible ammonia transporter, RhBG, followed by mass spectrometry, we identified transcriptional regulatory perturbations by ethanol that explains the progressive sarcopenia despite abstinence. Finally, using a complementary multiomics and bioinformatics overlay approaches, β-hydroxy-β-methyl butyrate reversed sarcopenia and mitochondrial oxidative dysfunction in preclinical models of ALD (Cell.Physiol.Biochem.2021; PMID 33543862).

A3 *(9 minutes + 2 minutes discussion)*

Bone and muscle crosstalk: biological and clinical implications

Gustavo Duque
Australian Institute for Musculoskeletal Science (AIMSS), The University of Melbourne and Western Health, Melbourne VIC, Australia

Muscle and bone share their embryonic development and constitute 55% of the body mass in a healthy adult. In addition to their mechanical interactions, which have an anabolic effect on both tissues, there is a complex crosstalk system between muscle and bone. This communication system is composed of osteokines, myokines, and other secreted factors (i.e., extracellular vesicles, exosomes, and microRNAs), some of them having either positive or negative effects on muscle and/or bone metabolism and function. There is a concurrent decline in muscle and bone mass with aging that usually starts in the third decade of life. In conditions such as sedentarism, obesity, inflammation, or menopause, catabolic factors predominate, thus inducing tissue loss and dysfunction. In contrast, anabolic factors could be stimulated to prevent muscle and bone loss of mass and function. This session will discuss the biological roles of these factors, their relevance in the muscle/bone crosstalk, and their clinical significance in the context of tissue loss conditions such as osteoporosis, sarcopenia and osteosarcopenia.

References:

1- Kirk B, Feehan J, Lombardi G, Duque G. Muscle, Bone, and Fat Crosstalk: the Biological Role of Myokines, Osteokines, and Adipokines. Curr Osteoporos Rep. 2020 Aug;18(4):388-400.
2- Kirk B, Miller S, Zanker J, Duque G. A clinical guide to the pathophysiology, diagnosis, and treatment of osteosarcopenia. Maturitas. 2020 Oct;140:27-33.

A4 (*9 minutes + 2 minutes discussion)*

Results of the SPRINTT trial

Francesco Landi
Fondazione Policlinico Universitario “Agostino Gemelli” IRCCS, Rome, Italy

The sustainability of health and social care systems is threatened by a growing population of older per- sons with heterogeneous needs related to multimorbidity, frailty, and increased risk of functional impairment. Since disability is difficult to reverse in old age and is extremely burdensome for individuals and society, novel strategies should be devised to preserve adequate levels of function and independence in late life. The development of mobility disability, an early event in the disablement process, precedes and predicts more severe forms of inability. Its prevention is, therefore, critical to impede the transition to overt disability. For this reason, the Sarcopenia and Physical fRailty IN older people: multi-componenT Treatment strategies (SPRINTT) project is conducting a randomized controlled trial (RCT) to test a multicomponent intervention (MCI) specifically designed to prevent mobility disability in high-risk older persons (1). SPRINTT is a phase III, multicentre RCT aimed at comparing the efficacy of a MCI, based on long-term structured physical activity, nutritional counselling/dietary intervention, and an information and communication technology intervention, versus a healthy aging lifestyle education program designed to prevent mobility disability in more than 1500 older persons with physical frailty and sarcopenia who will be followed for up to 36 months. The primary outcome of the SPRINTT trial is mobility disability, operationalized as the inability to walk for 400 m within 15 min, without sitting, help of another person, or the use of a walker. Secondary outcomes include changes in muscle mass and strength, persistent mobility disability, falls and injurious falls, disability in activities of daily living, nutritional status, cognition, mood, the use of healthcare resources, cost-effectiveness analysis, quality of life, and mortality rate.
Mean age of the 1519 participants (1088 women) was 78.9 (standard deviation 5.8) years (2). The average follow-up was 26.4 (SD 9.5) months. Among participants with SPPB scores of 3-7, mobility disability occurred in 283/605 (46.8%) assigned to the multicomponent intervention and 316/600 (52.7%) controls (hazard ratio 0.78, 95% confidence interval 0.67 to 0.92; P=0.005). Persistent mobility disability occurred in 127/605 (21.0%) participants assigned to the multicomponent intervention and 150/600 (25.0%) controls (0.79, 0.62 to 1.01; P=0.06). The between group difference in SPPB score was 0.8 points (95% confidence interval 0.5 to 1.1 points; P<0.001) and 1.0 point (95% confidence interval 0.5 to 1.6 points; P<0.001) in favour of the multicomponent intervention at 24 and 36 months, respectively. The decline in handgrip strength at 24 months was smaller in women assigned to the multicomponent intervention than to control (0.9 kg, 95% confidence interval 0.1 to 1.6 kg; P=0.028). Women in the multicomponent intervention arm lost 0.24 kg and 0.49 kg less appendicular lean mass than controls at 24 months (95% confidence interval 0.10 to 0.39 kg; P<0.001) and 36 months (0.26 to 0.73 kg; P<0.001), respectively. Serious adverse events occurred in 237/605 (39.2%) participants assigned to the multicomponent intervention and 216/600 (36.0%) controls (risk ratio 1.09, 95% confidence interval 0.94 to 1.26). In participants with SPPB scores of 8 or 9, mobility disability occurred in 46/155 (29.7%) in the multicomponent intervention and 38/159 (23.9%) controls (hazard ratio 1.25, 95% confidence interval 0.79 to 1.95; P=0.34).
A multicomponent intervention was associated with a reduction in the incidence of mobility disability in older adults with physical frailty and sarcopenia and SPPB scores of 3-7. Physical frailty and sarcopenia may be targeted to preserve mobility in vulnerable older people.

Reference:

1) Landi F, Cesari M, Calvani R, Cherubini A, Di Bari M, Bejuit R, Mshid J, Andrieu S, Sinclair AJ, Sieber CC, Vellas B, Topinkova E, Strandberg T, Rodriguez-Manas L, Lattanzio F, Pahor M, Roubenoff R, Cruz-Jentoft AJ, Bernabei R, Marzetti E; SPRINTT Consortium.The "Sarcopenia and Physical fRailty IN older people: multi-componenT Treatment strategies" (SPRINTT) randomized controlled trial: design and methods. Aging Clin Exp Res. 2017;29(1):89-100.
2) Bernabei R, Landi F, Calvani R, Cesari M, Del Signore S, Anker SD, Bejuit R, Bordes P, Cherubini A, Cruz-Jentoft AJ, Di Bari M, Friede T, Gorostiaga Ayestarán C, Goyeau H, Jónsson PV, Kashiwa M, Lattanzio F, Maggio M, Mariotti L, Miller RR, Rodriguez-Mañas L, Roller-Wirnsberger R, Rýznarová I, Scholpp J, Schols AMWJ, Sieber CC, Sinclair AJ, Skalska A, Strandberg T, Tchalla A, Topinková E, Tosato M, Vellas B, von Haehling S, Pahor M, Roubenoff R, Marzetti E; SPRINTT consortium. Multicomponent intervention to prevent mobility disability in frail older adults: randomised controlled trial (SPRINTT project). BMJ 2022 May 11;377:e068788.

B1 *(9 minutes + 2 minutes discussion)*

An immune-neuron-adipocyte axis guides catabolic adipose tissue remodeling in cancer associated cachexia

Martina Schweiger[1,5], Hao Xie[1], Isabella Pototschnig[1], Sophia Chrysostomou[1], Thomas Rauchenwald[1], Zhiyuan Tang[2], Gernot F. Grabner[1], Silvia Schauer[3], Wenwen Zeng[4], Gerald Höfler[3], Rudolf Zechner[1,5]
[1]University of Graz, Graz, Austria; [2]Affiliated Hospital of Nantong University, Nantong, China; [3]Medical University Graz, Graz, Austria; [4]Tsinghua University, Beijing, China; [5]BioTechMed-Graz, Graz, Austria

Background and aim: Cancer associated cachexia (CAC) is a hypermetabolic syndrome characterized by body weight loss due to muscle- and adipose tissue (AT) wasting. Survival rates for cancer patients with solely AT wasting are as poor as for patients with combined skeletal muscle and AT wasting, attributing an important role to AT loss in CAC [1]. The signals triggering catabolic reprogramming and tissue wasting are not understood. We aimed to find the mechanisms underlying adipose tissue loss in CAC.
Material and methods: Lewis lung- (LLC) or colorectal (C26) cancer cells were implanted into dopamine-β-hydroxylase deficient (DBHΔper), interleukin-4-receptor-α deficient (IL4rako), and the respective wild-type mice. Macrophages were locally depleted by injecting clodronate liposomes. White adipose tissue (WAT) was analyzed by immunofluorescence, immunohistochemistry, qPCR, and Western blotting analyses. Primary murine adipocytes and macrophages were isolated from WAT and bone marrow, respectively.
Results: In CAC, WAT loss resulted from catabolic reprogramming associated with elevated norepinephrine (NE) synthesis by peripheral sympathetic neurons. Tumor bearing DBHΔper mice were protected from WAT atrophy. NE stimulated adipocytes promoted alternative activation of macrophages. Depletion of macrophages using IL4rako mice or by clodronate injection reduced NE production, remodeling, and atrophy of WAT in tumor bearing mice [2].
Conclusion: Initiated by inflammatory tumorkines, a sustained β-adrenergic stimulus which is maintained by neurons, macrophages, and adipocytes causes a spiral toward complete adipose tissue loss in CAC.

References:
[1] Kays, J.K. et al., Three cachexia phenotypes and the impact of fat-only loss on survival in FOLFIRINOX therapy for pancreatic cancer. J. Cachexia. Sarcopenia Muscle 2018, 9, 673–684, doi:10.1002/jcsm.12307.
[2] Xie H, et al., An immune-sympathetic neuron communication axis guides adipose tissue browning in cancer-associated cachexia. Proc Natl Acad Sci U S A. 2022 Mar 1;119(9):e2112840119. doi: 10.1073/pnas.2112840119. PMID: 35210363.

B2 *(9 minutes + 2 minutes discussion)*

Angiocrine signals promote adipose tissue wasting in cancer cachexia

Andreas Fischer and colleagues
Division Vascular Signaling and Cancer, German Cancer Research Center (DKFZ), Heidelberg, Germany & Department of Clinical Chemistry, Göttingen Medical Center, Göttingen, Germany

White adipose tissue wasting is a multifactorial condition that can precede weight loss in cancer patients. Impaired lipid storage is accompanied by local inflammation and ultimately leads to fibrosis, a hallmark of adipose tissue remodeling during cachexia development. Pro-fibrotic stimuli also induce adipocyte de-differentiation and inhibit adipogenesis, an important contributor to fat loss. The continuous endothelium in adipose tissue prevents direct contact of circulating factors (e.g. cachectokines) with tissue cells, therefore raising the question whether the endothelium itself may orchestrate tissue remodelling. This hypothesis is based on the fact that the endothelium controls development, regeneration and metabolism of several organs by the release soluble factors (angiocrine signaling).
We show that during pre-cachexia, tumors overactivate Notch1 signaling in the adipose tissue endothelium of mice and that an endothelial Notch1 target gene signature is enriched in adipose tissue from pre-cachectic and cachectic cancer patients. Endothelial Notch1 signaling leads to adipose tissue wasting in mice through the local production of soluble factors acting on adipocytes and resident immune cells.
This demonstrates that cancer acts through the endothelium to induce adipose tissue wasting during cachexia.

B3 *(9 minutes + 2 minutes discussion)*

Brown adipose tissue activation is not related to hypermetabolism in (emphysematous) COPD patients

Annemie Schols
Maastricht University Medical Centre, The Netherlands

Introduction
Brown adipose tissue (BAT) has been primarily researched as a potential target for mitigating obesity. However, the physiological significance of BAT in relation to cachexia remains poorly understood. The objective of this study was to investigate the putative contribution of BAT on different components of energy metabolism in emphysematous chronic obstructive pulmonary disease (COPD) patients.
Methods
Twenty COPD patients (mean ± SD age 62 ± 6, 50% female, median [range] BMI 22.4 [15.1-32.5] kg/m^2 and 85% low FFMI) were studied. Basal metabolic rate (BMR) was assessed by ventilated hood, total daily energy expenditure (TDEE) by doubly labelled water and physical activity by triaxial accelerometry. BMR was adjusted for fat-free mass (FFM) as assessed by deuterium dilution. Analysis of BAT and WAT was conducted in a subset of ten patients and six age-matched, gender-matched and BMI-matched healthy controls. BAT glucose uptake was assessed by means of cold-stimulated integrated [18F]FDG positron-emission tomography and magnetic resonance imaging. WAT was collected from subcutaneous abdominal biopsies to analyse metabolic and inflammatory gene expression levels. Lung function was assessed by spirometry and body plethysmography and systemic inflammation by high sensitivity C-reactive protein.
Results
Mean TDEE was 2209 ± 394 kcal/day, and mean BMR was 1449 ± 214 kcal/day corresponding to 120% of predicted. Upon cooling, energy expenditure increased, resulting in a non-shivering thermogenesis of (median [range]) 20.1% [3.3-41.3] in patients and controls. Mean BAT glucose uptake was comparable between COPD and controls (1.5 [0.1-6.2] vs. 1.1 [0.7-3.9]). In addition, no correlation was found between BMR adjusted for FFM and BAT activity or between cold-induced non-shivering energy expenditure and BAT activity. Gene expression levels of the brown adipocyte or beige markers were also comparable between the groups.
Conclusions
Although COPD patients were hypermetabolic at rest, no correlation was found between BMR or TDEE and BAT activity. Furthermore, both BAT activity and gene expression levels of the brown adipocyte or beige markers were comparable between COPD patients and controls.

References:
Sanders K, Wierts R, van Marken Lichtenbelt WD, de Vos-Geelen J, Plasqui G, Kelders M, Schrauwen-Hinderling V. Bucerius J, Dingemans A, Mottaghy F, Schols A. Brown adipose tissue activation is not related to hypermetabolism in (emphysematous) COPD patients. JCSM 2022 Apr;13(2):1329-1338.
Sanders K, Klooster K, Vanfleteren L, Plasqui G, Dingemans A, Slebos D, Schols A. Effect of Bronchoscopic Lung Volume Reduction in Advanced Emphysema on Energy Balance Regulation. Respiration 2021 Feb 5;1-8.

B4 *(9 minutes + 2 minutes discussion)*

MRI-determined muscle fat infiltration for risk stratification in cancer cachexia

Dimitrios Karampinos
Technical University of Munich, Munich, Germany

Non-invasive methods for an early detection of cancer cachexia and further disease monitoring are needed in order to allow for early intervention in cases of prospective disease progression [1]. Computed tomography (CT) is part of the clinical cancer staging routine and therefore easy to implement for monitoring tissue changes. CT allows to determine muscle volume and muscle fat infiltration by measuring the Hounsfield Unit (HU) of individual muscles. However, CT does not provide measurements of volumetric changes of contractile muscle volume or muscle fat volume. Magnetic resonance imaging (MRI) is a radiation-free imaging modality that provides the possibility to directly measure muscle fat content and thus differentiate between muscle fat and contractile tissue. Specifically, proton density fat fraction (PDFF) mapping enables the non-invasive spatially-resolved standardized fat quantification in different tissues and organs [2]. The purpose of the present study was to evaluate the suitability of psoas and erector spinae muscle proton density fat fraction (PDFF) and fat volume as biomarkers for monitoring cachexia severity in an oncological cohort, and to evaluate regional variances in muscle parameters over time. In this prospective study, 58 oncological patients were examined by a 3 T MRI receiving between one and five scans. Muscle volume and PDFF were measured, segmentation masks were divided into proximal, middle and distal muscle section. A regional variation of fat distribution in erector spinae muscle at baseline was found ($p<0.01$). During follow-ups significant relative change of muscle parameters was observed. Relative maximum change of erector spinae muscle showed a significant regional variation. Correlation testing with age as covariate revealed significant correlations for baseline psoas fat volume ($r= -0.55$, $p<0.01$) and baseline psoas PDFF ($r= -0.52$, $p=0.02$) with maximum BMI change during the course of the disease. In erector spinae muscle a regional variation of fat distribution at baseline and relative maximum change of muscle parameters was observed. Our results indicate that psoas muscle PDFF and fat volume could serve as MRI-determined biomarkers for early risk stratification and disease monitoring regarding progression and severity of weight loss in cancer cachexia [3].

References:
[1] Baracos, V. E., L. Martin, M. Korc, D. C. Guttridge and K. C. H. Fearon. Cancer-associated cachexia. Nat Rev Dis Primers 4 (2018): 17105. doi: 10.1038/nrdp.2017.105.
[2] Reeder, S. B., H. H. Hu and C. B. Sirlin. Proton density fat-fraction: A standardized MR-based biomarker of tissue fat concentration. Journal of Magnetic Resonance Imaging 36 (2012): 1011-14. doi: 10.1002/jmri.23741.
[3] Patzelt, L., D. Junker, J. Syväri, E. Burian, M. Wu, O. Prokopchuk, U. Nitsche, M. R. Makowski, R. F. Braren, S. Herzig, M. B. Diaz, and D. C. Karampinos. MRI-determined psoas muscle fat infiltration correlates with severity of weight loss during cancer cachexia. Cancers 13(17) (2021):4433. doi: 10.3390/cancers13174433.

C1 (12 *minutes + 3 minutes discussion)*

Appetite is key in geriatric syndromes: a pre-release of SCWD International Guidelines on Anorexia of Aging

Ivan Aprahamian
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Anorexia of aging (AA) is a common condition among older adults, defined as a primary decrease in appetite and/or food intake related to an exaggerated aging process. Its prevalence ranges from 25 to 85%, influenced by the setting and the instrument used for measurement of anorexia. AA can precede other geriatric syndromes such as sarcopenia, frailty and malnutrition, and many other adverse health outcomes. Currently, no guidelines were published to recommend diagnosis operationalization and treatment of AA, and evidence is mixed and heterogeneous. Recently, we started developing a guideline on AA with the support of SCWD. First, a steering committee used the GRADE approach intended to review quality of evidence and provide background to the strength of recommendation. Second, as a next step, a Delphi consensus will be held after ethical board approval, and the document will be reviewed by experts in the field.

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C2 *(12 minutes + 3 minutes discussion)*

Development of the cachexia consensus in Asia

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Purpose: The Asian Working Group for Cachexia (AWGC) comprising multi-disicplinary exeprts from the region was convened to propose the diagnostic algorithm and outcomes of cachexia in Asian populations based on the available evidence and consensus among the AWGC members.
Methods: The AWGC, consisting of experts from Asian countries, had four online meetings on the diagnosis and outcomes of cachexia. We conducted a systematic review in 2020 and used the Delphi method to reach a consensus for the diagnostic algorithm and outcomes of cachexia.
Results: We reached a consensus after 3 rounds of the Delphi process. For the diagnosis of cachexia, we recommend the following: presence of underlying disease (cancer, congestive heart failure, COPD, chronic renal failure, rheumatoid arthritis, chronic respiratory failure, chronic liver failure, collagen diseases, progressive worsening chronic infections) and anorexia, plus one of the following: a) Low BMI or progressive weight loss based on the BMI-adjusted weight loss grading system, b) Low grip strength (<28kg in men, <18 kg in women), or c) Elevated CRP (≥0.5mg/dL). In terms of the outcomes, the three items which achieved more than 80% consensus in the third Delphi round were death, quality of life (QOL), and functional status. The QOL evaluation methods included EQ-5D, FAACT, and others e.g. EORTC-QLQ-C30. The evaluation methods for functional disability were Clinical Frailty Scale, Barthel Index, and others such as Katz Index, Lawton scale, and 6-minute walk.
Conclusion: The AWGC 2022 consensus outlines the evidence-based recommendations for the diagnostic algorithm and outcomes for cachexia which are specific for the Asian context. We believe that our consensus recommendations will provide the catalyst to drive further epidemiological and intervention studies, and to increase awareness for translation to clinical practice amongst Asian countries.

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C3 *(12 minutes + 3 minutes discussion)*

Recent guidelines on cancer cachexia: ESPEN, ESMO and ASCO

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During the last decades, the clinical management of patients with cancer focused mainly on disease-modifying therapies, in the genuine belief that individual patients' needs would have been also addressed by providing extended survival. Robust evidence now show that in real life disease-modifying therapies may not deliver as well as reported in clinical trials. Also, it is being recognized that overall survival may not represent the optimal outcome measure for patients with advanced cancer, particularly when it is considered that improved survival is not associate with improved quality of life. Early implentation of supportive care is therefore now recommended by international guidelines. Malnutrition and cachexia in cancer are clinically relevant factors influencing patients' quality of life as well as tolerance and response to anti-cancer therapies. Guidelines have been therefore developed by nutrition and oncological societies, including ESPEN, ESMO and ASCO. When reviewing the available evidence to draw practical recommendation, ESPEN, ESMO and ASCO acknoweldged that the methodological quality of the published studies is in general poor, definitely lower than drug trials. ASCO conclusions are therefore that any form of nutrition support cannot be recommended in patients with cancer. In contrast, ESPEN and ESMO guidelines are based on a clinically-driven and pragmatic approach: considering the negative impact of malnutrition, it is preferable to take the risk that nutritional support is minimally effective, rather than accepting the certainty that patients will suffer the clinical consequences of malnutrition. They are therefore recommending that all patients with cancer should be screened and regularly re-screened for malnutrition and their first oncological visit, and that nutrition care is included in the early comprehensive approach to patients with cancer. International guidelines on cancer cachexia should now prompt the devise of methodologically stronger clinical trials aiming at specific clinical outcomes rather than only at nutrition outcomes.

D1 *(9 minutes + 2 minutes discussion)*

Doxorubicin-induced skeletal muscle atrophy, underlying molecular pathways and potential protective effects of exercise: Evidence from pre-clinical and clinical data

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Introduction: Loss of skeletal muscle mass is a common clinical finding in patients with cancer, which could negatively affect clinical and patient-reported outcomes. Preclinical studies have shown that chemotherapy alone, independent of neoplastic disease, can promote muscle loss. Therefore, it is important to develop a countermeasure to prevent chemotherapy-induced skeletal muscle atrophy by acquiring a detailed understanding of the mechanisms responsible. The purpose of this meta-analysis and systematic review was to quantify the effect of chemotherapy (i.e., doxorubicin) on skeletal muscle and report on the proposed molecular pathways possibly leading to doxorubicin-induced muscle atrophy in both human and animal models.
Methods: A systematic search of the literature was conducted in PubMed, EMBASE, Web of Science and CENTRAL databases. The internal validity of included studies was assessed using SYRCLE's risk of bias tool. A meta-analysis was performed to assess effects of doxorubicin on skeletal muscle weight and muscle fibre cross-section area (CSA).
Results: Twenty eligible articles were identified (no human studies).[1] Doxorubicin significantly reduced skeletal muscle weight by 14% (95% CI: 9.9; 19.3) and muscle fibre CSA by 17% (95% CI: 9.0; 26.0) when compared to vehicle controls. Parallel to negative changes in muscle mass, muscle strength was even more decreased in response to doxorubicin administration. Mechanistic data suggest that mitochondrial dysfunction, which is associated with an increased ROS production, plays a central role in doxorubicin-induced skeletal muscle atrophy. Furthermore, doxorubicin activated all major proteolytic systems (i.e., calpains, the ubiquitin-proteasome pathway and autophagy) in the skeletal muscle. Although each of these proteolytic pathways contribute to doxorubicin-induced muscle atrophy, the activation of the ubiquitin-proteasome pathway is hypothesized to be key.
Conclusions: Results of this meta-analysis show that doxorubicin induces skeletal muscle atrophy in preclinical models, which can be explained by various interacting molecular pathways. More research is needed to confirm the proposed signaling pathways in humans, paving the way for potential therapeutic approaches**.** Emerging preclinical and clinical evidence suggests that exercise might ameliorate the detrimental effects of doxorubicin on skeletal muscle tissue.[2]

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D2 *(9 minutes + 2 minutes discussion)*

A randomised, feasibility trial of an Exercise and Nutrition-based Rehabilitation programme (ENeRgy) in people with cancer

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Background: Despite rehabilitation being increasingly advocated for people living with incurable cancer, there is limited evidence supporting efficacy or component parts. The progressive decline in function and nutritional in this population would support an approach that targets these factors. This trial (ClinicalTrials.gov: NCT03316157) aimed to assess the feasibility of an exercise and nutrition based rehabilitation programme in people with incurable cancer.[1]
Methods: We randomised community dwelling adults with incurable cancer to either a personalized exercise and nutrition based programme (experimental arm) or standard care (control arm) for 8 weeks. Endpoints included feasibility, quality of life, physical activity (step count) and body weight. Qualitative and health economic analyses were also included.
Results: 45 patients were recruited (23 experimental arm, 22 control arm). There were 26 males (58%), and the median age was 78 years (IQR 69-84). At baseline, the median BMI was 26 kg/m2 (IQR 22-29) and median weight loss in the previous 6 months was 5% (IQR -12% to 0%). Adherence to the experimental arm, was >80% in 16/21 (76%) patients. There was no statistically significant difference in the following between trial arms: step count - median % change from baseline to endpoint, per trial arm (experimental -18.5%[IQR -61 to 65], control 5% [IQR -32 to50], p=0.548); weight – median % change from baseline to endpoint, per trial arm (experimental 1%[IQR -3 to 3], control -0.5% [IQR -3 to 1], p=0.184); overall quality of life - median % change from baseline to endpoint, per trial arm (experimental 0%[IQR -20 to 19], control 0% [IQR -23 to33], p=0.846). Qualitative findings observed themes of capability, opportunity and motivation amongst patients in the experimental arm. The mean incremental cost of the experimental arm versus control was £-319.51 [CI -7593.53- 6581.91] suggesting the experimental arm was less costly.
Conclusions: An exercise and nutritional rehabilitation intervention is feasible and has potential benefits for people with incurable cancer.[2] A larger trial is now warranted to test the efficacy of this approach.

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D3 *(9 minutes + 2 minutes discussion)*

Resistance training during chemotherapy for non-metastatic colon cancer: The FORCE study: Effects on body composition and physical function

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Introduction: It is well known that a cancer diagnosis can involve multiple catabolic consequences. Tumors may sequester muscle tissue for its own growth [1]. Excessive bed rest and decreased steps after surgery lead can lead to muscle loss and inability to anabolize new muscle. Lastly, substantial evidence suggests that chemotherapy treatments can lead to loss of muscle mass [2]. Furthermore, evidence demonstrates that patients who have low muscle at the initiation of chemotherapy may be at increased risk of chemotoxicities and receive less than the optimal recommended dose, potentially leading to worse survival [3]. Exercise can maintain or increase muscle for cancer patients receiving chemotherapy [4].
Methods: We conducted an intervention trial of resistance training (RT) vs. usual care (UC) in Stage II and III colon cancer patients receiving chemotherapy with the goal to increase muscle mass of 1 kg or at a minimum maintain muscle mass over the course of chemotherapy (N=181). The main outcome was relative dose intensity (RDI), a measure of the percentage of chemotherapy delivered in comparison to a patient's planned treatment**.** Secondary outcomes were changes in body composition and changes in functional status. Both dual-energy x-ray absorptiometry (DXA) and The D_3-creatine (D_3Cr) dilution method (D3 creatine) were administered before randomization and after trial completion to measure body composition. The short physical performance battery (SPPB) test and handgrip strength were used to measure functional status.
Results: *Body Composition*: Measured by DXA (n=163), slightly over 75% of the total study sample either maintained or gained lean mass while less than 25% lost lean mass. When comparing RT to UC, patients in RT increased lean mass and had a smaller decrease in their lean/fat mass ratio, however none of these changes were statistically significant. In a priori determined subgroup analyses there was a significant interaction by sex for change in lean mass (p for interaction 0.04). Males in RT increased lean mass 0.75 kg more than males in UC [mean difference +0.75kg (–0.67, 2.18)] while differences between RT and UC for females was smaller [mean difference 0.35 kg (–0.54, 1.25)]. Also, those patients who were frail at baseline (defined as low muscle or low functional status) and in RT increased their lean mass more than those in UC [mean difference +1.01kg (–0.02, 2.04) p<0.05] but no differences were seen between treatment groups in the non-frail. There was also a significant interaction in change in the lean/fat mass ratio by baseline frailty status (p for interaction 0.002). Those frail in RT significantly increased their lean/fat mass ratio compared to UC [mean difference +0.19 (0.05, 0.33)]. In those not frail there was a small non-significant decrease in lean/fat mass ratio for RT compared to UC [mean difference -0.02 (-0.15, 0.10)]. In the subset of patients with D3 creatine (n=93), those in the RT increased D3 muscle compared to those in UC [(mean difference +1.02 kg (0.7 SD)]. *Functional Status*: Overall, there was no difference in the change in SPPB scores or change in handgrip strength between those patients in RT vs UC. In a priori subgroup analyses there was a significant interaction in change in the SPPB score by frailty status (p for interaction <0.001). Patients with frailty had larger improvements in their SPPB score compared to UC [mean difference +0.70 (0.08, 1.33); p 0.03]. Patients who were not frail and in RT had similar scores to those in UC.
Conclusions: Resistance training done during chemotherapy increases lean mass and improves functional status but only in those who at the start of chemotherapy have either poor functional status or have sarcopenia. Future studies should design interventions specifically targeting the frail.

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D4 *(9 minutes + 2 minutes discussion)*

Effects of exercise in patients after curative treatment for esophageal cancer: body composition and adequacy of energy and protein intake (the PERFECT study)

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Introduction: After esophageal cancer treatment, a persistent decline in muscle mass has been observed. Strategies to counteract malnutrition-related skeletal muscle loss involve exercise and nutritional interventions. The Physical ExeRcise Following Esophageal Cancer Treatment (PERFECT) study was performed to investigated the effects of supervised exercise on quality of life in patients after surgery for esophageal cancer. Since these patients are already at risk for malnutrition, it is important that the diet meets the patient's energy and protein requirements, especially during an exercise intervention. Therefore, we assessed whether participants in the PERFECT study meet energy and protein requirements. Additionally, effects of the PERFECT exercise program on body composition, malnutrition risk and energy expenditure were addressed.
Methods: The multicenter PERFECT trial randomly assigned 120 patients (age 64±8) in the first year after esophagectomy to an exercise intervention (EX) or usual care (UC) group.[1] EX patients participated in a 12-week supervised aerobic and resistance exercise program. We measured dietary intake (3-day food diary) of all participants and performed additional dietetic measurements (i.e. bio-impedance analysis and indirect calorimetry) in a subgroup at baseline and 12 weeks post-baseline. Data were analyzed as between group differences using ANCOVA.
Results: Adherence and compliance with the exercise program was high (>90%). Participation in the exercise program significantly improved cardiorespiratory fitness and QoL.[2] At baseline, 63.2% and 37.6% of all 120 participants had an adequate energy and protein intake, respectively. In total, 37 patients participated in the additional dietetic measurements (EX=19, UC=18). The EX group had a non-significant lower weight at 12 weeks compared to UC (-1.5 kg, 95% CI -4.6; 1.5). This decline was mainly due to a significantly decreased fat mass index from baseline to 12 weeks (-0.5, 95% CI -0.9; -0.09), whereas the fat free mass (FFM) index remained stable. Compared to UC, the EX group had a significant higher measured resting energy expenditure (1.6 kcal/kg, 95% CI 0.4; 2.8, effect size=0.6) at 12 weeks. The risk for malnutrition tended to be lower in the EX group compared to UC (-2.2, 95% CI -5.8; 1.4, ES=0.5).
Conclusions: Although esophageal cancer survivors are at risk for malnutrition, it seems safe and feasible to exercise following esophagectomy. However, based on the low protein intake and stable FFM, a nutritional intervention, in addition to the exercise program, is recommended to allow for larger effects of the exercise program.

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E1 *(9 minutes + 2 minutes discussion)*

Activation of Akt-mTORC1 signaling reverts cancer-dependent muscle wasting

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Background: Cancer-related muscle wasting occurs in most cancer patients. An important regulator of adult muscle mass and function is the Akt-mTORC1 pathway. While Akt-mTORC1 signaling is important for adult muscle homeostasis, it is also a major target of numerous cancer treatments. Which role Akt-mTORC1 signaling plays during cancer cachexia in muscle is currently not known. Here we aimed to determine how activation or inactivation of the pathway affects skeletal muscle during cancer cachexia.
Methods: We used inducible, muscle-specific Raptor ko (mTORC1) mice to determine the effect of reduced mTOR signaling during cancer cachexia. On the contrary, in order to understand if skeletal muscles maintain their anabolic capacity and if activation of Akt-mTORC1 signaling can reverse cancer cachexia, we generated mice in which we can inducibly activate Akt specifically in skeletal muscles.
Results: We found that mTORC1 signaling is impaired during cancer cachexia, using the Lewis-Lung Carcinoma (LLC) and C26 colon cancer model, and is accompanied by a reduction in protein synthesis rates of 57% ($P<0.01$). Further reduction of mTOR signaling, as seen in Raptor ko animals, leads to a 1.5-fold increase in autophagic flux ($P>0.001$), but does not further increase muscle wasting. On the other hand, activation of Akt-mTORC1 signaling in already cachectic animals completely reverses the 15-20% loss in muscle mass and force ($P<0.001$). Interestingly, Akt activation only in skeletal muscle completely normalizes the transcriptional deregulation observed in cachectic muscle, despite having no effect on tumor size or spleen mass. In addition to stimulating muscle growth, it is also sufficient to prevent the increase in protein degradation normally observed in muscles from tumor-bearing animals.
Conclusions: Here we show that activation of Akt-mTORC1 signaling is sufficient to completely revert cancer-dependent muscle wasting. Intriguingly, these results show that skeletal muscle maintains its anabolic capacities also during cancer cachexia, possibly giving a rationale behind some of the beneficial effects observed in exercise in cancer patients.

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E2 *(9 minutes + 2 minutes discussion)*

New insights into the role of GCN2-eIF2alpha signaling in the regulation of autophagy

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Alongside variations in the availability of dietary nutrients, the body may experience significant changes in amino acid profiles as a result of pathological conditions. For example, a number of diseases are associated with a catabolic state and deregulated amino acid homeostasis. To cope with fluctuations in essential amino acid (EAA) availability, mammals have evolved a broad spectrum of adaptive mechanisms. Among these, the kinase GCN2 is activated in cells undergoing EAA scarcities, thereby leading to the phosphorylation of eIF2alpha, a signaling node contributing to adaptation to stress [1]. The phosphorylation of eIF2alpha notably leads to protein synthesis reduction and initiates a gene expression program, mediated by the translationally upregulated transcription factor ATF4. We aimed at characterizing the role of GCN2-eIF2alpha signaling in the regulation of autophagy. In a cell model of deprivation of a single EAA, we observed that proteolysis was rapidly increased in response to leucine starvation, an effect that was mainly due to autophagy and dependent on GCN2. One-hour leucine deprivation upregulated autophagy in both cultured cells and *in vivo* in mouse liver, as reflected by an increase in [S278]-ATG16L1 phosphorylation and LC3B conversion, and decreased p62 protein level [2]. Using cells and mice with genetic ablation of *Gcn2* as well as genetic reconstitution experiments *in vitro*, data showed that GCN2 was required for this upregulation of autophagy in response to short-term EAA deprivation. The phosphorylation of eIF2alpha was also required while the expression of ATF4 was not [2]. These results complete our previous data demonstrating that activation of the GCN2-eIF2alpha-ATF4 pathway is involved, for longer-term EAA deprivations, in upregulating the transcription of many autophagy genes [3]. Taken together, our data thus indicate that GCN2-eIF2alpha signaling plays an important role in the regulation of autophagy, by the way of both ATF4-mediated transcriptional upregulation of autophagy gene expression and ATF4-independent mechanisms. This should contribute to the adjustment of protein and AA homeostasis in response to EAA limitation. Our data contribute to define eIF2alpha signaling as an important regulator of autophagy during physiological stress and/or pathology.

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E3 *(9 minutes + 2 minutes discussion)*

Interventions for improving mitochondrial function to counteract cancer and chemotherapy-induced cachexia

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The presence of cachexia in cancer patients severely impacts on anti-cancer treatment tolerance and effectiveness, eventually reducing QoL and survival. Given the complexity and the multisystemic pathogenesis of cachexia, affecting several organs beyond the skeletal muscle, defining an effective therapeutic approach has failed so far. In the last decade, the researcher's attention has focused on mitochondrial alterations occurring in the skeletal muscle as potential triggers of several metabolic derangements, resulting in muscle protein catabolism and tissue wasting. Mitochondrial damage and dysfunction cause inefficient energy production, thus inducing protein catabolism as a compensatory mechanism, however, other peculiar cachexia features may rely on the loss of mitochondrial health. Chemotherapy, especially cytotoxic compounds, also impacts on muscle mitochondrial function, likely impairing both adult fiber energy homeostasis and muscle regeneration due to insufficient energy production from damaged mitochondria. Improving mitochondrial function in cancer cachexia could thus ameliorate the energetic status, chemotherapy tolerance and allow proper myogenesis. Exercise training, adopting specific exercise protocols, resistance or endurance based, represents a potential non-pharmacological intervention that targets both muscle quality and quantity, in both cases through improved mitochondrial health. When exercise is not feasible due to intolerance, comorbidities or end-stage disease, the adoption of drugs mimicking specific aspects of exercise-induced beneficial effects in cancer hosts is desirable. Mitochondria-targeted exercise mimetics might have a dual implementation in cancer patients, extending the pre-cachexia stage or relieving the limitations to exercise and allowing the completion and effectiveness of anti-cancer treatments. This presentation will summarize the most effective mitochondria-targeted interventions for improving cancer cachexia and will report on novel targets for prospective new treatments.

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E4 *(9 minutes + 2 minutes discussion)*

Fighting muscle loss: lessons from hibernation in brown bear

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Muscle atrophy is one of the main deleterious consequences of ageing, diseases (e.g. cancers and AIDS), and physical inactivity. It is especially detrimental to locomotion, heat production, and metabolism thus leading to frailty, increased dependency and metabolic disorders. Apart from being a major clinical problem for older people, muscle loss is also observed during physical inactivity, which has become a major leading cause of death worldwide. Although basic knowledge regarding the underlying mechanisms of muscle atrophy is continuously growing, essentially from rodent models and clinical trials in humans, there are still no efficient therapeutic strategies for its prevention and treatment.
Hibernating bears exhibit a strong and unique ability to preserve muscle mass in conditions of muscle disuse and food deprivation, conditions during which muscle atrophy is observed in human. Bears remain inactive in winter during up to seven months without arousal episodes (without eating, drinking, urinating or defecating), with only very limited loss in muscle protein content and strength, whereas muscle and fibre cross-sectional area are preserved.
Underlying mechanisms have not been understood yet, but our approaches combine molecular and cellular studies of bear muscle as well as human muscle cells exposed to bear serum. Our recent demonstration of trans-species effects of bear serum controlling protein degradation in cultured human muscle cell holds promising potential. Hence, exploration of winter bear serum therefore holds potential for developing new tools to fight human muscle atrophy and related metabolic disorders.

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F1 *(9 minutes + 2 minutes discussion)*

Measuring muscle in oncology research and interventions

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Low skeletal muscle mass increases the risk of surgical complication, chemotherapy toxicity and mortality in cancer patients. This session discusses relative advantages and pragmatic considerations related to muscle assessment methods in oncology research and interventions. The three methods studied include D3-creatine dilution to measure total body muscle mass (D3Cr); lean body mass from dual energy x-ray absorptiometry (DXA); and cross-sectional muscle area at the third lumbar vertebra on computed tomography (CT). We first discuss the implementation of these assessment methods in the context of a behavioral intervention (the FORCE trial of resistance training during chemotherapy for colon cancer), as well as the correlations of each measure with the others and with physical performance. Next, we discuss the use of diagnostic and surveillance CT images for body composition assessment in observational research in oncology, and report the correlations between single-slice muscle area and multi-slice muscle volume measured from CT using automated methods. Finally, we share future directions for the use of existing clinical data in combination with imaging biomarkers of muscle health for the assessment of patient frailty and prediction of surgical morbidity and cancer mortality.

F2 *(9 minutes + 2 minutes discussion)*

Artificial Intelligence approaches to improve speed, dimensionality and entry into clinical workflows

Mirza Faisal Beg
Functional, Anatomical Image and Shape Analysis Lab, Michael Smith Foundation for Health Research Scholar, Simon Fraser University, Vancouver, Canada

Despite numerous studies showing the value of assessing body/muscle composition from routinely acquired CT images for predicting clinical outcomes, it is not performed in clinical workflows. In this talk, I will focus on the barriers that prevent the integration of CT imaging-based body composition in clinical workflows and approaches to overcoming these with automation. I will showcase our fully automated platform, DAFS, for multislice multi-tissue multiorgan segmentation and measurements, focusing on the efficiencies gained at each step of the workflow such as the curation of dicom images, the automated labeling of slices with vertebral annotations for extracting slices and volumetric fields of view other than L3, automated segmentation of skeletal muscle, intramuscular adipose tissue, visceral adipose tissue, subcutaneous adipose tissue, and delivering a fully automated body composition report. I will also showcase how DAFS can be used to study muscle areas, volumes and radiodensities, along with IMAT for characterizing localized/systemic muscle remodeling and wasting and potentially integrating other organs in characterizing body habitus for precision medicine.

F3 *(9 minutes + 2 minutes discussion)*

Surrogate markers of muscle mass and quality

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There is an increasing need to assess muscle mass in clinical practice, as low muscle mass has been associated with adverse outcomes in several clinical conditions. Muscle mass assessment is also a key component for diagnosing malnutrition, sarcopenia, and cachexia. Notwithstanding, body composition methods to perform an adequate skeletal muscle assessment are not widely available in all clinical settings. Therefore, there is a demand for simple tools or surrogate markers of muscle mass that could be applied in routine clinical use.
Calf circumference (CC) has been highlighted as a muscle marker in the last decades, especially in studies with older adults for sarcopenia diagnosis. As a marker of lower limb muscle mass, it better captures the age-associated muscle loss, and it has been considered a predictor of mortality at any age and disability in older subjects. There are several cutpoints suggested for different populations/ethnicities. Edema and body mass index are two factors that may influence CC measures, and correction for both factors may improve its performance.
Another surrogate marker for muscle mass and quality is phase angle (PhA), obtained directly as a ratio between reactance and resistance from bioelectrical impedance analysis (BIA). Recent studies have shown a good correlation between PhA and muscle area and density from computed tomography. Previous studies showed that a low PhA predicts impaired muscle function and physical performance, suggesting that PhA can be valuable in identifying sarcopenia.
Echo intensity (EI) from ultrasound has been considered a promising marker for muscle quality, as it reflects the muscle and its non-contractile elements, intramuscular adipose, and fibrous tissue. Several studies have reported an age-related increase in EI, more evident in trunk musculature, and an association with functional performance. Further studies may show its usefulness in assessing muscle quality in clinical practice.

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F4 *(9 minutes + 2 minutes discussion)*

A mechanistic perspective of specialized nutrition for muscle health

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The major components of specialized nutrition include macronutrients (for energy storage/ substrates), vitamins and minerals (micronutrients) and other indicated "nutraceuticals" e.g. the leucine metabolite, β-hydroxy β-methylbutyrate. It is certainly the case that deficiencies in micronutrients affect muscle health (e.g., Vitamin D deficiency causing muscle weakness). However, it is dietary protein constituent essential amino acids (EAA) that drive maintenance of muscle mass (1) via replenishment of fasted losses due to protein degradation. The efficacy of protein nutrition in muscle maintenance depends upon: digestibility, absorption of protein AA constituents, splanchnic metabolism, peripheral utilization for protein synthesis / ATP production, and nitrogen excretion via urea. The mechanistic basis of EAA anabolic effects, occurs via activation of muscle intracellular signaling pathways (1) that culminate in increased efficiency of mRNA translation i.e., muscle protein synthesis (MPS). This anabolic response is short lived i.e., ~2 h (1,2), after which exhibiting tachyphylaxis (3). Evidence indicates a re-stimulation of MPS may be possible around 4 h after consumption of an optimal protein bolus.

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G1 *(9 minutes + 2 minutes discussion)*

Mechanisms of ammonia induced sarcopenia - a common mediator in multiple diseases

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Ammonia is a cytotoxic nitrogenous metabolite generated during a number of physiological functions including amino acid catabolism, purine breakdown and gut microbial metabolism. Hyperammonemia with perturbations in ammonia disposal occurs in a number of chronic diseases including heart failure, chronic obstructive lung disease, liver disease, renal failure, and rapidly growing malignancies all of which have sarcopenia. Ureagenesis in hepatocytes is the primary mechanism of ammonia disposal in mammals but in non-hepatic organs, hyperammonemia causes perturbations in signaling, metabolic and functional consequences. Skeletal muscle ammonia uptake is increased during hyperammonemia via transcriptional upregulation of an inducible ammonia transporter, RhBG. Dysregulated proteostasis with lower mRNA translation and increased autophagy flux result in a sarcopenic phenotype. Signaling perturbations include lower mTORC1 signaling and a unique, hyperammonemic stress response that are responsive to L-leucine. There is also increasing recognition of reduced mitochondrial oxidative function with increased free radical generation that contributes to post-mitotic senescence during hyperammonemia that is reversed by ammonia lowering in preclinical models. These data lay the foundation for potential therapeutic approaches to prevent and reverse sarcopenia in a number of chronic diseases.

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G2 *(9 minutes + 2 minutes discussion)*

Amino acid perturbations in hyperammonemia

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Main alterations in aminoacidemia due to hyperammonemia are decreased concentrations of branched-chain amino acids (BCAAs; valine, leucine, and isoleucine) and increased concentrations of glutamine (GLN). Several studies have reported that these alterations are involved in pathogenesis of hepatic encephalopathy, impaired function of mitochondria, and muscle wasting (1-3).
The decrease of the BCAA is due to their use as the main donor of amino nitrogen to alpha-ketoglutarate to form glutamate, which is a direct substrate for ammonia detoxification to GLN in GLN synthetase reaction in muscles. The results of several studies have shown that hyperammonemia directly activates the BCAA catabolism (2). The increased needs of the BCAA for glutamate synthesis are fulfilled by enhanced breakdown of muscle proteins and from extracellular fluid, probably by exchange with GLN via L-transport system. Excessive glutamate synthesis drains alpha-ketoglutarate from tricarboxylic acid cycle (cataplerosis) and thus impedes aerobic oxidation in mitochondria. The suggestion is supported by increased levels of markers of muscle protein breakdown and decreased levels of ATP and alpha-ketoglutarate in muscles (1,3).
Various recommendations have been postulated to use BCAAs in hyperammonemic states to prevent or treat hepatic encephalopathy and improve muscle protein balance. Unfortunately, the results of the clinical trials are not consistent. Potential adverse effect of the BCAA supplementation is increased drain of alpha-ketoglutarate from citric cycle and increased GLN synthesis, which is degraded to ammonia in visceral organs. It has been suggested that cataplerosis can be attenuated by dimethyl-alpha-ketoglutarate or glutamate administration. In conclusion, the search for strategies attenuating adverse effects of alterations in amino acid metabolism due to hyperammonaemia is needed for proper therapy of encephalopathy and hepatic cachexia.

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G3 *(9 minutes + 2 minutes discussion)*

Multiomics based approaches to identify novel cellular and tissue responses

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Current approaches towards understanding physiology and disease have primarily used targeted, hypothesis driven experimental approaches in preclinical models that are then tested in human subjects for translational relevance. However, there is increasing recognition that cellular, tissue and organismal level adaptive and maladaptive responses involve multiple intersecting pathways. We used an integrated multiomics analytical approach to study global landscapes to stressors. We defined an integrated multiomics approach across datasets. We defined *vertical integration* as multiomics analyses across layers of untargeted data across chromosome access for transcriptional regulation by assay for transposase accessible chromatin sequencing, transcriptomics (for mRNA expression), proteomics, post-translational modifications, including phosphoproteomics and acetylomics, and metabolomics in different models. *Horizontal integration* was defined as multiomics analyses across different models including organelle, cellular, murine and human tissue models. Standard and customized pipelines and analytical approaches were used to dissect the intersection of cellular and tissue reactions at different levels by identifying shared, unique, concordant and discordant responses. Such approaches that have been overlaid over known chemical/molecular responses allow for identifying novel mechanisms and therapeutic targets for disease. We have used hyperammonemia and ethanol exposure in myotubes and muscle tissue to identify protein kinase A, mTORC1 signaling and other pathways and molecules and intersecting mediators of mRNA translational control. Subsequent experimental validation in cellular and mouse models with loss and gain of function approaches have allowed us to identify novel genes including glucose fructose oxidoreductase in mediating responses to hyperammonemia. Such approaches have broad interdisciplinary applications in biology and medicine.

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G4 *(9 minutes + 2 minutes discussion)*

The significance of myosteatosis in surgical cancer patients

Steven Olde Damink, The Netherlands

H1 *(9 minutes + 2 minutes discussion)*

Which parameters determine optimal protein metabolism in the older adult?

Dominique Dardevet, Isabelle Savary-Auzeloux, Laurent Mosoni, Marie-Agnès Peyron, Sergio Polakof, Didier Rémond
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There seems to be a consensus that the need for protein is increased in the elderly to maintain optimal all the body functions. In several countries, the RDA for proteins has recently been increased to 1g/kg/d for adults over 65 years of age with dietary proteins of good quality abdthis even if they are considered in “good health”. Apart from the quantity to be ingested, which can still remain a problem to reach for this population, the quality of the proteins ingested is essential and involves much more than just the amino acids composition of the dietary protein. The lower the quality of these proteins, the more the quantity to be ingested to meet the AA requirement will be important and therefore difficult to achieve in a population characterized by a lower appetite or food intake, and by a palatability for dietary protein which is decreased. The quality of a dietary protein is related to its amino acids composition (AA) but also to other determinants including the speed of digestion, the presence of specific AAs, the food matrix in which the dietary proteins are included and the processes involved in the production of food products (gelation, cooking temperature). We can also mention the interaction with other macro or micro-nutrients associated to the meal that could interfere with the dietary proteins. This include the plant bioactives such as the polyphenols and the anti-nutritional factors found in the plant proteins sources. The search for alternative protein sources and transitioning towards more sustainable, plant-based nutrition has received much attention in the past decade. But, is this transition compatible with optimal protein nutrition in the elderly?

Dardevet D, Mosoni L, Savary-Auzeloux I, Peyron MA, Polakof S, Rémond D. Important determinants to take into account to optimize protein nutrition in the elderly: a complex equation but with solutions.
Proceedings of the Nutrition Society, 2020 Nov 17:1-27

H2 *(9 minutes + 2 minutes discussion)*

Manipulating the microbiome to counteract frailty

Patrizia Brigidi
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Age is one of variables mostly impacting on the gut microbiota composition and function (1). Indeed, the gut microbiota describes an adaptive trajectory along human aging in which its changes provide the host with ecological services calibrated for each stage of life from infancy to elderly.
Overall, the aged-type microbiome is reported to be characterized by an altered diversity, with increased representation of opportunistic bacteria and potential pathobionts, and reduced relative abundance of microbes producing short-chain fatty acids (SCFAs), as well as an altered functional profile characterized by a strong rearrangement in metabolic pathways related to carbohydrate, amino acid and lipid metabolism and a progressive age-related increase in genes devoted to xenobiotic degradation (2).
We demonstrated the efficacy of a Mediterranean diet, tailored to elderly needs, to modulate the microbiome profile, supporting specific bacterial components with a negative association with frailty and inflammatory markers, and a positive association with cognitive function (3). Furthermore, we explored the associations between the microbiome profile and the DXA-derived body composition data, with a specific focus on abdominal fat, assessing that an enrichment in genera belonging to *Christensenellaceae* (*Christensenellaceae* R7 group), *Porphyromonadaceae* (*Parabacteroides*) and *Rikenellaceae* (*Alistipes*) families was inversely associated with visceral adipose tissue (4).
It is reasonable to expect that in the near future the targeted manipulation of the elderly intestinal microbiota will become an integral component of current strategies aimed at contrasting age-related deterioration in body composition and multiple bodily functions, thus supporting healthy aging.

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H3 *(9 minutes + 2 minutes discussion)*

Nutrition and anorexia of ageing

Reshma Merchant
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Anorexia of ageing (AA) is prevalent in 30% of community dwelling older adults, and associated with negative outcomes such as weight loss, loss of muscle mass, frailty and mortality. AA is caused by dysregulation of peripheral appetite hormonal release and action, physiological changes with ageing (reduced fundal compliance, slower gut motility, diminished smell, taste and vision), comorbidities including neurogenerative diseases, medications including those which exacerbate dry mouth and / or suppress appetite, poor oral health and social factors (loneliness, poverty, lack of access to food) (Merchant, Woo et al. 2022). AA can lead to macronutrient and micronutrient deficiencies with accelerated ageing and mitochondrial dysfunction. Multidimensional interventions depending on underlying cause with personalized care plan such as management of depression, oral care, oral nutrition supplementation, flexibility in dietary restriction, food presentation e.g flavor, smell and design of innovative food with high energy and nutrient density e.g high protein soup or snacks may be the most effective means of improving food intake, preventing weight loss and other adverse outcomes such as frailty (Lutz, Petzold et al. 2019, de Souto Barreto, Cesari et al. 2022).

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H4 *(9 minutes + 2 minutes discussion)*

Combining power food and fasting in cachexia: no go or wise go?

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Cancer cachexia is characterized by procatabolic and hypoanabolic processes, driven by proinflammatory mediators and other mechanism. Clinically muscle wasting and also myosteatosis occurs, as symptoms loss of appetite, taste and smell disturbances, early satiety and mostly physical fatigue. Management of cancer cachexia requires multimodal interventions including nutritional assessment and interventions, strenght training and enhancement of physical activity, as well as psychological support. Anticachectic medications are rare, Anamorelin is approved only in Japan, a recent study suggests that cancer cachexia associated fatigue may be improved.[1]

Patients with cancer cachexia experience the existential threat with decreasing muscle mass and appetite and typically aim to engage in self-management including diets, which have the potential to slow down cancer activity. The current «anti-cancer nutrition» includes mediterran diet, antiinflammatory diet, diet low in toxins (biological, no ultraprocessed food), diet low in carbohydrates (up to ketogenic diet), vegetarian or even vegan diets avoiding animal proteins, and certain micronutrients. Also there is increasing evidence of caloric restriction interventions, including fasting (intervall, 1-2 days/week, periods), fasting-mimicking diets, or caloric restriction mimetics, Preclinical evidence suggest that 2 days/week fasting is associated with increased tumor control in tumorbearing (cachectic) animals.[2]

Current recommendations for protein intake range from 1.2 g/ kg BW to 2 g/ kg BW[3] and a recent systematic review clarifies, that ≥1.4 g/ kg BW is associated with maintenance of muscle mass during anticancer treatment.[4] Also a recent expert group review highlights the importance of a mixture of animal- and plant-based proteins in cancer.[5]

In clinical care we need to advise patients how to eat (and not eat) to slow down the cancer disease and simultaneously ensure adequate energy and protein intake, which can be metabolized.

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J1 *(9 minutes + 2 minutes discussion)*

Hepatic and intestinal microbial disturbances as therapeutic targets in cancer cachexia

Laure B. Bindels
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Cancer cachexia is a complex multi-organ syndrome characterized by weight loss, muscle atrophy, fat mass loss, anorexia, and inflammation. With a prevalence of 1 million people in Europe and only limited therapeutic options, there is a high medical need for new approaches to treat cachexia. In this context, we started a few years ago studying the therapeutic interest of modulating the gut microbiota in the context of cancer cachexia.

We discovered not only that the gut microbiota composition and function were deeply altered in cancer cachexia but also that the gut function itself was altered at several levels (gut immunity, gut barrier, epithelium renewal, intestinal morphology), independently of any chemotherapeutic intervention (1-3). Furthermore, our experimental results establish that nutritional modulation of the gut microbiota could constitute an interesting adjuvant therapeutic tool for cancer and associated cachexia. Among the mechanisms involved in these beneficial effects, we can pinpoint some microbial metabolites being able to influence cancer progression outside the gastrointestinal tract, including the liver. Indeed, our recent findings support a role for microbial metabolites in the regulation of the hepatic inflammation associated with cancer development (4, 5 and unpublished data). These recent findings will be presented during this talk.

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J2 *(9 minutes + 2 minutes discussion)*

A novel tissue inhibitor of metalloproteinases1/liver enzyme/cachexia (TLC)-score predicts prognosis of gastrointestinal cancer patients

Olga Prokopchuk[1,3], Chris D. Hermann[1], Benjamin Schoeps[1], Ulrich Nitsche[3], Oleksii L. Prokopchuk[1], Percy Knolle[2], Helmut Friess[3], Marc E. Martignoni[3] & Achim Krüger[1]
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Introduction: Tissue inhibitor of metalloproteinases-1 (TIMP-1) is an easily accessible cachexia-associated biomarker in the blood, known to alter liver homeostasis. Here, we tested whether blood levels of TIMP-1 together with parameters of liver functionality allow more reliable prediction of survival of cancer patients as compared to conventional determination of weight loss (WL).
Methods: Blood levels of TIMP-1, C-reactive protein, ferritin, gamma-glutamyl transferase, albumin, and total protein and WL were determined in cohorts of colorectal cancer (CRC) patients (n=82; 35.4% women, 64.6% men, median age: 70 years) and correlations were established upon statistical analyses. For validation of the findings, the same approach was taken with a cohort of pancreatic cancer (PC) (n=84; 54.8% women, 45.2% men, median age: 69 years) patients.
Results: Plasma TIMP-1 levels were confirmed as reliable cachexia marker, identified prognostically distinct subpopulations within WL-defined cachectic patients, correlated with parameters of liver functionality, and, in combination with the latter, reliably predicted survival of CRC patients. Cachexia was reflected by combination of plasma levels of TIMP-1with plasma levels of tested liver parameters. The value of TIMP-1 level was necessary and its combination with the values of levels of only two of the five parameters of liver functionality was sufficient to categorize CRC patients according to their risk (low (LO) *vs* intermediate (IM) *vs* high (HI)). The prognostic power of the cachexia-associated TLC-score [P<0.001, HR:7.37(2.80–19.49)] and its application to define risk groups (LO*vs*IM: P= 0.032, LO*vs*HI: P<0.001, IM*vs*HI: P=0.014) was validated and confirmed in a cohort of PC patients. The prognostic power of the score was independent of presence of liver metastases in CRC or PC patients and was superior to clinically established staging classifications.
Conclusions: Straightforwardly determined blood parameters represent an objective cachexia-associated clinical tool, easily applicable in a cell-phone-App, for precise survival prediction of gastrointestinal cancer patients.

J3 *(9 minutes + 2 minutes discussion)*

Inflammation and impairment of hepatic metabolism and function in cachectic cancer patients

Daniela Gonçalves, Silvio Gomes, Gabriela de Castro, Rodrigo das Neves, Paulo Alcântara, Jose Pinhata Otoch and Marilia Seelaender
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The liver plays a major role in the control of intermediary metabolism, among many other fundamental functions. Cancer cachexia is associated with robust metabolic derangement, impacting cell/tissue/organ function and homeostasis. Little is known, nevertheless, about the hepatic effects of the syndrome in cancer patients, probably owing to the difficulty in obtaining biopsies. Animal models provide evidence that in cachexia, the liver, while facing increased energy demand as to comply with the conversion of tumour-derived lactate into glucose *de novo* (Cori cycle), shows decreased capacity to oxidize fatty acids, its main energy substrate. Additionally, immune cell infiltration, fibrosis and hepatocyte morphological changes, all reported in rodent models, further contribute to liver function impairment in the scenario. We shall discuss the changes in liver metabolism and morphology, as well as the possible consequences to the outcome of the disease in weight stable and cachectic colorectal cancer patients.

J4 *(9 minutes + 2 minutes discussion)*

Transcriptional reprogramming of hepatocyte function in cancer cachexia

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Cancer cachexia is a multi-factorial metabolic wasting condition classically characterized by massive loss of fat tissue and skeletal muscle mass, whereas the liver has received relatively little attention in this context, despite its central role in other metabolic diseases. While some recent studies have reported changes in hepatic function that are likely to contribute to peripheral tissue and overall body wasting, such a role remains to be formally demonstrated by liver-specific intervention.
Here, we investigated the effects of cachexia progression on the chromatin and gene landscape in hepatocytes. To circumvent potentially confounding signals from infiltrating immune cells, we have applied an approach relying on transgenic labeling and affinity-based pulldown of nuclei to generate maps of the hepatocyte chromatin and gene landscapes in murine cachexia. These analyses revealed a cachexia-associated hepatocyte transcriptional landscape, clearly distinguishable from that in healthy or weight stable cancer bearing mice. Using integrative computational analyses, we have generated models of intrahepatic crosstalk and immune cell recruitment and predicted key transcriptional regulators of the cachexia-associated gene program in hepatocytes. These include the core clock repressor Rev-erbα, which was downregulated in cachectic mice, and hepatocyte-specific overexpression of which attenuated loss of adipose tissue, muscle, and heart mass in cancer cachexia. Mechanistically, hepatocyte clock disruption promotes expression of several cachexia-induced genes encoding secreted proteins, capable of promoting adipocyte lipolysis and/or myotube and cardiomyocyte atrophy in *in vitro* cultures. The serum levels of these secreted proteins further associate with cachexia progression in human cancer patients. Collectively, our work outlines novel liver centric communication pathways involved in cancer cachexia progression.

K1 *(9 minutes + 2 minutes discussion)*

Muscle stem cells in age and disease

Julia von Maltzahn
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Skeletal muscle has diverse functions in the organism and a remarkable ability to adapt to physiological demands such as growth, training and injury. Furthermore, it is one of the organs with the highest ability to regenerate, a process depending on muscle stem cells. During aging muscle stem cell numbers are reduced, but most importantly their functionality decreases resulting in impaired regeneration of skeletal muscle. The reduced regenerative capacity of skeletal muscle can be attributed to intrinsic changes in muscle stem cells, changes in their niche as well as systemic changes and changes in supporting cells.
Changes in JAK/STAT signaling in muscle stem cells, reduced systemic levels of the anti-aging hormone klotho as well as changes in the extracellular matrix are examples for age-related changes affecting muscle stem cell functionality and thereby regeneration of skeletal muscle in the aged. However, inhibition of aberrantly active signaling pathways such as the JAK/STAT signaling pathway or replenishing klotho levels allows the improvement of regeneration in the aged.
Muscle mass and muscle stem cell functionality are impaired in conditions like cancer cachexia showing similarities to the aging process. Here, we could demonstrate that the extracellular ligand Wnt7a is able to counteract muscle wasting in cancer cachexia through activation of the AKT/mTOR pathway and to improve muscle stem cell functionality.

K2 *(9 minutes + 2 minutes discussion)*

Neurofibromatosis type 1-associated muscle weakness traces back to muscle stem cell metabolic reprogramming in a mouse model

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Introduction: Neurofibromatosis type 1 (NF1) is a multi-organ disease caused by mutations in Neurofibromin (*NF1*). NF1 patients frequently show reduced muscle mass and strength, impairing patients' mobility and increasing the risk of fall. The role of *NF1* in muscle and the cause for the NF1-associated myopathy is mostly unknown.
Methods: We used conditional inactivation of *Nf1* in mice to assess the cell-autonomous function in the myogenic lineage.
Results: Conditional loss of *Nf1* caused decreased postnatal growth, reduced muscle size, and fast fiber atrophy. Proteome and transcriptome analysis indicated decreased protein synthesis and increased proteasomal degradation, and decreased glycolytic and increased oxidative activity in muscle tissue confirmed by high-resolution respirometry. *Nf1*-deficient muscles showed decreased mTORC1 activation and increased expression of atrogenes. Loss of *Nf1* promoted fatty acid catabolism and induction of genes encoding catabolic cytokines, in line with a drastic reduction of white, but not brown adipose tissue resulting in an overall cachectic appearance. Intriguingly, *Nf1* was not required in muscle fibers, but specifically in early postnatal muscle stem cells (MuSCs), where *Nf1* loss led to cell cycle exit and differentiation blockade, depleting the MuSC pool resulting in reduced myonuclear accrual. This was caused by precocious induction of stem cell quiescence coupled to metabolic reprogramming of MuSCs impinging on glycolytic shutdown, which was conserved in muscle fibers. We show that a Mek/Erk/NOS pathway hypersensitizes *Nf1*-deficient MuSCs to Notch signaling, consequently, early postnatal Notch pathway inhibition ameliorated premature quiescence, metabolic reprogramming and muscle growth in our model.
Conclusions: We reveal an unexpected role of Ras/Mek/Erk signaling supporting postnatal MuSC quiescence in concert with Notch signaling, which is controlled by *Nf1* safeguarding coordinated muscle growth and MuSC pool establishment. Furthermore, we propose transmission of MuSC metabolic reprogramming across cellular differentiation, affecting fiber metabolic and proteostatic homeostasis, altering cross-tissue communication and mobilization of lipid reserves.

K3 *(9 minutes + 2 minutes discussion)*

Fibro-adipogenic progenitors coordinate muscle regeneration

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Fibro-adipogenic progenitors (FAPs) are a unique population of muscle-resident mesenchymal stromal cells that are the source of fibrosis and adipogenic infiltration in disease or age. Nevertheless, FAPs are essential for muscle regeneration and provide a beneficial microenvironment for muscle stem cells (MuSCs). Factors that intrinsically regulate FAPs pro-regenerative function are unknown, and mechanisms that balance between beneficial and detrimental effects of FAPs are not well understood. We previously identified the transcription factor Osr1 as a marker for an embryonic FAP-like cell pool that is required for developmental myogenesis. In adult mice, Osr1 is not expressed in FAPs under homeostatic conditions, but re-expressed specifically in FAPs activated by acute injury. Conditional inactivation of Osr1 concomitant with muscle injury led to delayed formation and smaller size of regenerating fibers as well as persistence of eMyHC^{+} fibers suggesting impaired regeneration. Osr1^{-}deficient FAPs showed reduced proliferation and increased apoptosis resulting in decreased cell numbers, as well as a skew in their differentiation capacities with increased propensity towards fibrogenic conversion. Transcriptome analysis of FAPs on different timepoints after injury suggested that Osr1 is upstream of secreted signaling molecules mainly targeting the inflammatory response, as well as extracellular matrix (ECM) and ECM-modifying factors in part paralleling its developmental function. In line, macrophage polarization was affected in Osr1 mutants indicating a function of Osr1^{-}FAPs in coordinating the acute injury-associated immune response. Moreover, persistence of fibrotic tissue and lower tissue stiffness reflected the pro-fibrogenic capacity of Osr1-deficient FAPs and indicated a lasting defect in ECM turnover. In vitro matrix deposition assays confirmed that ECM produced by Osr1-deficient FAPs failed to promote muscle formation. In sum, Osr1 is required for efficient muscle regeneration, orchestrating both the post-injury immune response as well as MuSC-dependent muscle regeneration via a complex array of secreted signaling molecules and ECM cues.

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K4 *(9 minutes + 2 minutes discussion)*

Muscle stem cells drive post-sepsis skeletal muscle recovery and regeneration

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Persistent loss of skeletal muscle mass and function is frequently observed in severe sepsis survivors. Studies examining sepsis-associated tissue wasting from a stem cell/regeneration perspective are scarce. With our work we aimed to better define and understand 1) the regenerative properties/potential of post-sepsis skeletal muscle, 2) molecular and biochemical changes occurring in the post-sepsis skeletal muscle microenvironment, and 3) the role of muscle stem cells (i.e. satellite cells) in post-sepsis muscle recovery. Our data show that muscle regeneration is involved in post-sepsis muscle recovery and that sepsis triggers persistent molecular changes in stem cells and the broader tissue microenvironment. We further highlight several opportunities to combat long-term post-sepsis muscle wasting. Moving forward, we strive to leverage a more complete understanding of post-sepsis regenerative defects to identify and test novel therapies that promote muscle recovery and improve quality of life in sepsis survivors.

L1 *(9 minutes + 2 minutes discussion)*

Abnormal liver-bone-muscle axis in cancer cachexia

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Colorectal cancer (CRC) is frequently accompanied by the development of cachexia, a multi-systemic wasting syndrome that affects the majority of patients, especially when the disease recurs with liver metastases (LMs). Muscle and bone loss are amongst the most detrimental symptoms of cachexia and directly cause increased morbidity and mortality. We have shown that CRC also promotes metabolic and genomic perturbations of the liver (1), and that formation of LMs exacerbates muscle and bone wasting. Recent evidence has shown that the liver not only plays a crucial role in whole-body metabolic homeostasis, but also acts as an endocrine organ by secreting *'hepatokines'*, some of which are known to influence musculoskeletal health (2). In this regard, IGFBP1 – a liver-derived hormone belonging to the insulin-like growth factor family of binding proteins (IGFBPs) – was reported to directly promote osteoclastogenesis and bone resorption by binding to the integrin b-1 (ITGB1) receptor on the osteoclast surface (3), whereas high levels were found to correlate with sarcopenia and reduced BMI. Moreover, in line with the idea that tumor growth promotes changes in the hepatic microenvironment that ultimately support and influence cancer outcomes, IGFBP1 was shown to influence tumor progression and to correlate with CRC risk and survival in cancer patients. In our preliminary studies, we observed high IGFBP1 circulating levels in cachectic CRC patients. Recombinant IGFBP1 promoted myotube atrophy and osteoclast differentiation. MC-38 CRC hosts displayed muscle and bone loss, along with elevated plasma IGFBP1 levels. Similar to hepatocyte-CRC mixed cultures, mice bearing C26 LMs exhibited markedly increased liver and circulating IGFBP1, in line with exacerbated musculoskeletal wasting. Anti-IGFBP1 antibodies prevented tumor-induced myofiber atrophy and osteoclastogenesis in cultures, whereas IGFBP1 knock-outs (KOs) and mice with AAV-mediated depletion of liver IGFBP1 were protected against CRC-induced bone loss and muscle wasting. Altogether, our data implicate IGFBP1, an exquisitely liver-derived factor, as a novel mediator of musculoskeletal deficits in CRC cachexia and supports novel strategies to counteract host-derived factors in the treatment of cancer-associated multi-organ complications.

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L2 *(9 minutes + 2 minutes discussion)*

Impact of exercise and chemotherapy on the respiratory neuromuscular system

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Exercise intolerance and fatigue are debilitating symptoms affecting up to 70% of cancer patients. These effects often persist after the cessation of treatment and significantly compromise prognosis and quality of life. The presentation of exertional dyspnea and the sensation of breathlessness are often a consequence of respiratory insufficiency and are caused in part by respiratory muscle dysfunction. Chemotherapy-related diaphragm dysfunction causes impaired ventilation that is independent of any tumor effects. Therefore, defining the mechanisms of chemotherapy-induced diaphragm pathology is critical to alleviating breathing discomfort and inhibiting physiological changes related to respiratory muscle weakness in cancer patients and survivors. Direct effects to the diaphragm muscle include mitochondrial dysfunction, oxidative damage, and protein degradation, resulting in muscle fiber atrophy. However, neuronal pathology also occurs following the use of many chemotherapeutics, which may contribute to the development of respiratory dysfunction. In particular, the anthracycline doxorubicin has been shown to have neurotoxic effects, including nerve fiber degeneration and axonal swelling, but it is currently unclear whether doxorubicin treatment elicits defects to the phrenic nerve or impairs neuromuscular transmission. Our work in this area has identified a link between phrenic motoneuron morphology, the phrenic-diaphragm neuromuscular junction and diaphragm function following exposure to doxorubicin. Importantly, exercise preconditioning can stimulate beneficial adaptations to the respiratory neuromuscular system resulting in improved respiration, and reduced diaphragm fatigue and weakness.

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L3 *(9 minutes + 2 minutes discussion)*

Cancer-induced muscle and bone deficits

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Various primary and metastatic cancers are associated with deficits in the skeletal muscle and bone. Muscle and bone share close mechanical and biochemical relationship, giving rise to a muscle-bone crosstalk. Both tissues release either muscle-derived myokines or bone-derived osteokines that positively or negatively affect bone and muscle metabolism. Several secreted molecules and extracellular vesicles have been recently identified that contribute to cancer cell growth and metastasis leading to bone destruction and muscle atrophy. The pathological crosstalk between bone and muscle in cancer involves, among other factors, TGF-β, which is released from the bone matrix upon cancer-induced bone destruction and impairs muscle function [1]. Recently, tumor-derived RANKL was demonstrated to increase bone turnover and skeletal muscle atrophy in cancer-bearing mice [2]. Consistently, treatment anti-RANKL antibody or bisphosphonates that inhibit bone resorption preserved bone and partially prevented the loss of muscle mass and strength. Moreover, the administration of bisphosphonates in mice exposed to a chemotherapeutic agent had beneficial effect on muscle mass and strength, acting through bone preservation and inhibiting the release of bone-derived factors upon bone resorption. Hence, pharmacological approaches for bone health could be efficient in preserving muscle mass and function in the context of cancer. In this presentation, most recently identified mechanisms implicated in cancer-induced bone and muscle defects will be discussed. A better understanding of the pathways involved in cancer-mediated bone resorption and muscle wasting may provide new insights for discovering novel antiresorptive, anticachectic and possibly anticancer therapies.

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L4 *(9 minutes + 2 minutes discussion)*

A prospective study of hand-grip strength to predict mortality in patients with cancer with and without cachexia

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Hand grip strength (HGS) is widely used as a criterion for cancer cachexia. The aim of this study was to evaluate the prognostic value of HGS in patients with advanced cancer without significant cardiovascular disease or active infection at baseline and to establish reference values for a European-based population.

M1 *(9 minutes + 2 minutes discussion)*

Sex-dependent response of adipose tissue and lipid metabolism in cancer cachexia

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Differences between males and females exist in lipid metabolism and storage of fat which presents an often overlooked source of variation in clinical studies. Males generally store fat into the visceral region and females in the gluteofemoral region under the influence of sex hormones. Not only does the location of adipose tissue vary but also the function and behavior of adipose tissue. Sex-specific ranges for adipose tissue depots have been defined and have prognostic value in the oncology setting. Differences according to sex also exist for measures of fatty acid status which may have implications for nutritional interventions with n-3 fatty acids. Sex considerations in research in the oncology setting are required.

M2 *(9 minutes + 2 minutes discussion)*

Tumor microenvironment evolution and its relevance to cachexia

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TRACERx is a UK-wide national prospective lung cancer evolution programme in which patients with stage I-IIIB surgically resectable non-small cell lung cancer (NSCLC) undergo tumour sampling of primary, recurrent and subsequent progressive disease, in addition to blood sampling for circulating biomarker analysis (1, 2). TRACERx has established a longitudinal resource of tissue and blood, as well as CT imaging and detailed clinical annotation, in over 800 patients with NSCLC from early to late stage disease. Such a resource can be used to investigate the prevalence of weight loss and alerted body composition, in keeping with the cachexia phenotype, and adopt a discovery approach to help identify the potential mediators of this phenotype by integrating genomic and transcriptomic studies with clinical phenotyping. Furthermore, the use of multi-region tissue sampling performed in TRACERx can facilitate the study of heterogeneity in relation to tumour metabolism, tumour microenvironment (TME) and immune landscape. Using CT imaging at diagnosis and at relapse, patients who develop features of cachexia can be identified, and by integrating their respective tumour-intrinsic and -extrinsic studies, we can begin to shed light on the potential mediators involved in the cachexia cascade. Preliminary data from TRACERx in patients who develop cachexia, compared to those who do not, at the point of first relapse has shown distinct genomic alterations and differential signalling pathways, differences in the lung microbiome and cell subsets in the TME, and specific peripheral T cell phenotypes warranting further investigation in future studies.

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M3 *(9 minutes + 2 minutes discussion)*

Sex variation in cachexia

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Past research has been focused on understanding how diseases affected humans, but the vast majority had been done on men and the scientific community assumed that the effects were simply the same in women. Nowadays, there is a tendency to worry about the impact of the diseases on women because doctors began to recognize that sex has a different impact on them, not only in the physical effects but also on the treatment response[1].

Exactly the same happened (and happens) in experimental models: only males have usually been used, meaning that there is an important lack of data concerning the female response due to the cachexia. Current research is demonstrating that males and females are clearly different on some aspects related with muscle metabolism and fiber composition. An exhaustive review from Rosa-Caldwell and Greene on muscle phenotype and physiology between males and females defines how the differences may contribute to differential responses to atrophic stimuli. Accordingly to the reviewed results, females appear to be more susceptible to disuse induced muscle wasting but they show a protection from inflammation induced muscle wasting compared to males. They suggest that this protection may be due to the differences in muscle protein turnover, satellite cell content and proliferation, hormonal interactions, or mitochondrial function[2].

Another recent revision highlights the sex differences in manifestations of cancer cachexia: male cancer patients generally have higher prevalence of cachexia, greater weight loss and worse outcomes compared with female cancer patients, and this could be attributed to the composition of muscle fibers, mitochondrial function, differential effects of hormones and also sex chromosomes (with a possible relevant role of miRNAs) among others. Females seem to be protected in some way from cachexia because of their resistance to fatigue and better mitochondrial quality[3].

But still there are only a few articles about that therefore it is evident that more studies specifically examining muscle effect in females suffering from cachexia are necessary to more fully understand the sex-based differences between both males and females and especially how they may affect different clinical treatments. The medical community faces a long way to reach the same amount of knowledge in women, but it is our responsibility to make it happen, and to start the research as soon as possible on the effects of cachexia on women.

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M4 *(9 minutes + 2 minutes discussion)*

Tumor-specific ribosomal deficits in muscle wasting

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Cancer-induced muscle wasting is facilitated by a reduced capacity for protein synthesis. The ribosomal capacity of the muscle is of primary importance in determining protein synthesis rates, and is modulated by transcription of the ribosomal (r)RNA genes (rDNA)[1,2]. We recently showed that muscle wasting in ovarian cancer is accompanied by a diminished ribosomal capacity as a consequence of impaired rDNA transcription[3]. However, whether ribosomal-driven anabolic deficits result from other types of tumors remains to be determined. To address this gap in knowledge, we investigated ribosomal deficits in pre-clinical models of lung (LC) and colorectal (CRC) cancer. First, we examined two different LC models. Both LP07 and Lewis lung carcinoma (LLC) tumors resulted in similar reductions in gastrocnemius muscle mass. The LP07 tumors caused a reduction in ribosomal (r)RNA and a decrease in rDNA transcription elongation, while no changes in ribosomal capacity were evident in LLC hosts despite a two-fold higher tumor mass. These findings suggest that despite both tumor types targeting the lungs, ribosomal deficits highlight tumor type-specific anabolic suppressing mechanisms between these LC models. We then focused on the impact of tumor burden on muscle wasting in xenograft (x) and metastatic (m) models of colorectal cancer (CRC). Mice injected subcutaneously or intrasplenically with HCT116 or C26 tumor cells underwent significant muscle wasting regardless of tumor type or model, although muscle loss was more pronounced in mHCT116 hosts. The mHCT116 model decreased rRNA content and rDNA transcription initiation, while the mC26 tumor showed no loss of rRNA and the upregulation of rDNA transcription initiation and elongation. Collectively, our findings revealed novel tumor-specific mechanisms of anabolic deficits via reductions of ribosomal capacity consequent to impaired rDNA transcription initiation, elongation or both. In some pre-clinical models, muscle wasting does not involve reductions in ribosomal capacity at the time point studied. Because chemotherapeutic agents can also impair muscle ribosome production[4], understanding the regulatory mechanisms impairing rDNA transcription will be critical for the development of effective therapeutic interventions to prevent or ameliorate muscle wasting in cancer sufferers.

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N1 *(9 minutes + 2 minutes discussion)*

Integrated evaluation of body composition in the oncology setting: paradigm change

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Weight loss is prevalent in oncologic patients, usually accompanied by alterations in body composition, including muscle wasting. These alterations have a multifactorial aetiology secondary to insufficient caloric intake, antineoplastic treatment, and metabolism alterations, such as increased rest energy expenditure, chronic inflammation and other factors produced by tumour cells, which maintain the process of proteolysis and lipolysis constantly active.

Low body mass index (BMI) has a negative impact on the prognosis of cancer patients[1], however, patients with similar BMI may have different body composition. Computed Tomography (CT) Scan has shown precision evaluating body composition, including muscle mass.

Sarcopenia is a disease, characterized by the reduction of muscle strength, in association with the reduction of muscle quantity or quality[2]. It has impact on prognosis, quality of life, surgical complications, toxicities associated with antineoplastic treatments and increased costs to healthcare institutions[3,4,5,6]. Oncologic patients with sarcopenic obesity are at particular risk of increased toxicities and worst prognosis.

The evaluation of body composition in cancer patients with CT scan, provides valuable information, identifying those in need of special care before and after surgery, and those in need of close monitorization or dose optimization due to expected toxicities of systemic treatment.

Body composition alterations in cancer patients are a multifactorial problem that requires a multimodal approach with pharmacologic treatment, physical exercise, and personalised nutritional intervention.

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N2 *(9 minutes + 2 minutes discussion)*

Nutrition options in 2022: what is on the market?

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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 a strong tendency toward catabolism and a negative protein–energy balance that is difficult to restore. The reversal or prevention of cancer cachexia and muscle wasting represent a major clinical challenge, thus urging an adequate, early and integrated nutritional intervention throughout the disease course and treatments.
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. 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. Clinical studies do show potential benefits for some specific nutrients, specially when combined with exercise training.
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. Thus, a higher range of protein intake (1.2–1.5 g/kg/ day) seems needed to promote muscle mass balance. Research is needed to determine clinical effect and feasibility of high protein intake and the optimal composition of amino acids.
*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, although future investigations in the efficacy of BCAAs alone in different 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, thus, HMB has been investigated as a potentially effective nutritional supplement. Currently, HMB supplementation has a beneficial effect on muscle mass and function in patients with cancer. 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 in individuals at risk for body composition alterations. High protein oral nutrition supplements enriched with EPA may help ameliorate weight and muscle mass loss to a greater extent than isocaloric control supplements.
Glutamine is a non-essential amino acid that has many roles in human metabolism and can become conditionally essential in disease states. It is recommended that its benefits should be explored for the prevention/treatment of low muscle mass, given the potential to ameliorate treatment side effects. 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. Studies conducted are rather small, included distinct cancer populations and had short durations. 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 functionbut 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 showed 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; in older adults low levels have been associated with loss of appendicular skeletal muscle and adequate levels have been associated with improved muscle function. 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.

N3 *(9 minutes + 2 minutes discussion)*

Nutrition in ambulatory cytotoxic treatment: new data on the role of the clinical pharmacist

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Ambulatory oral cytotoxic therapy (AOCT) presents increasing challenges for professionals: complex dose regimens, toxicity, adverse reactions, need for strict monitoring, clinically relevant drug-food interactions, risks with skipping daily dose, lack of compliance. Cancer treatment is multidisciplinary and inclusive, thus more demanding. Notably, malnutrition is frequent in oncology and relates to reduced QoL, treatment(s) response and survival.
We aimed to evaluate: risk of undernutrition, AOCT compliance, and feasibility of pharmaceutic intervention in the multidisciplinary team (Oncology/Haematology). Therapeutic management and nutritional risk were assessed and the feasibility of pharmaceutical intervention was tested in the multidisciplinary team in the day hospital (Oncology and Haematology) through transversal, observational, analytical study, in 72 consecutive adult outpatients (outpts) with solid/haematologic cancers under AOCT.
Applying the Morisky/Green Therapeutic Adherence Test and the PG-SGA nutritional assessment in a sample of 72 patients aged 66±13 (20-92) years, where 57% are female, and prevalent diagnoses were multiple myeloma(n=12/72), cancer of breast (n=13/72), prostate(n=8/72); 42% of the patients reported difficulties/uncertainties about the prescribed OCT: dose, adverse effects, interactions, adequate diet during treatment, correct administration, differences between therapies. Of note that 49% had adverse reactions during OCT: generalized skin rash, variations in blood pressure/heart rate, GI or systemic symptoms. Notably 17%outpts did not comply with OCT, yet outpts started therapy, but discontinued it without notification, due to limiting adverse reactions. Significant weight loss in 6-months occurred in 33%outpts; 25% gained significant weight. As for symptoms, 63%outpts recognized substantial limitations of intake due to pronounced fatigue, pain and xerostomia; 30% acknowledged the need of nutrition intervention/counselling and appropriate symptom control, to maintain adequate nutrition.
The Pharmacist now integrates multidisciplinary team for treatment decision, of all patients with cancer. A 100% acceptance rate of pharmacist intervention was reported by outpts and attending physicians. All outpts identified its need in a systematic and mandatory fashion; physicians identified the added value of a pharmacist as a differentiated element to manage pharmacologic issues, interactions, concerns.
In conclusion, this study substantiates the need to optimize the follow-up of cancer patients under active OCT in the ambulatory setting. More than half outpts had worrying weight changes, that represent by themselves a “red flag”, since significant weight oscillations during cancer treatment proved to be deleterious. Patients and physicians praised the integration of pharmaceutic intervention for drug control and nutrition.
Given that patients go to the outpatient clinic of the Hospital Pharmacy to collect their medication, this timing is likely to be the proper opportunity for pharmaceutical intervention: it is the appropriate place, time, and assembles the structural, organizational and human resources in this setting.
To full fill this pharmaceutical intervention necessity, it was elaborated a protocol of a pharmaceutical follow up appointment, to take place at the day hospital of oncology department of Hospital Santa Maria.

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N4 *(9 minutes + 2 minutes discussion)*

Head and neck cancer and sarcopenia – a high risk cancer and higher risk treatments

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Sarcopenia refers to the gradual loss of skeletal muscle mass (SMM) and strength (e.g. hand grip strength or gait speed) as defined by the European Working Group on Sarcopenia (EWGSOP). Since muscle function is not measured frequently and SMM can be determined retrospectively, the terms sarcopenia and low SMM are often used interchangeably.
Patients at high risk of development of sarcopenia are the elderly and patients with underlying disease e.g. cancer. Since, a chronic systematic inflammatory process may be induced due to the microenvironement of the tumor itself, cancer patients are at high risk of development of (secondary) sarcopenia. In head and neck cancer (HNC) patients, this may be accompanied by the fact that the tumor location causes dysphagia and malnutrition or even a catabolic state at the time of diagnosis, which in turn can trigger the development of sarcopenia. The most commonly used method for SMM assessment is measuring the cross-sectional skeletal muscle area (CSMA) of all skeletal muscles on a single slice at the level of the third lumbar vertebra (L3) on abdominal CT imaging. However, abdominal CT imaging is unfortunately not routinely performed in HNC patients or is only available in patients with advanced disease. Therefore, a novel method for measurements of SMM in HNC patients was developed and validated measuring the CSMA of the paravertebral and both the sternocleidomastoid muscles on a single slice at the level of the third cervical vertebra (C3). A multivariate formula including gender, age and weight was created to estimate the lumbar skeletal muscle index (LSMI) from the CSMA at the level of C3 with a strong to excellent correlation as a result. Both the interobserver and intraobserver agreement has been proven to be excellent. CSMA measurements on the level of C3 can be performed on both CT and MRI of the head and neck are interchangeably since a high correlation was found. The prevalence of sarcopenia in oncological patients varies considerably due to the use of different cut-off values. Most used cut-off values in the field of research are the ones defined by Prado et al. and Martin et al. (1). However, both Prado et al and Martin et al used their stratification analysis in (obese) patients with respiratory or gastrointestinal malignancies. In addition, these cut-off values are based on CSMA measured at the level of L3. Wendrich et al established a cut-off value of LSMI <43.2 cm2/m2 in a group of HNC patients (2). This cutoff value is applied in various studies in HNC patients. Using this (or a comparable) cutoff value the prevalence of sarcopenia in HNC patients is about 50% in most of the studies. This relatively high percentage is most likely due to the high incidence of dysphagia and malnutrition in this group of patients. Radiologically assessed low SMM has become an important predictive and prognostic biomarker in HNC patients. In HNC patients undergoing chemoradiotherapy, a low SMM has been proven to be predictive for dose-limiting toxicity (DLT) defined as dose-reduction of ≥ 50% (e.g. due to neutropenia or nephrotoxicity), a postponement of treatment of ≥ 4 days (e.g. in the case of bone marrow suppression) or a definite termination of chemotherapy after the first or second cycle of therapy (2). In HNC patients undergoing solely radiotherapy, a low SMM has been demonstrated to both acute as late adverse events like oral mucositis, dysphagia and aspiration pneumonia. Evidence that low SMM is associated with higher rates of surgical complications is mounting (3). Severe postoperative complications such as pharyngocutaneous fistula after total laryngectomy, free flap reconstruction related complications like wound disruption and venous thrombosis, pneumonia, prolonged ventilation and delirium have been described to be associated with low SMM. These complications may result in longer intensive care unit stay and longer length of hospital stay. In addition, multiple meta-analyses and studies have indicated that low SMM is predictive of reduced survival in HNC patients. This is true for both disease free survival, disease specific survival and overall survival. The measurement of low SMM on routinely performed CT or MRI imaging holds the potential to become a viable prognostic tool in the clinical decision making of HNC patients. Identification of high-risk patients allows for alternative treatment planning. Studies are currently underway on alternative cisplatin dosing and surgical treatment planning in patients with low SMM and high risk for treatment related toxicity and complications. Future research is needed on patients undergoing prehabiliation, involving exercise and nutrition programs, to improve low SMM before start of treatment and whether this could affect treatment outcomes and survival.

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O1 *(9 minutes + 2 minutes discussion)*

Early neutrophilia marked by aerobic glycolysis sustains host metabolism and delays cancer cachexia

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Understanding the longitudinal events that drive cancer associated cachexia is important. An elevated neutrophil-to-lymphocyte ratio negatively predicts the outcome of patients with cancer and is associated with cachexia. Here, we show using murine model systems of colorectal and pancreatic cancer that neutrophilia in the circulation and multiple organs, accompanied by extramedullary hematopoiesis, is an early event during cancer progression. Transcriptomic and metabolic assessment reveals that neutrophils in tumor-bearing animals utilize aerobic glycolysis, alike to cancer cells. Although pharmacological inhibition of aerobic glycolysis slows down tumor growth in C26 tumor-bearing mice, it precipitates cachexia, thereby shortening overall survival. This negative effect may be explained by our observation that acute depletion of neutrophils in pre-cachectic mice impairs systemic glucose homeostasis secondary to altered hepatic lipid processing. Thus, changes in neutrophil number, distribution and metabolism play an adaptive role in host metabolic homeostasis during cancer progression. Our findings provide insight into early events during cancer progression to cachexia, with implications for therapy.

O2 *(9 minutes + 2 minutes discussion)*

Tumor-derived cachexia mediators and biomarkers

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Cancer cachexia (CCx) is a multifactorial condition characterized by involuntary loss of body weight, which negatively affects quality of life, efficacy of tumor treatment, and ultimately survival of cancer patients [1]. We performed a quantitative secretome analysis to identify specific factors more abundantly secreted by cachexia-inducing cancer cell lines as compared to cancer cell lines, which do not induce wasting following implantation into mice. By these means, we identified the secreted phospholipase A2 group VII (PLA2G7) as novel, potential biomarker of cancer cachexia in mice and humans [2]. Circulating PLA2G7 activity was increased in different mouse models of CCx, and was associated with the severity of tissue wasting. Consistently, increased PLA2G7 levels were also a marker of CCx in independent cohorts of colorectal and pancreatic cancer patients. Moreover, by receiver operating characteristic (ROC) curve analysis, we demonstrated that both plasma PLA2G7 protein and enzymatic activity levels significantly distinguished cachectic and non-cachectic patients with pancreatic cancer. Despite no immediate pathogenic role, the early increase in circulating PLA2G7 levels in pre-cachectic mice supports future prospective studies to assess its potential as biomarker for early detection of cancer patients at risk to develop cachexia as well as to assess cachexia treatment response.
Furthermore, by functionally characterizing additional tumor-secreted proteins both in vitro and in vivo, we identified a novel mediator of cachexia contributing to muscle atrophy and adipose tissue wasting. Knockdown in cachexia-inducing C26 cells markedly reduced the capacity of these cells to induce myotube atrophy and adipocyte lipolysis in vitro, as well as cachexia development upon implantation into mice. In this presentation, we will discuss the first data on the underlying molecular mechanism and the assessment as a therapeutic target for cachexia treatment.

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O3 *(9 minutes + 2 minutes discussion)*

Tumor-derived extracellular vesicles

Paola Costelli
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Extracellular vesicles (EVs) mediate the intercellular exchange of classical soluble and insoluble signaling factors, as well as of structural proteins, nucleic acids and lipids; they can be released in the circulation and convey functional information to distant sites. EVs can be secreted by many cell types, including tumor cells (1).
Tumor-derived EVs can alter the homeostasis of the tumor microenvironment by directly targeting fibroblasts, endothelial and immune cells or by altering the structure and composition of the extracellular matrix (1). Consistently, EVs derived from pancreatic cancer mediate the cross-talk between the tumor and its microenvironment (2). Few studies suggested that EVs are also involved in the pathogenesis of muscle wasting in cancer cachexia. Indeed, lung cancer- and pancreatic tumor-derived EVs induce apoptosis of skeletal muscle cells. In particular, miR-21 secreted through EVs activates Toll-Like Receptor (TLR)7 on murine myoblasts and promotes apoptosis through c-Jun N-terminal kinase (3). In addition, tumor-derived EVs, likely due to their miR content, impinge on oxidative metabolism and mitophagy in cultured myotubes and EVs isolated from tumor-bearing mice transiently cause muscle wasting when infused into healthy animals. Last, but not least, tumor-derived EVs also appear to impinge on myogenic differentiation in C2C12 cultures (4).
The picture above supports the idea that cancer cells use EVs as an additional mean to
transmit specific signals to both the tumor microenvironment and distant tissues such as the skeletal muscle. In this latter, EVs likely contribute to generate the atrophic phenotype characterizing cancer cachexia. Along this line, tumor-derived EVs could become one of the potential targets of anticancer/anti-cachexia strategies that could be designed to include
tools able to modulate EV secretion and/or fusion with myofibres or to antagonize specific sncRNAs vehicled by EVs.

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O4 *(9 minutes + 2 minutes discussion)*

KLF10: a novel mediator of cancer-associated skeletal muscle wasting

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Cancer cachexia represents a significant roadblock to better cancer outcomes. Many potential therapies have been proposed and tested – including appetite stimulants, targeted cytokine blockers, and nutritional supplementation – yet effective therapies remain elusive. Thus, new approaches are warranted. Members of the Kruppel-like factor family play wide-ranging and important roles in the development, maintenance, and metabolism of muscle. With our work we 1) identified KLF10 upregulation as a defining feature of wasting muscle in multiple murine cancer models and human datasets, 2) performed loss-of-function and gain-of-function experiments to query KLF10 necessity and sufficiency in the context of muscle wasting, and 3) linked KLF10 to TGF beta-associated wasting/atrogene induction. Taken together, we report a novel role for KLF10 in wasting muscle and highlight the potential utility of KLF10 inhibition as a strategy to counteract cancer-associated muscle wasting.

P1 *(9 minutes + 2 minutes discussion)*

Exercise and tumor control: expanding the field of exercise oncology to cancer progression and cachexia

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The last two decades has witnessed a significant increase in research and clinical interest in exercise therapy in individuals diagnosed with cancer. The vast majority of work to date in the field now known as “exercise oncology” has focused on the role of exercise therapy to attenuate cancer treatment-related toxicities during anticancer therapy as well as improve toxicity-related late effects in patients following the completion of therapy. In recent years, a corollary line of investigation has emerged evaluating whether the benefit of exercise therapy extends beyond symptom control to impact tumor-related outcomes such as therapeutic response and risk of cancer recurrence or progression. In this presentation, Dr. Jones will adopt a translational approach to overview published as well as unpublished evidence of exercise on cancer pathogenesis.

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P2 *(9 minutes + 2 minutes discussion)*

Cardiac wasting in cancer

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Cachexia is a commonly reported in cancer patients and its prevalence varies among different cancer types and stages. Many signs and symptoms are associated with cancer cachexia, including involuntary weight loss, asthenia, fatigue, impaired physical performance, and dyspnoea. Since these symptoms are also frequently observed in chronic heart failure we hypothesized that cancer patients suffer from a specific heart failure syndrome[1] associated with whole body wasting. Cachexia is characterized mainly by loss of skeletal muscles and adipose tissue but whether cachexia can extend to the cardiac muscle and cause clinically relevant impairments in cancer patients needs to be further investigated. Different studies on animals describe evidence of cardiac wasting and its association with different cardiac structural[2] and hemodynamic alterations[3] but this form of wasting and its clinical implications in patients remains understudied: two of most relevant studies on cardiac wasting in humans are based on autopsy reports[2, 4]. A third one describes loss of left ventricular (LV) mass over time in a small number of cancer patients and only in one cancer type[5]. This demonstrates that there are major knowledge gaps about the extent of cardiac wasting in patients with advanced cancer and whether this has pathophysiological consequences and prognostic value. In our prospective, observational study we aimed to assess cardiac wasting in cancer by measuring LV mass using transthoracic echocardiography. The presentation will show evidence of *cardiac wasting-associated cardiomyopathy* in 300 cancer patients and its association with clinical outcomes.

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P3 *(9 minutes + 2 minutes discussion)*

A review of the evidence for multi-modal interventions in cachexia management

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Cachexia is a complex multifactorial syndrome. The prevalence of cachexia is growing in line with rising numbers of citizens who have chronic illnesses, affecting about 0.5–1.0% of the population [1]. Cachexia can have a devasting holistic impact on both patients and their carers and currently there are no standardized direct treatments for this syndrome. Reflective of the multifactorial pathogenesis of cachexia, recent trials have adopted multimodal interventions consistent with scientific consensus, which supports combination therapy that includes exercise, nutritional support, and anti-inflammatory agents to treat the severe wasting [2]. It is thought that these components may act synergistically to improve nutritional and physical status, leading to positive primary and secondary outcomes, such as improvement in quality of life [3]. The number of citizens who have cachexia and its consequential impact underscores the significance of this research direction. This presentation will explore: the literature in relation to multimodal treatments that aim to alleviate and/or stabilize cachexia; and the role of the multidisciplinary team, the citizens who are affected by cachexia and their carers in future research.

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P4 *(9 minutes + 2 minutes discussion)*

ACTAs for cancer cachexia

Andrew Coats, Australia

Q1 *(9 minutes + 2 minutes discussion)*

MyomiRNA, systemic and local inflammation and muscle wasting

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Cancer cachexia has a complex pathophysiology in which systemic inflammation, impaired energy metabolism, loss of muscle and adipose tissues result in unintentional body weight loss and profound changes in body composition (1). In particular, not only cachexia negatively affects patients' prognosis, but the presence of skeletal muscle depletion reduces the tolerability to chemo/radio-therapy treatments (2). Besides inflammation, other mechanisms including circulating and tissue-specific factors could be implicated in the pathogenesis of muscle cancer-related muscle wasting and could also represent biomarkers and therapeutic targets of muscle wasting. Among these, non-coding RNAs (ncRNAs) are being progressively recognized as potential actors in a variety of physiological and pathological events including cell proliferation, differentiation and death, DNA repair, oxidative stress response and tissue catabolism (3). MicroRNAs (miRNAs), are a subset of ncRNAs consisting in short sequences of approximately 22 nucleotides detectable in different tissues, included the blood, where they may circulate either in extracellular vesicles or protein-bound. MyomiRNAs, alternatively myomiRs, are enriched in the skeletal muscle and have been proposed as potential drivers of cancer-induced muscle wasting (4). Whether MyomiRNAs act independently of, or in combination with systemic and local inflammation in promoting wasting is currently a matter of investigation. This topic is of particular clinical interest because, since MyomiRNAs can be detected both in muscle tissue and in the blood, they may represent on one side easily accessible and promising biomarkers of cachexia and, on the other, new targets for the development of specific strategies to counteract muscle wasting.

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Q2 *(9 minutes + 2 minutes discussion)*

FoxP1 is a transcriptional repressor associated with cancer cachexia that induces skeletal muscle wasting and weakness

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Skeletal muscle wasting accompanies several pathophysiological conditions, including cancer, sepsis, aging and nutrient deprivation. The loss of muscle mass is associated with structural and functional deterioration of skeletal muscles, which leads to reduced quality of life, and directly contributes to poor outcomes. Understanding mechanisms driving muscle wasting in these conditions may thus lead to novel treatments that preserve muscle mass and function, and improve long term outcomes and quality of life. In recent work we identified the transcriptional repressor protein, forkhead box P1 (FoxP1), as a novel downstream target gene of FoxO1 that is upregulated in multiple models of cancer cachexia and in muscle biopsies from cachectic cancer patients, with the levels of FoxP1 mRNA correlated positively with body weight loss, and negatively with CT-defined measures of skeletal muscularity (1). Based on these findings we investigated the role of FoxP1 in skeletal muscle mass regulation under baseline conditions, and in the context of cancer cachexia. We found that inducible skeletal muscle-specific FoxP1 overexpression ($FoxP1^{iSKmTg/Tg}$) in adult mice induced key features of cachexia, including body wasting and skeletal muscle wasting characterized by reduced cross-sectional area of type IIX/B muscle fibers (1). Although the oxidative soleus did not atrophy in FoxP1 iSkmTg/+ mice, it was significantly weaker, identifying an additional role for FoxP1 upregulation in muscle dysfunction. RNA sequencing of skeletal muscles from $FoxP1^{iSkmtg/tg}$ mice confirmed FoxP1 as a key transcriptional repressor in skeletal muscle, with enrichment of gene networks involved in cell quality control, muscle development and muscle function. Since FoxP1 has been shown in other cell types to promote gene repression through recruitment of histone deacetylase (HDAC) proteins to gene promoters, we treated $FoxP1^{iSkmtg/tg}$ mice with the HDAC inhibitor, Trichostatin A, and found that this prevented the induction of muscle wasting, thereby supporting HDAC proteins as key mediators of FoxP1-dependent effects in muscle. Our data further indicate that FoxP1 is also required for the normal atrophy response to cancer, as knockdown of FoxP1 in skeletal muscle attenuated fiber atrophy in the Colon-26 model of cancer cachexia (1), whilst mice conditionally deleted for FoxP1 in skeletal muscle displayed marked protection against muscle wasting in an orthotopic model of pancreatic cancer cachexia. Transcriptomic analyses suggest that FoxP1 may contribute to cancer-induced muscle loss, at least in part, through mediating the repression of target genes of the myocyte enhancer factor 2 (MEF2) and myogenic differentiation 1 (MYOD1) transcription factors that regulate muscle maintenance and function, and whose gain of function counter muscle wasting in mouse models of cancer (2). In summary, we identify FoxP1 as a novel transcriptional repressor in skeletal muscle whose upregulation is both sufficient to induce skeletal muscle wasting and weakness, and required for the normal wasting response to cancer.

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Q3 *(9 minutes + 2 minutes discussion)*

Beyond good and evil: Discovering novel anabolic targets to overcome cancer related-muscle wasting

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Chronic disease-related muscle atrophy is a serious public health problem since it reduces mobility and contributes to increases in hospitalization costs. Unfortunately, there is no approved treatment for muscle wasting at present. Thus, an understanding of the mechanisms underlying the control of muscle mass and function under chronic diseases can pave the way for the discovery of innovative therapeutic strategies to counteract muscle wasting. Since numerous types of cancer induce cachexia, which has no cure nor an effective treatment, our main proposal was to study the effects of Aerobic Exercise Training in cancer cachexia, and to investigate, through in vivo manipulation of the Akt/mTORC1 signalling pathway, whether the cachectic muscle still presents anabolic conditions to respond adaptively to hypertrophic stimuli. With our results we hope provide a basis for innovative research lines to better understand skeletal muscle plasticity, and to investigate potential therapeutic approaches necessary to prevent muscle wasting.

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Q4 *(9 minutes + 2 minutes discussion)*

Skeletal muscle mitochondrial dysfunction and lipid accumulation in breast cancer

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Cancer-cachexia progresses through distinct stages: 1) pre-cachexia, where individuals have not lost significant bodyweight but experience other cachexia-related symptoms; 2) cachexia, where patients have lost 5% or more of their pre-diagnosis body weight; 3) refractory cachexia, where body weight loss is irreversible. Perhaps due, in part, to established surveillance protocols, most patients diagnosed with breast cancer (BC) do not lose a significant amount of body weight and would be considered pre-cachectic. However, this does not necessarily imply that muscle dysfunction, in the form of persistent fatigue, is not adversely affecting patients' quality of life. It is important to understand that distinct and independent pathways within skeletal muscle are dysregulated in cancer patients presenting with symptoms of muscle fatigue and muscle wasting. The central hypothesis of the laboratory is that clinically relevant muscle fatigue occurs in early-stage BC in the absence of muscle wasting. Data from our laboratory in muscle from BC patients and in mouse models of BC suggest that dysregulation of the transcription factor peroxisome proliferator-activated receptor gamma (PPARγ) is central to this phenotype. The PPAR family of proteins are lipid sensing, ligand activated transcription factors implicated in a variety of pathologies. These transcription factors aid in regulating whole body energy homeostasis via regulation of genes involved in lipid metabolism and mitochondrial functions. Dysregulation of PPARγ may explain the accumulation of lipid in muscles of BC patients. Skeletal myotubes exposed to BC cell conditioned media show an increase in lipid with a distinct pattern that resembles lipid droplets, in addition to a deficiency of ATP synthesis that suggests mitochondrial dysfunction. Exogenous over-expression of PPARγ in myotubes rescues the lipid accumulation and mitochondrial dysfunction in this in vitro model system. However, a PPARγ agonist drug was only able to rescue the lipid accumulation. Basal expression of PPARγ protein in muscle is relatively low, proving an explanation for the ability of exogenous PPARγ to rescue these phenotypes. Collectively, these data provide support for the concept of targeting the PPARs in muscle to improve quality of life in survivors of BC.

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R1 *(9 minutes + 2 minutes discussion)*

Muscle mass criterion for cachexia: measuring muscle mass in clinical trials

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Clinical cancer cachexia research is extensively focused on loss of skeletal muscle mass as a defining characteristic of cachexia, associated with key outcomes. Depletion of muscle mass is associated with functional deficit, mortality, chemotherapy toxicity, complications of cancer surgery, health care costs and quality of life. Three-dimensional imaging (magnetic resonance, computed tomography (CT)) provides specificity and precision in the measurement of skeletal muscle. Since 2008, over 100,000 patients with cancer have been characterized for muscle mass metrics using CT images acquired for cancer diagnosis and follow-up. This combined evidence base, the availability of CT systems in cancer centres and patient familiarity with CT examinations, the potential for harmonization with imaging acquired for cancer follow-up, and the high precision and specificity of CT make it a strong choice for muscle mass outcomes in clinical trials. Muscle change over time shows intra-individual and and clinical variation, as well as technical factors, which must be carefully considered as part of clinical trial design.

R2 *(9 minutes + 2 minutes discussion)*

Selecting populations for clinical trials

Eric Roeland
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An unmistakable tension exists in the clinical evaluation and regulatory approval of promising novel drugs to treat cancer cachexia. Currently, no drugs are approved for treating cancer cachexia in the United States or Europe. This tension is driven by many factors, including the selection of the patient population. Within oncology, most supportive care drugs (e.g., antiemetics, pain medications, and growth factors) have been approved broadly across various cancer types and treatments. The ideal cancer cachexia therapy would improve cachexia-related symptoms across multiple diseases, stages, and treatments. Yet, cancer cachexia investigators have adopted an opposite approach, focusing on a specific cancer histology, stage, and treatment.[1] This approach also has limited patient participation to those who meet specific weight loss criteria that often identify patients with advanced cancer and cachexia (e.g., >5% weight loss in the proceeding 6 months[1]) or refractory cachexia (e.g., BMI<20 kg/2 with involuntary weight loss of >2% within 6 months[2]).

Preclinical data should elucidate an intervention's mechanism of action and hypothesized clinical benefit, followed by early phase clinical trials demonstrating safety and identifying patients most likely to benefit. The primary endpoint should align with the drug's mechanism of action (e.g., improvement in appetite), emphasizing early signs and symptoms. Additionally, efforts should focus on the early identification of cachexia-related symptoms, including lower thresholds of weight loss for study entry. Prevention and mitigation of cachexia-related signs and symptoms must also be prioritized, as targeting interventions in refractory cachexia are unlikely to demonstrate benefit. Moreover, given that patient-reported anorexia and changes in quality of life likely precede the measurable losses in weight or skeletal muscle, patient selection should be driven by patient-reported outcomes and/or early biomarkers. Waiting for measurable weight or skeletal muscle loss thresholds leads to interventions being applied to patients in a more refractory stage when patients are less likely to respond to cachexia interventions.[3]

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R3 (9 *minutes + 2 minutes discussion)*

Endpoints for cancer cachexia clinical trials

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Clinical trials serve several different purposes, from regulatory approval, reimbursement decision making to informing the medical community and international guidelines.
For this, trials need appropriate and valid endpoints. The presentation will review available options for cachexia and sarcopenia trials and comment on strengths and weakness of the different approaches that can be taken for morbidity/mortality endpoints, functional outcomes and PROs.

R4 *(9 minutes + 2 minutes discussion)*

Use of biomarkers to assess treatment effect in cancer cachexia

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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 in cancer cachexia (CC) may include laboratory measurements (i.e.; inflammatory markers [CRP, IL-6, IL1a], GDF-15, testosterone), radiographic images (aLBM, muscle mass/density), or physical signs (BMI, weight history, weakness, poor performance). Other, non-biomarker, relevant surrogate endpoints include measures of patient-reported outcomes (PROs) assessing physical dysfunction, anorexia, or fatigue. 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.
Biomarkers should be validated in the target population and their relationship with a “direct” endpoint must be well established and not simply correlations. Also, the magnitude of effect must be clinically meaningful. The ideal method for validation are analyses of multiple studies of known effective therapies assessing both direct and surrogate endpoints, to establish and quantitate the relationship. This is challenging in CC as there are no effective pharmacological treatments in most of the world. Ideally, the biomarker should be part of the therapeutic pathway impacted by the therapy tested with a strong biological rationale for the benefit proposed. Biomarkers are likely to be disease-, host-, pathway-, target-specific measures. Once validated, they may be useful for future treatments, particularly those with same mechanism of action.
The development of biomarkers as a tool to assess treatment effects in CC requires well-designed trials showing that the effect on the biomarker is “likely to predict clinical benefit based on epidemiologic, therapeutic, or pathophysiologic evidence”. As there are currently no validated biomarkers for CC, their development is greatly needed.

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R5 *(9 minutes + 2 minutes discussion)*

Regulatory perspective on cancer cachexia trials

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S1 *(9 minutes + 2 minutes discussion)*

Energy tradeoffs enable recovery from T cell driven infection associated cachexia

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The activation of the immune system requires high quantities of energy substrates[1]. At the same time, sufficient energy must be provided to processes guarantying immediate survival. Life history theory predicts that this will impose a tradeoff of energy between competing processes[2]. Glucose provides ~70% of the energy requirements of the immune system during activation[3]. However, energy availability can be compromised by the anorectic behavior experienced during infections. Energy metabolism can be additionally affected by the development of infection-associated cachexia (IAC)[4]. We have previously reported the loss of muscle and fat mass in a T cell activation - dependent manner in the chronic infection model of lymphocytic choriomeningitis virus (LCMV). There, cachexia is transient and coincides with the peak of T cell expansion and of free fatty acids in circulation. Intriguingly, forced feeding had a negative impact on total body weight. Together, this suggests that the reprogramming of energy metabolism taking place during IAC supports recovery from infection. Supporting this, we identified an unexpected energy tradeoff allowing survival of mice during IAC. This was characterized by organ - specific changes in fuel selection. Acute pharmacological inhibition of these metabolic reprogramming resulted in a shift in energy substrate utilization, systemic metabolic decompensation and the death of infected mice. By studying energy metabolism in a systemic manner, we have identified an unexpected essential energy tradeoff during IAC. This could have important implications for our understanding of infectious diseases and the involvement of cachexia.

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S2 *(9 minutes + 2 minutes discussion)*

Aging exacerbates neuromuscular junction disruption after injury that stimulates inflammation.

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Aging is associated with delayed skeletal muscle repair and regeneration. Loss of innervation occurs after degenerative muscle injury, however, the extent of denervation, whether the kinetics of reinnervation changes with aging, and the cellular consequences of neuromuscular junction (NMJ) disruption remain underexplored. Herein, we show that after degenerative muscle injury, there is a progressive denervation and delayed reinnervation in aged compared to adult muscle that correlates with delayed muscle regeneration. We found a positive relationship between innervation status and enlarged myofiber size in aged regenerating muscle, and improvement in regeneration after degenerative muscle injury through inhibition of pro-inflammatory activity was not associated with an increase in reinnervation. Single cell profiling revealed denervation triggers a pro-inflammatory response within aged macrophages and fibroadipogenic progenitors compared to a pro-regenerative response in adult cells. Thus, denervation and delayed reinnervation of NMJs after injury is a feature of persistent pro-inflammatory signals associated with delayed repair and regeneration of aged muscle.

S3 *(9 minutes + 2 minutes discussion)*

Targeting macrophage-specific glutamate dehydrogenase 1 (GLUD1) as novel therapeutic strategy for muscle degenerative conditions

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Inflammatory responses orchestrate muscle adaptations during degenerative conditions. Within the immune cells populating skeletal muscle tissue during acute or chronic degenerative conditions, macrophages are crucial mediators in the regulation of degeneration/regeneration processes. Besides their known role in the contribution of the activation of muscle precursors and the resolution of injuries, macrophages are emerging as important interplayers in restoring metabolic homeostasis during muscle damage. We recently found that macrophage-specific genetic targeting or pharmacologic blockade of glutamate dehydrogenase 1 (GLUD1), which converts L-glutamate into α-ketoglutarate and vice versa, confers regenerative advantages to muscles by incrementing muscle interstitial glutamine[1]. The latter boosts both proliferation and differentiation of satellite cells (SCs), the main source of adult muscle precursors, during muscle degenerative conditions. Our findings show that pharmacological inhibition of GLUD1 (i.e. treatment with the selective inhibitor R162) increases glutamine synthetase (GS) activity, which ultimately results in an overproduction of glutamine by macrophages, its release in muscle milieu, and consequent stimulation of SC proliferation and differentiation during trauma, ischemia and aging[1]. We are currently extending these findings in the context of muscular dystrophy, where under GLUD1 inhibition we observe reduced muscle degeneration and preserved muscle function in dystrophic mice.

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S4 *(9 minutes + 2 minutes discussion)*

Downregulation of PGC1-α in the skeletal muscle endothelium mediates cancer cachexia by compromising vascular barrier integrity

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Background: Cachexia is characterized by body weight loss due to extensive skeletal muscle wasting. Seventy percent of pancreatic cancer patients suffer from cachexia as a major disease complication which worsens the quality of life and also increases mortality. However, there are currently no approved treatments that can effectively counteract cachexia. Vascular endothelial cells (ECs) are essential for maintaining skeletal muscle perfusion, nutrient supply and preventing inappropriate transmigration of immune cells into the muscle tissue. However, little is known about the role of the muscle vasculature in cancer cachexia. We hypothesized that vascular endothelial dysfunction in the skeletal muscle mediates cancer cachexia.
Methods and Results: Using genetically modified KPC-pancreatic ductal adenocarcinoma (PDAC) mice and a tissue clearing and high-resolution 3D-tissue imaging approach, we found that the loss of skeletal muscle vascular density precedes the loss of muscle mass. To determine the translational relevance of the muscle EC loss seen in the KPC-cachexia model, we evaluated muscles of control and cancer cachexia patients. Cancer patients show surprisingly small and irregular muscle fibers (severe muscle atrophy) in cross sectional areas, and markedly decreased muscle vascular density. These data suggest that the loss of muscle vasculature we observed in experimental models also occurs in the clinical setting in cancer patients. Mechanistically, circulating Activin-A released by the tumor suppresses expression of the transcriptional co-activator PGC1α in the muscle endothelium of cachexic mice, thus disrupting junctional integrity in the vasculature and increasing vascular leak. Furthermore, an EC-specific inducible PGC1α deletion ($EC^{\Delta PGC1\alpha}$) mouse phenocopied the decreased vascular density and muscle loss observed in KPC mice.
Conclusion: Our study suggests that EC-PGC1α is essential for maintaining the integrity of the skeletal muscle vascular barrier and that restoring healthy endothelial function in the skeletal muscle may be required for the therapies targeting cancer cachexia.

U1 *(9 minutes + 2 minutes discussion)*

Host factors: sexual dimorphism in murine models of cancer cachexia

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In 2015, the United States National Institutes of Health issued a notice designed to enhance the consideration of biological sex as a variable in biomedical research. Since that time, the emphasis on the role of biological sex across a variety of conditions has enhanced greatly in the literature. Specifically in cancer cachexia, works within the $Apc^{Min/+}$ mouse have long established a dependency on IL-6 for the development of cachexia in colorectal cancers. More recently, however, data have suggested such IL-6 dependency may not be present in females, establishing a biological sex difference in mechanisms of colorectal cancer cachexia. Furthermore, recent data in pancreatic cancer suggest male-specific dependence on Activin for development of cachexia[1]. Prior work from our laboratory established early degeneration of the mitochondrial network during Lewis Lung Carcinoma (LLC) induced cachexia in male mice[2]. Yet, our more recent works suggest a relative protection of the mitochondrial network in female LLC-tumor bearing mice with such degenerations only seen after onset of cachexia. Similarly, we observed protection of the mitochondrial network in females during disuse-induced atrophy, further suggesting mitochondrial protection within muscles of female animals. Current evidence from our laboratory now suggests females may exhibit classic phenotypical losses in fat mass with concomitant splenomegaly in a similar timeline to males, but delayed onset of muscle loss during C26 colorectal cancer cachexia. Currently we are working to establish potential variations in the transcriptomic and methylomic responses to cancer-induced cachexia between sexes. Clearly, mechanisms of cancer-induced cachexia vary by tumor type and biological sex. Therefore, effective approaches to prevention and reversal of this condition likely require tumor and sex specific modalities.

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U2 *(9 minutes + 2 minutes discussion)*

Host factors: aging and host genotype in cancer cachexia

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Background: Mouse models represent important tools for cachexia research. Most mouse studies on cancer cachexia are conducted using young adolescent mice, although cancer is primarily a disease of high age in humans. The importance of mouse age is increasingly acknowledged in cancer research (1). Metabolism and muscle function change with age, but it is unclear how aging affects cachexia progression in mouse models. Likewise, metabolic vulnerabilities of different mouse strains are known (2) but have not yet been studied in the context of cachexia.
Methods: We compared tumor development and cachexia progression in young and aged mice of three different strains (C57BL/6J, C57BL/6N, BALB/c) and with two different tumor cell lines (Lewis Lung Cancer, Colon26). We measured tumor size, body weight, organ weights, fiber cross-sectional area, circulating cachexia biomarkers, and molecular markers of muscle atrophy and adipose tissue wasting in the different age groups and mouse strains. Levels of inflammatory markers were correlated to body weight dependent on age in mice and patients with cancer.
Results: Fundamental differences between mouse strains were noted regarding the effect of aging on individual parameters of cachexia progression. Aging aggravated weight loss in LLC-injected C57BL/6J mice, induced it in C57BL/6N mice, and did not influence weight loss in C26-injected BALB/c mice. Inflammatory markers correlated significantly with weight loss in young but not aged mice and patients (3).
Conclusions: Aging affects cachexia development and progression in mice in a strain-dependent manner and influences the inflammatory profile in both mice and patients. Age is an important factor to consider for future cachexia studies.

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U3 *(9 minutes + 2 minutes discussion)*

Tumor factors: tumor molecular and cellular heterogeneity mediates cancer cachexia phenotype

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The frequency and severity of cachexia in cancer differs by tumor type, with high cachexia burden associated with tumors of the upper gastrointestinal tract, for example, and lower cachexia burden in breast and prostate cancer. Within a single tumor type there is also heterogeneity in presentation. We seek to determine the factors responsible for heterogeneity in cachexia phenotypes as a means of defining causal, targetable pathways for therapeutic intervention. Here I will discuss converging lines of evidence that point to tumor-specific pathways. These include associations of tumor gene expression with muscle mass in clear cell renal cell carcinoma and other cancers, as well as published data linking expression of cachexia inducing factors with frequency of cachexia across cancers. Functional studies in experimental mouse models have long demonstrated central roles of specific tumor-derived cytokines in driving wasting in cancer, including Interleukin-6 (IL-6) indicating a causal link between tumor gene expression and the systemic phenotype. Leveraging multiple cancer cell lines, patient-derived orthotopic xenografts and patient data and biorepositories, we have explored tumor-derived determinants of wasting in pancreatic cancer. Our more recent studies move beyond cytokines to begin to examine the role of the tumor microenvironment and tumor immune microenvironment in driving inflammation and wasting in the periphery. Ultimately such studies should reveal novel strategies for tailoring cancer therapy.

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U4 *(9 minutes + 2 minutes discussion)*

Identification of molecules that contribute to NSCLC cancer cachexia

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Cancer cachexia (CC), a wasting syndrome of muscle and adipose tissue, occurs in 33% of non-small cell lung carcinoma (NSCLC) patients at the time of diagnosis. Management of CC is limited by the absence of biomarkers and knowledge of molecules that drive the phenotype. To identify such molecules, we injected 54 human non-small cell lung carcinoma (NSCLC) lines into immunodeficient mice, 17 of which produced an unambiguous phenotype of either cachexia (n=10) or non-cachexia (n=7). Comparative analysis of these lines has identified molecules that associate with cancer cachexia.

V1 *(9 minutes + 2 minutes discussion)*

Impact of protein intake on CKD cachexia and sarcopenia

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Muscle wasting and cachexia are prevalent among patients with chronic kidney disease (CKD). The so-called protein-energy wasting (PEW) is to be distinguished from malnutrition, which is defined as the consequence of insufficient food intake or an improper diet. Malnutrition is characterized by hunger, which is an adaptive response, whereas anorexia is prevalent in patients with wasting/cachexia. Energy expenditure decreases as a protective mechanism in malnutrition whereas it remains inappropriately high in cachexia/wasting. In malnutrition, fat mass is preferentially lost and lean body mass and muscle mass is preserved. In cachexia/wasting, muscle is wasted and fat is relatively underutilized. Restoring adequate food intake or altering the composition of the diet reverses malnutrition. Nutrition supplementation may not totally reverse cachexia/wasting. The diagnostic criteria of cachexia/protein-energy wasting in CKD are considered. The association of wasting surrogates, such as serum albumin and prealbumin, with mortality is strong making them robust outcome predictors. At the patient level, longevity has consistently been observed in patients with CKD who have more muscle and/or fat, who report better appetite and who eat more. Although inadequate nutritional intake may contribute to wasting or cachexia, recent evidence indicates that other factors, including systemic inflammation, perturbations of appetite-controlling hormones from reduced renal clearance, aberrant neuropeptide signaling, insulin and insulin-like growth factor resistance, and metabolic acidosis, may be important in the pathogenesis of CKD-associated wasting.
Recent data pose the question whether conservative management of CKD by means of a low-protein diet can be a safe and effective means to avoid or defer transition to dialysis therapy without causing protein-energy wasting or cachexia. We have systematically reviewed with meta-analyses of the controlled clinical trials with adequate participants in each trial, providing rigorous contemporary evidence of the impact of a low-protein diet in the management of uremia and its complications in patients with CKD. We identified 16 controlled trials of low-protein diet in CKD that met the stringent qualification criteria including having 30 or more participants. Compared with diets with protein intake of >0.8 g/kg/day, diets with restricted protein intake (<0.8 g/kg/day) were associated with higher serum bicarbonate levels, lower phosphorus levels, lower azotemia, lower rates of progression to end-stage renal disease, and a trend towards lower rates of all-cause death. In addition, very-low-protein diets (protein intake <0.4 g/kg/day) were associated with greater preservation of kidney function and reduction in the rate of progression to end-stage renal disease. Safety and adherence to a low-protein diet was not inferior to a normal protein diet, and there was no difference in the rate of malnutrition or protein-energy wasting. Hence, a low-protein diet appears to enhance the conservative management of non-dialysis-dependent CKD and may be considered as a potential option for CKD patients who wish to avoid or defer dialysis initiation and to slow down the progression of CKD, while the risk of protein-energy wasting and cachexia remains minimal.

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V2 *(9 minutes + 2 minutes discussion)*

Physical activity and nutrition in CKD

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CKD is a global health challenge with an estimated prevalence ranging between 9 -14%. Nutrition intervention plays an important role in CKD management. It aims to slow down CKD progression, delay the need for dialysis, maintain good health and nutrition status and quality of life of patients. It also ameliorates various kidney and cardiovascular risk factors in this population such as blood pressure, diabetes, and dyslipidemia. Emerging data suggested that adopting a healthy dietary pattern or Mediterranean dietary pattern (MDP) may be associated with reduced risk of overall mortality, CKD and albuminuria. Increasing fiber intake may also be associated with reduced risk of mortality and major adverse cardiovascular events in dialysis patents. On the other hand, CKD patients generally have a sedentary lifestyle and low physical activity due to low energy, easily fatigue and multi-comorbidities. Poor physical activity may promote muscle protein catabolism and wasting, impair physical performance and cardiorespiratory fitness and adversely impact health outcomes of these patients.
To better understand dietary pattern and physical activity pattern of these patients, we performed a simple 9-item dietary questionnaire survey and a short physical activity questionnaire during patients' routine clinic visit. Our survey showed that majority of the CKD patients' dietary pattern were strikingly inconsistent with the MDP. More non-diabetics and more patients with no atherosclerotic vascular disease (AVD) had vegetables intake amount consistent with MDP than diabetics and patients with AVD, respectively. We also observed CKD patients had very low physical activity and exercise duration was far below that recommended by World Health Organization. Doing any forms of exercises appeared to be associated with less perceived impact of kidney disease or less perceived impact of performing peritoneal dialysis on patients' daily living activities. In conclusion, these data demonstrate disparity between actual dietary pattern and physical activity of CKD patients and healthy lifestyle habits recommended by professional bodies. More work is needed to engage our CKD patients to modify and adopt healthy lifestyle habits. Further randomized trials are needed to evaluate whether increasing physical activity and adopting a healthy dietary pattern may minimize symptom burden and improve health outcomes of patients with CKD.

V3 *(9 minutes + 2 minutes discussion)*

Inflammation and adipose tissue browning in CKD cachexia

Robert Mak
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Muscle wasting is prevalent in chronic kidney disease(CKD) and is associated with significant morbidity and mortality. It is associated with the syndrome of cachexia, which is defined by significant body weight loss(or lack of weight gain in children), with fat and muscle mass reduction. Anorexia(reduced appetite) and increased metabolic rate result in energy deficit which in turn causes the changes in body composition[1].

We have used 2 mouse model of CKD to study cachexia and muscle wasting: $Ctns^{-/-}$ mice to characterize genetic CKD and 5/6 nephrectomy to characterize acquired CKD. Indeed, the cachexia syndrome with anorexia, muscle wasting and increased metabolic rate are characteristic of these CKD models. We found that adipose tissue browning is an early event that precedes the onset of muscle wasting and is the mechanism underlying the increased metabolic rate[1]. We demonstrated that vitamin D deficiency and inflammation are important factors. Correction of vitamin D deficiency is obviously important but suppressing inflammation holds the key to preventing and correcting muscle wasting and cachexia associated with CKD[1]. We have shown that IL-1[3] and leptin[4] are central to the inflammation associated with CKD. By inhibiting the overactivity of these pathway, we are able to suppress inflammation and reverse muscle wasting. There are several therapies targeting IL-1 and leptin and pathway, some of which are already approved by the FDA, and others which are now undergoing clinical trials for safety and efficacy.

In conclusion several novel treatments could be available, in the very near future, to combat the devasting complications of cachexia and muscle wasting in CKD.

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V4 *(9 minutes + 2 minutes discussion)*

Activin signaling and GDF-15 in CKD cachexia

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The cachexia syndrome is a common comorbidity observed in advanced chronic kidney disease (CKD) patients that is characterized by skeletal muscle wasting, weakness, and inflammation. A large body of evidence has demonstrated the heightened morbidity (i.e., impaired function, worse health-related quality of life, increased hospitalizations) and mortality of CKD-associated cachexia, and skeletal muscle loss in and of itself has been associated with increased death in this population. However, there is a major unmet need for effective interventions that can ameliorate this prevalent CKD complication.

Higher levels of circulating pro-cachexia factors, including Activin A and Growth Differentiation Factor 15 (GDF15) have been identified in populations with malignancy, chronic obstructive pulmonary disease, and more recently in patients with underlying CKD likely due to increased production and impaired clearance. Activin A and GDF15 are both secreted proteins in the transforming growth factor β (TGF-β) superfamily. In animal models, higher circulating levels of Activin A and GDF15 have each been shown contribute to skeletal muscle atrophy, even in the absence of underlying disease. Furthermore, growing data underscore the roles of Activin A and GDF15 in CKD-associated cachexia, as well as key markers of adverse outcomes in the CKD population (i.e., CKD progression and mortality), signaling inter-organ crosstalk between the kidney and muscle. For example, recent experimental data have shown increased expression of Activin A in specific kidney cell populations, and that systemic pharmacological blockade of Activin A prevent muscle wasting in CKD mouse models. Additionally, GDF15 acts directly on the hypothalamus to reduce food intake and energy expenditure, and in cancer-associated cachexia has been associated with early satiety, weight loss, and death. Recent data from the NIH-sponsored “Malnutrition, Diet, and Racial Disparities in CKD” study has shown that, in a prospective, multi-center cohort of dialysis patients, higher GDF15 levels are associated with worse markers of body composition (decreased muscle and body fat) and higher (worse) Malnutrition Inflammation Score levels.

In this presentation, we will discuss the link between kidney and muscle function, the molecular mechanisms of CKD-associated cachexia including the roles of Activin A and GDF15, and modulation of these pro-cachexia factors as potential targets for therapeutic interventions to mitigate skeletal muscle wasting and cachexia in CKD.

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W1 *(9 minutes + 3 minutes discussion)*

The role of adipose tissue in Covid-19 cytokine storm: learning from cachexia

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Cachexia, a comorbidity of cancer is associated with wasting and chronic systemic inflammation. Results from studies with cancer patients or animal models show a relevant contribution of the adipose tissue to sustained inflammation in cachexia. The white adipose tissue is a heterogeneous organ and accordingly, different depots may exhibit variable response to this syndrome, which include lipolysis, immune cell infiltration, fibrosis, hypoxia and secretion of inflammatory factors. Exacerbated Inflammatory cytokine production and circulation is a feature common to cancer cachexia and COVID-19, as the severe form of the latter is frequently associated with the so-called “cytokine storm”. We shall discuss and compare the role of the white adipose tissue in sustaining systemic inflammation in these conditions, and comment on body composition relevance to disease outcome. The results obtained with Brazilian cohorts of COVID-19 patients suggest that, similarly to what happens in cancer cachexia, adipose tissue-derived factors may markedly impact disease severity and survival, and potentially serve as tools for clinical screening.

W2 *(9 minutes + 3 minutes discussion)*

Nutrition: a matter of life or death

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Covid-19 pandemia could be viewed and discussed as a challenge testing the global ability to effectively respond by international health organizations. When only considering the innovation capacity of pharma industries, the results obtained in less than 2 years of pandemia are extraordinary. However, less attention has been paid to the role of nutrition in individuals at risk of infection and in Covid-19 patients. Overnutrition has been shown to increase the risk of infection, yet international campaigns on increasing physical activity after periods of lockdowns have not been promoted. Healthy diets have been shown to possibly prevent infection, yet global dietary behaviours did not significantly change. Spontaneous food intake of hospitalized Covid-19 patients is frequently reduced, yet hospital malnutrition remains an unresolved issue. Covid-19 pandemia should now be used by international agencies to develop plans to improve not only the quality of the diet of world citizens but also to enhance iplementation of nutrition care in hospitals worldwide.

W3 *(9 minutes + 3 minutes discussion)*

Body composition and muscle quality in Covid-19

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Studies performed during the Covid-19 pandemic demonstrate an association between an increased body mass index (BMI) and severe outcomes from Covid-19 disease.[1] Therefore, assessment of body composition including assessment of muscle tissue composition (an indicator of muscle quality), may provide insight in risk of Covid-19 complications. Assessment of body composition, including muscle tissue composition, can be performed with methods such as bio-electrical impedance (BIA), ultrasound (US) or, if available, analysis of computed tomography images (CT). Each of these techniques can be used to provide an indication of the quantity of fat and/or muscle tissue and the quality of muscle tissue. Recent findings using BMI, BIA and CT analysis suggest that an excess of adipose tissue and reduced muscle quality in patients with Covid-19 is associated with more severe disease outcomes and mortality.[2,3] During ICU stay, muscle thickness and quality may further decline.[4] Patients who have post Covid-19 symptoms or Long Covid have been observed to develop weight loss, possibly related to muscle loss.[5] These changes in body composition may potentially be explained by systemic inflammation, reduced physical activity, and inadequate nutrient intake as a result of Covid-19 symptoms such as fatigue, shortness of breath, muscle weakness, and loss of smell and/or taste.[6]
Currently, body composition in patients with Covid-19 is mostly assessed in cross-sectional studies or studies with a case-control design, and more longer term prospective studies studying changes in body composition are needed in (recovered and Long) Covid-19 patients, to provide more insight in the association between Covid-19 and body composition.
Clinicians need to assess and monitor body composition in Covid-19 patients, to enable early recognition of patients at risk of severe complications and to optimize rehabilitation management. Since body composition and Covid-19 appear to be complexly related, an multimodal approach is needed. This approach may include physical exercise and dietary treatment since protein intake may be insufficient.

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W4 *(9 minutes + 3 minutes discussion)*

Frailty and rehabilitation in Covid-19 patients

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Physical activity, in its various blends, increases aerobic capacity, muscle mass, strength and endurance by ameliorating aerobic conditioning and/or strength. For most people, greater health benefits can be obtained by engaging in physical activity of more vigorous intensity or longer duration.
In COVID-19 patients, the long-term persistence of fatigue deserves adequate evaluation and appropriate interventions. For those who "struggle" to resume their usual activities of daily living and/or are unable to return usual activities and/or playing their favourite sport, tailored physical activity protocols should be implemented. It is also essential to provide the same service to patients who, during to the long period of isolation or the long hospitalization, have reduced physical activity or in whom, especially if elderly, this inactivity has turned into a decrease of autonomy condition. Furthermore, it is necessary to consider the positive impact of resuming physical activity on healed patients who have remained in isolation for some time, deprived of daily life and routine activities, which are essential for their psychophysical well-being.
To this aim, the post-COVID-19 service of Fondazione Policlinico Universitario A. Gemelli (Rome, Italy) has developed specific physical activity programmes. The physical activity protocol of "SPRINTT", a European project aimed at preventing mobility disability in frail older people with sarcopenia, has been re-shaped to adapt it to COVID-19 survivors. The programme is also offered to those, never hospitalized, who remained physically inactive during the two-month lockdown issued in Italy (@longevity_run).

Components of training

The physical activity program includes aerobic, strength, flexibility, and balance training. The program focuses on walking and fast walking as the primary mode of physical activity, given its widespread popularity and ease of administration across a broad segment of the sedentary population. Each session is preceded by a brief warm-up and followed by a short cool-down period. Following each bout of walking (30 minutes), participants perform flexibility exercises.

Intensity of training

Participants are introduced to the physical activity program in a structured way such that they begin with lighter intensity and gradually increase intensity over the first 2 weeks of the intervention. Walking for physical activity is promoted at a moderate intensity and tailored for each participant. The rating of perceived exertion (RPE) is used as a method to regulate physical activity intensity. Using the Borg's scale (range 6–20), participants are asked to walk at an intensity of 13 (activity perception of "somewhat hard"). They are instead discouraged from exercising at levels that approach or exceed 15 ("hard") or drop to a rating of 11 ("fairly light") or below. Lower extremity strengthening exercises are performed at an intensity of 15–16 ("hard").

Frequency and duration of training

The physical activity program comprises of continuing twice- per-week center-based group exercise sessions and a progression of home-based physical activity to other 2–3 times per week. The intervention comprises a general weekly walking goal of 150 min. This is consistent with the public health message from the Physical Activity Guidelines for Americans report that states that moderate physical activity should be performed for 30 min on most if not all days of the week (150–210 total minutes) (http://health.gov/paguidelines/pdf/paguide.pdf).

Aerobic component of the physical activity intervention

Walking is the primary mode of physical activity in post COVID-19 SPRINTT protocol. Participants have been trained to assess their RPE using the Borg's scale. Walking pace is encouraged at a moderate intensity (RPE=13). A characteristic physical activity session is composed of a 5-min warm-up consisting of low intensity walking (RPE<9) or, when walking cannot be performed at an RPE<9, stationary cycling. Participants then complete walking and strength training at the target RPE for each activity for the amount of time prescribed. At the end of each physical activity session, there are 3 minutes of cool down in which the walking speed is gradually reduced.

Strength training component of the physical activity intervention

Strength training focuses primarily on lower extremity exercises. Adjustable ankle weights have been provided to all participants. The goal is to include three sessions of strength training (RPE=15–16) throughout the intervention. Each strength exercise includes two sets of ten repetitions each, with 1-min rest in between. The target intensity is approached in a progressive manner over a 4-week period depending on the progress of each participant. At each exercise session, participants complete one strength training exercise from all of the five groups, for a total of five exercises.

Balance training protocol

Participants perform balance training according to five different levels of difficulty. Progression to the next level occurs when all exercises of a certain level can be performed correctly. Balance exercises are performed once a day every day throughout the intervention.

Upper body exercises

Upper body exercises are incorporated at the end of the session. Each week, one upper body exercise is chosen by the trainer and performed at the end of the group session.

Conclusion:

Physical activity increases aerobic capacity, muscle mass, strength and endurance by ameliorating aerobic conditioning and/or strength. According to the most recent WHO recommendations people of all ages have to include a minimum of 30 min of moderate intensity physical activity on most, if not all, days of the week. Accumulating evidence supports regular physical activity, in combination with appropriate nutritional support, as the most effective strategy for improving sarcopenia and physical function. Exercise protocol should be patient-centered and tailored to individual patient needs; any program should take into account comorbidities that may affect a patient's progress or ability to participate the activities. As COVID-19 is a novel disease, education about the implications of the disease and potential consequences will need to be discussed with patients. The successful story of the professional athletes brings a message of hope: close medical counselling and adapted physical activity may allow COVID-19 survivors to faster resume their pre-infection lives and daily habits. More studies are needed to determine if this may be more valid in COVID1-19 patients. There is a lack of evidence-based guidelines regarding exercise protocol and specific training following COVID-19. There is a need for further research around sequelae of and the long-term impact COVID-19 may have on survival subjects.

X1 *(9 minutes + 3 minutes discussion)*

Evolution and outcomes from a multidisciplinary cancer-cachexia clinic

Peter Martin
on behalf of the Cachexia and Nutrition Support Service Team

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There are only a small number of dedicated cancer cachexia service models that have been well described and even less who have evolved and established themselves over a long period. This presentation will briefly describe the 20-year evolution of a dedicated inter-disciplinary service model and the outcomes they have captured. It will describe what has shaped the latest iteration of the service model and what benefits, challenges, and further opportunities we believe come from investing in such a service. The service is embedded in an Australian regional cancer centre.[1-3]

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X2 *(9 minutes + 3 minutes discussion)*

Clarifying the role of palliative rehabilitation in cachexia management

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Unintentional weight loss in advanced progressive illness is often associated with muscle loss, reduced muscle strength, functional limitations and increased morbidity which all impact negatively on quality of life and may reduce length of survival. Patients with cachexia may however obtain both physical and psychosocial benefits from a rehabilitative approach to their care, even in the latter stages of illness.
Rehabilitation and palliative care are both essential parts of integrated, people-centred health services for universal health coverage and should be offered based on need not diagnosis or prognosis. Rehabilitative interventions are however underutilised within palliative care settings, both in early treatment phases and when patients approach end-of-life. Rehabilitative therapies will necessarily differ dependent on illness stage and symptom burden but may remain relevant at all stages of a patient's illness. Interventions must be chosen which are considerate of the person's individual circumstances, symptoms, and the likelihood that personally meaningful and relevant benefits will be gained. Individually tailored rehabilitative care requires the input of specially trained practitioners and as part of an integrated multidisciplinary palliative care team. This talk discusses the potential benefits and burdens of a palliative rehabilitative approach to care for patients with cachexia.

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X3 *(9 minutes + 3 minutes discussion)*

The importance of exercise and nutrition in an integrated response to cachexia management

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Cachexia is a devastating condition associated with increased morbidity and mortality. It is present in many disease conditions such as cancer, chronic kidney disease, chronic obstructive pulmonary disease and heart failure, and currently there is no standardised treatment. Goals of interventions include weight gain and weight stability; however, gains in skeletal muscle mass and function are considered most important and relevant in terms of outcomes. Therefore, interventions have been focused at improving this body compartment. Research has considered the development of multimodal interventions incorporating aspects such as nutrition, exercise, counselling and drug therapies (e.g. anti-inflammatory agents).
Exercise in particular has been suggested as a key component of multimodal interventions due to its potential to increase physical function and muscle hypertrophy (e.g. resistance training (RT)), along with anti-inflammatory benefits, and positive effects on mood, depression and quality of life. Different modes of exercise training require more research, although RT appears more effective, and high intensity interval training (HIIT) look promising.
Nutrition is a critical component of treatment alongside exercise, with key goals to maintain energy and protein balance. Specific aspects of nutrition and supplementation may also be useful in augmenting any possible gains from exercise training, such as amino acids, HMB and omega-3 fatty acids.
More research is required investigating different types and modes of multimodal interventions to clarify optimal strategies for management of cachexia. Furthermore, specific aspects such as exercise specificity and safety should be considered. Importantly, choosing suboptimal modes and dosages (exercise and nutrition) may lead to poor or little effect on outcomes and this should be considered when designing intervention studies and patient care. Finally, work is needed to address specific issues such as tailoring of exercise and nutrition interventions as part of routine clinical care.

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X4 *(9 minutes + 3 minutes discussion)*

Patient experience of a multi-professional cachexia clinic

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Cancer cachexia remains a complex unmet need in oncology care, despite its high prevalence and high impact. Patients with cachexia experience numerous complications, including reduced tolerance and effectiveness of anti-cancer therapy, reduced mobility, and reduced functional status, leading to decreased quality of life and survival.
Multidisciplinary cachexia service models have emerged to address practice gaps and needs identified by patients and clinicians, with person-centred approaches to cachexia care demonstrating promising improvements in patient outcomes. The involvement of patients and carers in the ongoing development and refinement of these services is critical to ensure their complex clinical and psychosocial needs are met.
The Barwon Health Cachexia & Nutrition Support Service is an outpatient clinic focused on improving clinical outcomes and quality of life for patients with or at high risk of cancer cachexia. Patients see an interdisciplinary team, incorporating a physician, physiotherapist, dietician and nurse practitioner concurrently. This study aimed to evaluate the patient and carer perspective of the service.
Semi-structured interviews were conducted with 12 patients and 9 carers. Interviews focused on two broad themes: 1) recounting memories and experience of the Cachexia & Nutrition Support Clinic, and 2) describing their ideal experience or expectation of a cachexia-specific support service. Thematic analysis was supplemented with data from reviews of the patient and carer literature.
Analysis generated four superordinate themes that reflected the complex dynamics of the clinic experience. Themes were: improved communication regarding health literacy/education for patients and carers, empowerment through person-centred care, evolution of perception of value, and importance of the interdisciplinary team-based approach. Generally, patients and carers reported overall positive experiences with the clinic, particularly with regard to improved communication and empowerment of the patient.
Findings confirmed that a cachexia-specific service was viewed as having a positive impact on quality of life and outcomes by patients and carers. A patient-centred and individualised approach by the multi-professional team were of particular importance to those interviewed. These insights have been critical step in the ongoing development of the service, and work is underway to further investigate the experience of cachexia care patients receive both within the cachexia service, and oncology services more broadly.

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Y1 *(9 minutes + 3 minutes discussion)*

MEF2c-dependent downregulation of myocilin mediates cancer-induced muscle wasting and associates with cachexia in patients with cancer

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Our understanding of the molecular mechanisms that are causative in cancer-induced skeletal muscle wasting and weakness are still in their infancy. As we continue to add to our mechanistic understanding using pre-clinical models, it is important to ensure translational relevance using clinical samples when possible. Data from our lab show that the levels of myocilin are significantly decreased in the skeletal muscle of cachectic pancreatic ductal adenocarcinoma (PDAC) patients as well as mice bearing C26 tumors, L3.6pl (human pancreatic) tumors and patient derived xenografts (PDX) [1]. Myocilin has previously been shown to bind and stabilize the dystrophin-associated glycoprotein complex in skeletal muscle [2] and function as a pro-hypertrophic protein, with skeletal muscle of transgenic mice overexpressing myocilin 40% larger than wild type control mice [2]. In the current work we show that loss of myocilin in cancer-free mice causes muscle fiber atrophy, sarcolemmal fragility, and impaired muscle regeneration following injury. We further show that myocilin gain of function partially protects against C26 tumor-associated muscle wasting. To determine potential mechanisms by which Myocilin is transcriptionally downregulated we analyzed the human and mouse *Myoc* gene promoters and identified a conserved binding motif for MEF2 approximately 200-bp upstream of the TSS. Mutagenesis of this MEF2-binding site within the *Myoc* proximal promoter significantly decreased its promoter reporter activity when transfected into skeletal muscle in vivo compared to non-mutagenized promoter reporter. Of the Mef2 isoforms, *Mef2c* is significantly decreased in the skeletal muscle of tumor bearing mice. We therefore determined whether MEF2c gain of function can prevent the C26 tumor-induced downregulation of *Myoc* and muscle atrophy via injection of an AAV vector expressing MEF2c under the control of a muscle specific promoter (tMCK). We found that MEF2c gain of function in skeletal muscle maintained muscle mass in C26 mice to levels comparable with non-cancer controls. To test whether this protection carried over to another pre-clinical model, we targeted the AAV9-tMCK-MEF2 to limb and diaphragm muscles of mice bearing orthotopic KPC (murine pancreatic) tumors. Here MEF2c gain of function was protective against the loss of muscle mass and muscle force. These findings suggest a disruption in MEF2c-dependent transcription of Myoc is one mechanism of cancer-associated muscle wasting.

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Y2 *(9 minutes + 3 minutes discussion)*

Weight loss in Cancer Patients Correlates with p38β MAPK Activation in Skeletal Muscle

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Unintentional weight loss due to muscle wasting is a major threat to cancer survival without a defined etiology. We previously identified in mice that p38β MAPK mediates cancer-induced muscle wasting by stimulating protein catabolism. However, whether this mechanism is relevant to humans is unknown. In this study, we recruited men with cancer and weight loss (CWL) or weight stable (CWS), and non-cancer controls (NCC), who were consented to rectus abdominis (RA) biopsy and blood sampling (n = 20/group). In the RA of both CWS and CWL, levels of activated p38β MAPK and its effectors in the catabolic pathways were higher than in NCC, with progressively higher active p38β MAPK detected in CWL. Remarkably, levels of active p38β MAPK correlated with weight loss. Plasma analysis for factors that activate p38β MAPK revealed higher levels in inflammatory cytokines as well as Hsp70 and Hsp90 in CWS and/or CWL. Thus, p38β MAPK activation appears a key signaling event associated with weight loss in cancer patients.

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Y3 *(9 minutes + 3 minutes discussion)*

Association between growth differentiation factor-15 (GDF-15) serum levels, anorexia and low muscle mass among cancer patients[1]

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Introduction: Anorexia is a clinically relevant problem in cancer patients and is associated with poor clinical outcomes including decreased survival. The pathophysiology of cancer-associated anorexia is multifactorial and still not completely clarified[1,2] and modulation of serum biomarkers, including growth and differentiation factor(s) (GDF)[3], may be implicated. For this reason, we aimed to assess primarily the association between GDF-15 circulating levels and anorexia, and secondarily with low muscle mass or body weight loss in cancer patients naïve to anti-cancer treatments[1].
Methods: We planned to study gastrointestinal (GI) and lung cancer patients and healthy controls. The FAACT-questionnaire was used to discriminate the presence of poor appetite (anorexia) and we calculated the L3 skeletal muscle index (L3-SMI) by CT scan to assess the level of muscularity, using as cutoff values the lowest tertile. GDF-15 serum levels were measured by ELISA.
Results: We enrolled 59 cancer patients and 30 controls; among cancer patients, 25 were affected by GI and 34 by lung cancer. Anorexia was diagnosed in 36% of cancer patients. Based on FAACT score, GI cancer patients were more anorexic compared to lung CP ($p=0.0067$). Reduced muscle mass was present in 34% of cancer patients and L3-SMI was lower in gastrointestinal compared to lung cancer patients ($p<0.05$). The GDF-15 concentrations were higher in cancer patients vs controls ($p<0.001$), as well as in anorexic vs. non-anorexic cancer patients ($p=0.005$) and vs controls ($p<0.0001$). GI cancer patients showed higher GDF-15 levels compared to lung cancer patients ($p=0.0004$). No difference was found in GDF-15 levels between cancer patients with reduced muscle mass and those with moderate/high muscularity and between patients with body weight loss and those with stable weight in prior six months.
Conclusion: Our results support the involvement of GDF-15 in the development of cancer-associated anorexia. The mechanisms of action of GDF-15 in cancer should be further investigated to unveil the impact on energy homeostasis and potential implications in changes in body composition.

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Y4 *(9 minutes + 3 minutes discussion)*

Adipose depot gene expression and intelectin-1 in the metabolic response to cancer and cachexia

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Background and Methods: During cachexia, different adipose depots demonstrate differential wasting rates. Animal models suggest adipose tissue may be a key driver of muscle wasting through fat-muscle crosstalk, but human studies in this area are lacking. We performed global gene expression profiling of visceral (VAT) and subcutaneous (SAT) adipose from weight stable and cachectic oesophago-gastric cancer patients (n=16) and healthy controls (n=8) using microarray analysis. ELISA for intelectin-1 (ITLN1) was performed on all VAT samples, and plasma samples from a larger cohort.
Results: In VAT vs. SAT comparisons, there were 2101, 1722, and 1659 significantly regulated genes in the cachectic, weight stable, and control groups, respectively. There were 2200 significantly regulated genes from VAT in cachectic patients compared with controls. Genes involving inflammation were enriched in cancer and control VAT vs. SAT, although different genes contributed to enrichment in each group. Energy metabolism, fat browning, and adipogenesis genes were down-regulated in cancer VAT. The gene showing the largest difference in expression was ITLN1, the gene that encodes for intelectin-1, a novel adipocytokine associated with weight loss in other contexts.
Literature review shows that ITLN1 levels are highly variable in cancer patients but different from healthy individuals. Patients with GI and prostate cancer show increased concentrations of circulating ITLN1, while patients with gynaecological, breast, bladder, and renal cancer have lower ITLN1 levels. In GI cancer, ITLN1 is increased in tumour tissue compared with adjacent healthy tissue. Consequently, the high levels of circulating ITLN1 might be determined by the tumour and by cancer-associated weight loss in GI cancer.
Conclusions: SAT and VAT have unique gene expression signatures in cancer and cachexia. VAT is metabolically active in cancer, and may play a fundamental role in cachexia, but the down-regulation of energy metabolism genes implies a limited role for fat browning in cachectic patients, in contrast to pre-clinical models. Intelectin-1 may be a target for therapeutic manipulation, and further investigations are ongoing.

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Late Breaking Trials Session *(9 minutes + 4 minutes discussion)*

Use of chirally pure S-enantiomers in the treatment of cancer cachexia: clinical development of S-pindolol benzoate in cancer cachexia in patients with advanced non-small cell lung and colo-rectal cancer

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Cancer cachexia is a major problem in patients with advanced cancer affecting up to 80 % of cancer patients and leading to functional impairment, loss of quality of life and mortality in about 20 % of those patients[1]. Cachexia impacts anti-cancer treatment and aggravates underlying conditions resulting in lower rates of survival[2],[3].
Pharmacologically active molecules may exist in two isomers, like mirror images, a left- and a right-handed form. These stereoisomers or enantiomers may have substantially different physico-chemical properties and pharmacological actions[4]. It was found that S-enantiomers of certain non-specific ß1- and ß2-receptor blockers exert potent anti-cachectic actions. S-pindolol has been characterized as an ACTA (anabolic-catabolic transforming agent) and was capable to improve survival in several cachexia models in rats[5].
S-pindolol has also been shown in a pilot proof-of-concept trial, the ACT-ONE trial, to significantly increase body weight, lean mass, and handgrip strength in patients with NSCLC and CRC[6].

We report here on the clinical development of S-pindolol benzoate, a new stable salt form of S-pindolol. A Phase I PK/PD study of single doses and multiple doses of S-pindolol vs Pindolol in healthy subjects will be described. The Phase IIb/III clinical development programme in two studies in patients with NSCLC and CRC will be outlined.

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Late Breaking Trials Session *(9 minutes + 4 minutes discussion)*

From ROMANA to SCALA program: The journey of Anamorelin - the ghrelin receptor agonist – towards treating the malignancy associated weight loss and anorexia in adult patients with non-small cell lung cancer (NSCLC)

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Weight loss and anorexia are hallmarks of cancer cachexia, a devastating syndrome occurring in approximately 80% of patients with advanced cancer and particularly prevalent in NSCLC, which often leads to treatment delays, disease progression and decreased survival. This syndrome has very limited treatment success and no pharmacological one approved yet. Anamorelin, an oral selective ghrelin receptor agonist with fast-acting anabolic and appetite-stimulating properties, was approved in Japan in 2021 for the treatment of cancer cachexia in different malignant tumors.
The efficacy results of the ROMANA program didn't show a significant effect on Hand-Grip-Strength but showed early and sustained over 24 weeks significant improvements in body composition and on the anorexia-cachexia symptoms and concerns, beside a good safety and tolerability profile. Based on these results and considering that patients with NSCLC have a high prevalence of weight loss and anorexia and different prognostic implications, and those with BMI < 20 kg/m2 are more in need for a treatment, the SCALA program was designed with the objective to demonstrate superiority of anamorelin vs placebo on the gain in body weight and improvement in anorexia symptoms.
The SCALA program consists of 2 identical international, double-blind, phase 3 studies (NCT03743051/NCT03743064). Eligible patients are adults with stage III (unresectable) or IV NSCLC, BMI <20 kg/m^2, involuntary weight loss of >2% within 6 months prior to screening, and cancer-associated anorexia symptoms defined through patient-reported sub-scales as ≤17 points on the 5-Item Anorexia Symptoms Subscale (5-IASS) and ≤37 points on the 12-item FAACT A/CS; 632 patients are planned to be enrolled and randomized 1:1 to receive 100 mg anamorelin or placebo for up to 24 weeks. Coprimary endpoints are duration of clinically meaningful treatment benefit in weight and 5-IASS until week 12. The SCALA program introduces the 5-IASS scale, and the clinical meaningful threshold established based on within patient clinically meaningful change on body weight and appetite needed for the determination of the duration of treatment benefit on body weight and anorexia.

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Late Breaking Trials Session *(9 minutes + 4 minutes discussion)*

Efficacy of empagliflozin in heart failure with preserved ejection fraction according to frailty status - insights from EMPEROR-Preserved trial

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Introduction: Frailty is one of the severe complications of heart failure with preserved ejection fraction (HFpEF), however, neither the effect of frailty on HFpEF outcomes nor on empagliflozin's effects on HFpEF are fully elucidated.
Methods: We calculated a cumulative deficit derived Frailty Index (FI) using 44 variables including clinical, laboratory, and quality of life parameters in EMPEROR-Preserved Trial. Similar to previous studies, patients were classified into 4-groups; non-frail (FI<0.21), mild frailty (0.21-0.30), moderate frailty (0.30-0.40), and severe frailty (>0.40). Clinical outcomes and health-related quality of life were evaluated according to baseline FI and the effect of empagliflozin on chronological changes of FI (at 12, 32, 52 weeks) were also evaluated.
Results: The patient distribution was 1514 (25.3%), 2100 (35.1%),1501 (25.1%), 873 (14.6%) in non-frailty, mild frailty, moderate frailty, severe frailty, respectively. Severe frailty patients tended to be female, have low Kansas City Cardiomyopathy Questionnaire (KCCQ) scores, and more complications. Incidence rate of primary outcome of cardiovascular death or hospitalization for heart failure increased as frailty worsened (hazard ratio [HR] of each FI category compared to non-frail group was 1.10 [95% CI 0.89-1.35], 2.00 [1.63-2.47], 2.61[2.08-3.27], in mild frailty, moderate frailty, severe frailty, respectively, p trend<0.0001). Compared with placebo, empaglilflozin reduced the risk for the primary outcome across the 4 FI categories, HR:0.59 [0.42-0.83], 0.79 [0.61-1.01], 0.77 [0.61-0.96], 0.90 [0.69-1.16], in non-frail to severe frailty categories, respectively (interaction-p trend =0.097). Empagliflozin also improved other clinical outcomes and KCCQ score consistently.
Interestingly, compared with placebo, empagliflozin treated patients had a higher likelihood of being in a lower FI category at week 12, 32, and 52 (p<0.05), odds ratio 1.12 [CI 1.01-1.24], at 12 week, 1.21 [1.09-1.34], at 32 week, 1.20 [1.09-1.33] at 52 week.
Conclusions: Empagliflozin improved key efficacy outcomes regardless of baseline frailty status. Of note, empagliflozin also improved frailty status during follow-up.

Z1 *(9 minutes + 3 minutes discussion)*

GDF15 neutralization as a transformative therapeutic approach - effects on restoring muscle function and physical performance

Ja Young Kim-Muller, LouJin Song, Brianna LaCarubba Paulhus, Evanthia Pasho, Xiangping Li, Anthony Rinaldi, Stephanie Joaquim, John C. Stansfield, Jiangwei Zhang, Andrew Robertson, Jincheng Pang, Alan Opsahl, Magalie Boucher, Danna Breen, Katherine Hales, Abdul Sheikh, Zhidan Wu, Bei B. Zhang
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Cancer cachexia is a disorder characterized by both involuntary weight loss and impaired physical performance. Decline in physical performance of patients with cachexia is associated with poor quality of life, and currently there are no effective pharmacological interventions that restore physical performance. Here we examined the effect of GDF15 neutralization in a mouse model of cancer-induced cachexia (TOV21G) that manifested weight loss and muscle function impairments. With comprehensive assessments, our results demonstrated that cachectic mice treated with the anti-GDF15 antibody mAB2 exhibited body weight gain with near-complete restoration of muscle mass and markedly improved muscle function and physical performance. Mechanistically, the improvements induced by GDF15 neutralization were primarily attributed to increased caloric intake, while altered gene expressions in cachectic muscles were restored in both caloric intake-dependent and -independent manners. The findings implicate the potential of GDF15 neutralization as an effective therapy to enhance physical performance of patients with cachexia.

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Z2 *(9 minutes + 3 minutes discussion)*

Activation of the hypothalamic–pituitary–adrenal axis by exogenous and endogenous GDF15

Hanna Kim[1], Irene Cimino[3], Stephanie Joaquim[1], Donald Bennett[2], Anthony P. Coll[3], Bei B. Zhang[1], Kendra K. Bence[1], Stephen O'Rahilly[3] and Danna M. Breen[1]

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An acute increase in the circulating concentration of glucocorticoid hormones is essential for the survival of severe somatic stresses. Circulating concentrations of GDF15, a hormone that acts in the brain through the GDNF-family receptor α-like (GFRAL) receptor to reduce food intake, are frequently elevated in stressful states. We report that GDF15 potently activates the hypothalamic-pituitary-adrenal (HPA) axis in rodents, consistent with an increased proportion of *Crh* neurons expressing *c-Fos* in the paraventricular nucleus of the hypothalamus. In wild-type mice exposed to cisplatin, a model of chemotherapy induced anorexia and weight loss, circulating levels of both corticosterone and GDF15 rose acutely and this effect was absent in *Gdf15* $^{-/-}$ mice. Similarly, in a mouse model of tumor (PDX- NSCLC)-induced cachexia, circulating GDF15 and corticosterone were elevated compared to non-tumor bearing mice. Treatment with anti-GDF15 mAB2 completely attenuated tumor-induced corticosterone and reversed cachexia. Consistent with its proposed role as a sentinel hormone, GDF15 is required for the activation of the protective HPA response to stress. Furthermore, GDF15 may contribute to cachexia through the catabolic effects of chronically increased circulating glucocorticoids, implying potential therapeutic utilities of neutralization of GDF15 in disease states.

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Z3 *(9 minutes + 3 minutes discussion)*

MC4R antagonism for appetite and body weight regulation – from human genetics to aged rat model

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Geriatric anorexia, loss appetite in adults late in life, is associated with adverse outcomes including involuntary weight loss, malnutrition, sarcopenia, frailty, and increased mortality (1). The melanocortin-4 receptor (MC4R) is a G protein-coupled receptor (GPCR) primarily expressed in the brain and has been demonstrated playing a key role in the regulation of appetite and body weight in human and preclinical models. Human MC4R loss-of-function variants exhibit hyperphagia and obesity (2), and numerous non-clinical studies demonstrate that deficiencies in MC4R signaling through genetic and pharmacological approaches result in increased food intake and body weight (3). An imbalance in MC4R signaling has been reported in aged rats where there is increased activity or hypersensitivity of the receptor, resulting in reduced food intake and weight loss. We hypothesized that antagonism of MC4R may improve appetite loss and increase weight gain in geriatric anorexia. To test the hypothesis, we assessed the efficacy of PF-07258669, a potent and selective MC4R antagonist, in the 24-month-old male Wistar rats. PF-07258669 demonstrated robust efficacy in increasing body weight and food intake in a dose-dependent manner. Circulating GDF15 level was reported to be elevated in chronic disease conditions such as cancer cachexia and was demonstrated to play a causal role in anorexia and weight loss in tumor models. It was also reported to be increased with aging in human and mice. We found plasma GDF15 was higher in the aged rats compared to the young rats (from ~ 0.1 ng/ml in 6-m old rat to ~0.2 ng/ml in 29-m old rats) which prompted us to examine if elevated GDF15 contributing to anorexia and weight loss in aged associated anorexia and weight loss in these animals. The aged rats were administered with an anti-GDF15 antibody mAb2. Unlike the MC4R antagonist, mAb2 did not improve food intake and bodyweight indicating GDF15 was not causal to anorexia and weight loss in the aged rats. Our results suggest MC4R antagonism is a potential therapeutic approach to alleviate appetite loss in older adult with involuntary weight loss and malnutrition.

Z4 *(9 minutes + 3 minutes discussion)*

Beyond cachexia: the inhibition of antitumoral immune responses by cachexia-inducing tumor-derived factor GDF-15

Christine Schuberth-Wagner
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Growth and differentiation factor 15 (GDF-15, also known as macrophage inhibitory cytokine MIC-1) is a divergent member of the transforming growth factor beta (TGF-ß) superfamily. In mice and monkeys, GDF-15 was shown to induce anorexia and cachexia via the brainstem-restricted receptor GFRAL. Importantly, various major tumor types secrete high levels of GDF-15 correlating with poor prognosis and reduced overall survival. However, in non-diseased conditions the highest physiological GDF-15 expression occurs during pregnancy. Anorexia or cachexia are, however, neither observed during pregnancy nor likely to protect the fetus, so why is it important for a viable pregnancy? Meanwhile, GDF-15 is understood as an essential factor for feto-maternal tolerance induction and low GDF-15 serum levels even predict miscarriage. Tumours hijack the mechanisms of GDF-15 mediated tolerance induction leading to modulation of the tumor microenvironment by direct and indirect effects on innate and adaptive immune cells: tumor-derived GDF-15 suppresses activation of antigen-presenting cells, inhibits priming of naïve T cells by dendritic cells, limits infiltration of immune cells into immune depleted tumors, and supports generation of immunosuppressive cell types to generate an anti-inflammatory tumor microenvironment. In conclusion, GDF-15 secretion helps tumors to generate a microenvironment of a tumor-promoting, anti-inflammatory phenotype. By overcoming low immune cell infiltration and low inflammation in tumors, GDF-15 neutralizing antibodies may synergize with other immunotherapeutic agents. A clinical phase 2 trial combining anti-GDF-15 (CTL002) with anti-PD-1 (NCT04725474) is ongoing.

POSTER SESSIONS

Poster Session 1.1 **Cancer cachexia I (posters 4-14 to 4-23 + 5-04)**
Chairs: Andrea Bonetto, Andreas Fischer

4-14
Presence of Sarcopenia, Cachexia or Low Muscle Attenuation is Associated with Poor Survival in Ambulatory Cancer Patients Receiving Systemic Therapy in Ireland (SARCONC Study)
***Erin Stella Sullivan*[1,2], *Louise E Daly*[1,2], *Éadaoin B Ní Bhuachalla*[1,2], *Samantha J Cushen*[1,2], *Derek G Power*[2,3], *Aoife M Ryan*[1,2]**
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4-15
Tumor metabolic activity is associated with myosteatosis and reduced survival in patients with non-small cell lung cancer
***Yan Sun*[1], *Min Deng*[1], *Olivier Gevaert*[2], *Shaimaa Hesham Bakr*[2], *Merel Aberle*[1], *Steven W.M.Olde Damink*[1,3], *Sander S. Rensen*[1]**
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4-16
Assessment of muscle and lean mass in colon cancer patients on chemotherapy: correlations of d3-creatine, dual energy x-ray absorptiometry and computed tomography
***Elizabeth M. Cespedes Feliciano*[1], *Mahalakshmi Shankaran*[2], *Edna Nyangau*[2] *Marc Hellerstein*[2], *William Evans*[2], *Peggy Cawthon*[3,4], *Jeffrey A. Meyerhardt*[5], *Bette Caan*[1]**
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4-17
Making cachexia reversible: What is the priority strategy for aggressive intervention? A systematic review
***Inês Tavares*[1,2], *Pedro Miguel Neves*[2,3], *Manuel Luís Capelas*[2,3], *Antti Makitie*[4,5,6], *Paula Ravasco*[2,7,8]**
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4-18

Genetic susceptibility to cancer cachexia – A literature review

***Joana M.O. Santos*[1,2], *Alexandra C. Costa* [1,3], *Valéria Tavares* [1,2,4], *Rui M. Gil da Costa* [1,5], *Rui Medeiros* [1,2,3,4,6,7]**

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4-19

NAD+ repletion with niacin counteracts cancer cachexia

***Marc Beltrà*[1], *Noora Pöllänen*[2], *Claudia Fornelli*[1], *Kialiina Tonttila*[3], *Myriam Y. Hsu*[4], *Sandra Zampieri*[5,6], *Lucia Moletta*[5], *Paolo E. Porporato*[4], *Riikka Kivelä*[3,7], *Marco Sandri*[6,8], *Juha J. Hulmi*[9], *Roberta Sartori*[6,8], *Eija Pirinen*[2], *Fabio Penna*[1]**

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4-20

The p97-Nploc4 ATPase complex plays a role in muscle atrophy during cancer and amyotrophic lateral sclerosis

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4-21

Colorectal Cancer-induced Cachexia Reduces *DNMT3a* and Differentially Alters the Skeletal Muscle Transcriptome by Biological Sex

***Ana Regina Cabrera*[1], *Francielly Morena da Silva*[1], *Seongkyun Lim*[1], *J. William Deaver*[1], *Tyrone A. Washington*[2], *Kevin A. Murach*[3], *Nicholas P. Greene*[1]**

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4-22

OPA1 overexpression may protect against cancer-induced muscle wasting

***Stavroula Tsitkanou*[1], *Seongkyun Lim*[1], *Francielly Morena da Silva*[1], *Ana Regina Cabrera*[1], *Eleanor R. Schrems*[2], *Tyrone A. Washington*[2], *Kevin A. Murach*[3], *Nicholas P. Greene*[1]**

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4-23

Activation of Akt-mTORC1 signaling reverts cancer-dependent muscle wasting

***Alessia Geremia*[1,2], Roberta Sartori[1], Martina Baraldo[1,2], Leonardo Nogara[1,2], Valeria Balmaceda[1], Georgia Ana Dumitras[2], Stefano Ciciliot[1], Marco Scalabrin[1,2], Hendrik Nolte[3], Bert Blaauw[1,2],**

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5-04

Targeted nutritional intervention attenuates experimental lung cancer cachexia

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Poster session 1.2 **Diagnosis of cachexia and sarcopenia I** (posters 1-25 to 1-33)
Chairs: Wolfram Doehner, Peter Martini

1-25

A standardized approach for the assessment of skeletal muscle index depletion based on T-scores in patients with cancer

***Catherine Kubrak*[1], Lisa Martin[2], Aaron J. Grossberg[3], Brennan Olson[4], Faith Ottery[5], Naresh Jha[6], Rufus Scrimger[6], Brock Debenham[6], Neil Chua[7], John Walker[7], *Vickie Baracos*[1]**

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1-28

Sarcopenic gastrointestinal cancer patients have higher plasma levels of ST2

***Friederike Stephan*[1], Simone Heisz[1], Tanja Kraußß[1], Hanna Kuzi[3], Klaus-Peter Janssen[3], Marc Martignoni[3], Hans Hauner[1,2], Olga Prokopchuk[3]**

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1-29

MicroRNA-22 as a potential diagnostic tool in males with sarcopenic heart failure: Results from the Studies Investigating Co-morbidities Aggravating Heart Failure (SICA-HF)

Mirela Vatić[1,2], Anselm A. Derda[3,4], Tania Garfias-Veitl[1,2], Goran Lončar[1,5,6], Stefan D. Anker[7,8,9], Thomas Thum[3,10,11], Stephan von Haehling[1,2]

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1-31

Verification of an effective grip-strength order for the diagnosis of possible sarcopenia in Korean population

Seon-Ho Eom[1], Hyeoijin Kim[2], Hyun-Joo Kang[3], Chul-Hyun Kim[3]

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1-32

Case-findings from the ESPEN EASO 2022 diagnosis procedure to detect sarcopenic obesity among community-dwelling older adults: insights from an observational study designed within a prevention care-path

Leo Delaire[1], Aymeric Courtay[1], Joannès Humblot[1], Emma Vivier[1], Rihab Hassoun-Barhamji[1], Marc Bonnefoy[1, 2]

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1-33

Novel adaption to the pediatric SARC-F score to classify pediatric hemato-oncology patients with functional sarcopenia

Emma J. Verwaaijen[1], Patrick van der Torre[1], Josef Vormoor[1,2,3], Rob Pieters[1], Marta Fiocco[1,4], Annelies Hartman[5], Marry M. van den Heuvel-Eibrink[1]

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Poster session 1.3 **Cachexia - mechanisms I** (posters 3-09 to 3-18)
Chairs: Alessio Molfino, Marco Sandri

3-09
Modulating the Sympathetic Nervous System: Role in tissue wasting and inflammation in a novel mouse model for Cancer-Associated-Cachexia
***Casian-Simon Aioanei*[1], *Latifa Bakiri*[1], *Marta Dudek*[1], *Rudolf Zechner3, Erwin F. Wagner*[1,2]**
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3-10
Interleukin-6 initiates wasting in a novel C57BL/6 model of cancer-associated cachexia
***Isabella Pototschnig*[1], *Ursula Feiler*[1], *Paul W. Vesely*[2], *Thomas Rauchenwald*[1], *Peter Hofer*[1], *Rudolf Zechner*[1,3], *Martina Schweiger*[1,3]**
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3-11
The effect of chemotherapy and fish oil supplementation on myosteatosis in a preclinical model of colorectal cancer: Does skeletal muscle fiber type composition matter?
Leila Baghersad Renani, Karen Martins, Sarah Morland, Alaa Almasud, Vera C. Mazurak
University of Alberta, Canada

3-12
Leucine-rich diet enhanced the PI3K-AKT-mTOR pathway expression profile during cancer cachexia but not in cancer cachexia-associated sarcopenia
Leisa Lopes-Aguiar, Gabriela de Matuoka e Chiocchetti, Rogério Willians dos Santos, Maria Cristina Cintra Gomes-Marcondes
Laboratory of Nutrition and Cancer, Department of Structural and Functional Biology, Biology Institute, University of Campinas, Campinas, São Paulo, Brazil

3-14
A mutation in desmin causes cardiac remodeling, altered proteome-wide protein fluxes, fibrosis and arrhythmia
***Agata A. Mossakowski*[*1,3], *Henning T. Langer*[*2], *Suraj J. Pathak*[1], *Alec M. Avey*[1], *Alec Bizieff*[4], *Phung N. Thai*[5], *Nipavan Chiamvimonvat*[5], *Hermann Zbinden-Foncea*[6], *Marc Hellerstein*[4] , *Keith Baar*[1,2]**
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*Contributed equally to the work

3-15
L-Leucine supplementation modulated muscle strength but unchanged the cachexia parameters in tumour-bearing mice
Natália Angelo da Silva Miyaguti, Laura Rodrigues Ferreira, Gabriela de Matuoka e Chiocchetti, Rogério Willians dos Santos, Maria Cristina Cintra Gomes-Marcondes
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3-16
C26 tumors induce body wasting independently of insulin resistance in Balb/c mice
***Pauline Morigny*[1], *Estefania Simoes*[1,2], *Honglei Ji*[1], *Angela Trinca*[1], *Doris Kaltenecker*[1], *Julia Geppert*[1], *José Pinhata Otoch*[2], *Stephan Herzig*[1], *Marilia Seelaender*[2], *Maria Rohm*[1]**
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3-17
Characterization of IL-6 and GDF15 expression during the transition from pre-anorexia to anorexia in the C26 tumor-bearing mouse model
***Ghita Chaouki*[1], *Laurent Parry*[1], *Laure Bindels*[2], *Céline Jousse*[1], *Isabelle Papet*[1], *Julien Averous*[1], *Alain Bruhat*[1], *Etienne Lefai*[1], *Pierre Fafournoux*[1] and *Anne-Catherine Maurin*[1]**
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3-18
Reduced homeostatic and enhanced hedonic feeding behavior in mice with Pancreatic ductal adenocarcinoma (PDAC)
***Fateema Muzaffar*[1], *Gauhar Ali*[1], *William Colmers*[2], *Vickie Baracos*[1]**
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Poster session 1.4 **Therapeutic development I** (posters 6-01 to 6-10)
Chairs: Andrew Judge, Jochen Springer

6-01
Cachexia Trials Advisory Board and Trials Network: A route map for cachexia research progression
Barry J A Laird*[1], *Richard J E Skipworth*[2], *Denis C Guttridge*[3], *Jose Garcia*[4,5], *Tora Solheim*[6], *Teresa A Zimmers*[7,8], *on behalf of the Cancer Cachexia Society
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6-04
Long term dietary fish oil treatment is more effective than short term fish oil in reducing FOLFIRI induced inflammation in a preclinical model of colorectal cancer
***Peter Isesele*[1], *Bhumi Bhatt*[2], *Sambasivarao Damaraju*[2], *Vera C Mazurak*[1]**
[1]Department of Agricultural Food and Nutritional Science, University of Alberta, Edmonton, Alberta, Canada, [2]Department of Laboratory Medicine and Pathology, Faculty of Medicine and Dentistry, University of Alberta, Edmonton, Canada

6-05
Comparison of low and medium frequency electromyostimulation on the lower extremities
Jae Woong Han, Hyeong Ho Baek, Tae Soo Bae
Jungwon University, Chungcheongbuk-do, South Korea

6-06
Testosterone levels dictating the maturation and antigen presentation of dendritic cells in a colorectal cancer cohort.
***Ioanna Drami*[1,2], *Edward T Pring*[1], *Lydia Durant*[1], *Dinh Mai*[2], *Laura E Gould*[2], *Nikolaos Demertzis*[1], *John T Jenkins*[1,2], *Stella C Knight*[1]**
[1]Imperial College London, South Kensington, London, UK; [2]St Mark's Hospital and Academic Institute, Harrow, UK

6-08
Metoprolol attenuates stimulated lipolysis in adipose tissue from cachectic patients with pancreatic cancer
***Lenka Rossmeislová*[1], *Jan Hrudka*[2], *Zuzana Varaliová*[1], *Marek Wilhelm*[1], *Jan Gojda*[3]**
[1]Department of Pathophysiology, Centre for Research on Nutrition, Metabolism and Diabetes, Third Faculty of Medicine, Charles University; [2]Department of Pathology, Kralovske Vinohrady University Hospital and Third Faculty of Medicine; [3]Department of Internal Medicine, Kralovske Vinohrady University Hospital and Third Faculty of Medicine, Czech Republic

6-09
Deletion of FNDC5/Irisin protects against cancer induced cachexia syndrome
***Anika Shimonty*[1], *Joshua R. Huot*[1,2], *Andrea Bonetto*[1,2,3,4,5] *Lynda F. Bonewald*[1,4,5], *Fabrizio Pin*[1,4,5]**
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6-10
Anti-RANKL treatment attenuates sarcopenia via suppressing inflammation and macrophage infiltration
***Can Cui*[1], *Yufeng Long*[1], *Wujian Lin*[1], *Chaoran Liu*[1], *Ronald Man Yeung Wong*[1], *Simon Kwoon-ho Chow*[1] *and Wing-hoi Cheung*[1]**
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Poster session 2.1 **Muscle wasting & sarcopenia – mechanisms I** (posters 2-20 to 2-29)
Chairs: Achim Krüger, Changhan David Lee

2-20
Hyperphosphatemia and chronic inflammation are associated with aging and could be involved in the development of sarcopenia.
***Ana Asenjo-Bueno*[1,2], *Elena Alcalde-Estévez*[1,2], *Javier Zamora*[3], *Gemma Olmos*[1,4,5], *Susana López-Ongil*[2,4,5], *Mª Piedad Ruíz-Torres*[1,4,5]**
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2-21
Mechanosignaling through YAP/TAZ drives fibroadipogenic progenitors activation and promotes paraspinal muscle fibrosis in degenerative scoliosis
Abdukahar Kiram*, *Jie Li*, *Zongshan Hu*, *Ziyang Tang*, *Yanjie Xu*, *Zezhang Zhu*, *Yong Qiu*, *Zhen Liu
Division of Spine Surgery, Department of Orthopedic Surgery, Nanjing Drum Tower Hospital, The Affiliated Hospital of Nanjing University Medical School, Nanjing, China

2-23

Hemichannels upregulation and inflammasome activation is associated with instability of the neuromuscular junction during unilateral lower limb suspension in humans

***Giuseppe Sirago*[1], *Julián Candia*[5], *Martino V. Franchi*[1], *Fabio Sarto*[1], *Elena Monti*[1], *Carlo Reggiani*[1,2], *Sandra Zampieri*[1,3,4], *Giuseppe De Vito*[1], *Luigi Ferrucci*[5] , *Marco V. Narici*[1,2,3]**

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2-24

In vitro and In vivo effects of cigarette smoke on adipose and skeletal muscle tissue

***Gert Folkerts*[1], *Lei Wang*[1], *Lieke E.J. van Iersel*[2], *Harry R. Gosker*[2], *Ramon C.J. Langen*[2], *Annemie M.W.J. Schols*[2], *Josep Argilés*[4], *Ardy van Helvoort*[2,3], *Paul A.J. Henricks*[1], *Saskia Braber*[1*]**

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2-25

Ethanol causes temporally clustered perturbations across the skeletal muscle multiome

***Nicole Welch*[1,2], *Ryan Musich*[1], *Avinash Kumar*[1], *Saurabh Mishra*[1], *Shashi Singh*[1], *Annette Bellar*[1], *Jinendiran Sekar*[1], *Amy Attaway*[1,3],*Manikandan Karthikeyan*[1], *Raya Tabbalat*[1], *Jasmine King*[1], *Alexis Kerr*[1], *Vandana Agrawal*[1], *Laura Nagy*[1], *Srinivasan Dasarathy*[1,2]**

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2-27

Comparison of skeletal muscle changes at three vertebral levels following radiotherapy in patients with oropharyngeal carcinoma

***Belinda Vangelov*[1,2], *Judith Bauer*[3], *Daniel Moses*[4,5], *Robert Smee*[1,2,6]**

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2-28

The change in skeletal muscle mass during (chemo) radiotherapy of head and neck cancer patients

***Anouk W.M.A. Schaeffers*[1], *H.Anette Scholten*[1], *Floris C.J. Reinders*[2], *Annemieke Kok*[3], *Carla H. van Gils*[4], *Caroline M. Speksnijder*[1,5], *Remco de Bree*[1]**

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2-29
Associations between body composition variables and tumor features in male clear cell renal cell carcinoma (ccRCC) patients
***Emily Stein*[1], *Stacey Petruzella*[1], *Andrea Knezevic*[1], *Patrick Bradshaw*[2], *Alejandro Sanchez*[3], *Michael Paris*[4], *Marina Mourtzakis*[5], *Bette Caan*[6], *Helena Furberg*[1]**
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Poster session 2.2 **Cancer cachexia II** (posters 4-24 to 4-36)
Chairs: Andrea Bonetto, Andreas Fischer

4-24
Low HMG-CoA Reductase Gene Expression in the Liver of Patients with Cancer Cachexia
***Silvio Pires Gomes*[1,4], *Gabriela Salim de Castro*[2,4], *Daniela Caetano Gonçalves*[3], *Ivanir Santana de Oliveira Pires*[2], *Alessandro Rodrigo Belon*[4], *Linda Ferreira Maximiano*[5], *Flávio Tokeshi*[5], *Paulo S Alcantara*[5], *José P Otoch*[4,5], *Marilia Seelaender*[4]**
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4-25
Muscle Wasting in Early-stage Cancer is Associated with Disorganized Extracellular Matrix Distinct from Fibrosis
***Erin E. Talbert*[1, 2], *Natalia Weinzierl*[1], *Denis C. Guttridge*[3, 4]**
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4-26
Elevated systemic lipocalin 2 levels in cachectic patients are associated with neutrophil activation
***Min Deng*[1], *Merel R. Aberle*[1], *Annemarie AJHM van Bijnen*[1], *Gregory van der Kroft*[1,2], *Kaatje Lenaerts*[1], *Ulf P. Neumann*[1,2], *Georg Wiltberger*[2], *Frank G. Schaap*[1,2], *Steven W.M. Olde Damink*[1,2], *Sander S. Rensen*[1]**
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4-27
Masseter thickness index as an anthropometric prognostic biomarker in head & neck cancer cachexia: A retrospective pilot study
***Julián Balanta-Melo*[1,2], *Alexander J. Jones*[3], *Michael G. Moore*[3], *Andrea Bonetto*[4]**
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4-29

Cardiomyoblasts mitochondrial activity is altered in an *in vitro* model of cardiac cachexia induced by Walker-256 tumour

Maiara C Colombera, Gabriela M Chiocchetti, André G Oliveira; Maria Cristina C Gomes-Marcondes

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4-30

Increase of TIMP-1 expression and volume loss in subcutaneous fat predict poorer survival of patients with pancreatic ductal adenocarcinoma

Olga Prokopchuk[1,2], Hanna Kuzi[1,2], Chris D. Hermann[1], Benjamin Schoeps[1], Daniela Junker[3], Percy Knolle[1], Helmut Friess[2], Marc E. Martignoni[2], Jeannine Bachmann[2], Achim Krüger[1]

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4-32

Study of the histological and inflammatory rearrangements of the subcutaneous adipose tissue among gastrointestinal cancer patients with cachexia

Alessio Molfino[1], Giovanni Imbimbo[1], Raffaella Carletti[1], Roberta Belli[1], Elena Belloni[2], Federica Tambaro[1], Maria Ida Amabile[1], Cesarina Ramaccini[1], Giuseppe Nigri[2] and Maurizio Muscaritoli[1]

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4-33

Gene expression analysis in lung cancer patients with anorexia

Alessio Molfino[1], Giovanni Imbimbo[1], Federica Tambaro[1], Francesca Ambrosani[2], Roberta Belli[1], Mari Ida Amabile[1], Silvia Udali[2], Sara Moruzzi[2], Cesarina Ramaccini[1], Simonetta Friso[2], Maurizio Muscaritoli[1]

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4-34

Intramuscular lipid alterations in human pancreatic cancer cachexia

Min Deng[1], Jianhua Cao[3], Gregory van der Kroft[1,2], Merel R. Aberle[1], Andrej Grgic[3], Ulf P. Neumann[1,2], Georg Wiltberger[2], Benjamin Balluff [3], Ron M. A. Heeren[3], Frank G. Schaap[1], Steven W.M. Olde Damink[1,2], Sander S. Rensen[1]

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4-36

Superior effects of the novel long-acting ghrelin agonist PEP-064 vs. Anamorelin in the LLC model of cancer cachexia

Søren Ljungberg Pedersen[1], Kristin Löbner[2], Annette G. Beck-Sickinger[2], Keld Fosgerau[1]

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Poster session 2.3 **Physical activity & training** (posters 7-02 to 7-08)
Chairs: Anne May, Ashley Smuder

7-02
The role of resistance exercise training for improving cardiorespiratory fitness in healthy older adults: a systematic review.
***Thomas FF Smart*[1,2,3], *Brett Doleman*[1,2,3], *Jacob Hatt*[1,2,3], *Melanie Paul*[1,2,3], *Suzanne Toft*[3], *Jonathan N Lund*[1,2,3], *Beth E Phillips*[1,2]**
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7-03
The relationship between CT-derived sarcopenia, measures of pre-treatment fitness, and systemic inflammation in patients with OG cancer
***Josh McGovern*[1], *Jenna Delaney*[2], *Matthew J Forshaw*[3], *Gerard McCabe*[1], *Andrew B Crumley*[1], *David McIntosh*[1], *Richard JE Skipworth*[4], *Barry J Laird*[4], *Paul G Horgan*[1], *Donald C McMillan*[1], *Stephen T McSorley*[1], *Ross D Dolan*[1]**
On behalf of The Caledonian Cachexia Collaborative
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7-08
Functional Capacity evaluation in older adults affected by CoVid-19
***Maria Teresa Tomás*[1], *Filipe Pereira*[2], *Anália Clérigo*[1], *Gonçalo Saldanha*[3], *Afonso Gonçalves*[3], *João Carrapiço*[3], *José Miguel Lopes*[3], *Margarida Ribeiro*[1]**
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Poster session 2.4 **Diagnosis of cachexia and sarcopenia II** (posters 1-02 to 1-12 + 1-26)
Chairs: Wolfram Doehner, Peter Martin

1-02
An investigation into the impacts of early access to a dietitian-led multimodal cancer cachexia intervention in metastatic cancer (CACHEXIA-CARE): Evaluating Utility of Cachexia Diagnostic Methods
***Erin Stella Sullivan*[1,2], *Clodagh M Scannell*[1,2], *Derek G Power*[2,3], *Aoife M Ryan*[1,2]**
[1]School of Food and Nutritional Sciences, College of Science, Engineering and Food Science, University College Cork, Cork, Ireland; [2]CancerResearch@UCC, University College Cork, Cork, Ireland; [3]Department of Medical Oncology, Mercy University Hospital, Cork, Ireland.

1-03
Investigating the expression pattern of a novel gene in a cancer cachexia biobank
***Bahareh Nemati Moud*[1], *Simone Heisz*[1], *Tanja Krauss*[1], *Olga Prokopchuk*[2], *Klaus-Peter Janssen*[2], *Marc Martignoni*[2], *Melina Claussnitzer*[3], *Claudine Seeliger*[1], *Hans Hauner*[1]**
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1-04

Body composition assessment by artificial intelligence from routine CT scans in colorectal cancer, introducing BodySegAI

***Dena Helene Alavi*[1], *Tomas Sakinis*[2], *Hege Berg Henriksen*[1], *Benedicte Beichmann*[1], *Ann-Monica Fløtten*[3], *Rune Blomhoff*[1,4], *Peter Mæhre Lauritzen*[3]**

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1-05

The association of body composition with postoperative complications and length of hospital stay after nephrectomy in patients with renal cell cancer: a multicenter population-based cohort study

***Scott Maurits*[1], *Michiel Sedelaar*[2], *Katja.Aben*[1,3], *Lambertus Kiemeney*[1,2], *Alina Vrieling*[1]**

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1-06

Anogenital distance and body composition in rectal cancer patients

***Ioanna Drami*[1,2], *Dinh Mai*[2], *Edward T Pring*[1], *Laura E Gould*[2], *John T Jenkins*[1,2]**

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1-07

Body composition and volumetric aortic calcification measurement in colorectal cancer patients

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1-11

Automated body composition assessment from single vs. multi-slice abdominal Computed Tomography: Concordance and associations with outcomes after colorectal cancer diagnosis

***Ijeamaka Anyene*[1], *Bette Caan*[1], *Grant R. Williams*[2], *Karteek Popuri*[3], *Leon Lenchik*[4], *Smith Giri*[2], *Vincent Chow*[3], *Mirza Faisal Beg*[2], *Elizabeth M. Cespedes Feliciano*[1]**

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1-12

Towards artificial intelligence: point-of-care musculoskeletal ultrasound correlates with body composition, muscle strength and physical performance in children with acute lymphoblastic leukemia

***Emma J. Verwaaijen*[1], *Annelienke M. van Hulst*[1], *Jeroen Molinger*[2], *Annelies Hartman*[3], *Martha A. Grootenhuis*[1], *Erica L.T. van den Akker*[4], *Marry M. van den Heuvel-Eibrink*[1]**

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1-26

Two years of aging – initial results on changes in muscle composition in the UK Biobank imaging study

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

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Poster session 3.1 **Muscle wasting & sarcopenia – mechanisms II** (posters 2-01 to 2-09)
Chairs: Denis Guttridge, Milan Holecek

2-01

Dynapenic abdominal obesity as a risk factor for cardiovascular mortality

***Paula Camila Ramírez*[1,2], Dayane Capra de Oliveira[1], Roberta de Oliveira Máximo[1], Aline Fernanda de Souza[1], Mariane Marques Luiz[1], Maicon Luís Bicigo Delinocente[3], Andrew Steptoe[4], Cesar de Oliveira[4], Tiago da Silva Alexandre*[*1,3,4,5]**

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2-02

Cross-sectional and longitudinal impact of congestion on body composition analysis in patients with heart failure

***Tania Garfias-Veitl*[1,2], Dahlia Al-Mudaris[1], Mirela Vatic[1,2], Goran Loncar[1,3,4], Wolfram Doehner[5,6,7], Stefan D. Anker[5,7,8], Stephan von Haehling[1,2]**

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2-04

Metabolites of gut microbiota and nutritional status in kidney transplant recipients and hemodialysis patients

Sylwia Czaja-Stolc, Sylwia Małgorzewicz

Department of Clinical Nutrition, Medical University of Gdansk, Gdansk, Poland

2-05

Frailty in the elderly after CoViD-19 – a pilot study

***Filipe Alexandre Pereira*[1], Maria Teresa Tomás[1,2]**

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2-07

Long-haul COVID-19 is related to lower pectoralis muscle mass at hospital admission for treatment of acute infection

***Gabriela S. de Castro*[1], Camila E. Orsso[2], Ana Paula N. Barrére[1], Marta Imamura[3,4], Linamara R. Battistella[3,5], Geraldo Busatto[6], Marcio Sawamura[7], José P. Otoch[8], Carla M. Prado[2], Marilia Seelaender[1]**

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2-09
Chronic mild stress and diabetes lead to muscle atrophy and osteopenia
Lorenza Guarnieri, Francesca Bosco, Annarita Coppoletta, Antonio Cardamone, Rosamaria Caminiti, Cristina Carresi, Micaela Gliozzi, Vincenzo Musolino, Ernesto Palma, Vincenzo Mollace
Institute of Research for Food Safety and Health IRC-FSH, Department of Health Sciences, University Magna Graecia of Catanzaro, 88100, Catanzaro, Italy

Poster session 3.2 **Nutrition & appetite** (posters 5-03 to 5-09)
Chairs: Philip Atherton, Adrian Slee

5-03
Leucine-rich diet improves cachexia index and alters tumour thermogenic capacity in Lewis Lung tumour-bearing aged mice
Guilherme Augusto da Silva Nogueira, Natalia Angelo da Silva Miyaguti, Rogerio Williams dos Santos, Maria Cristina Cintra Gomes-Marcondes
Laboratory of Nutrition and Cancer, Department of Structural and Functional Biology, Institute of Biology, University of Campinas—UNICAMP, Campinas, SP, Brazil

5-05
Digital food literacy for improved cancer care: a blended didactic and hands-on approach for healthcare professionals and medical students
Maria Raimundo[1,2], Paula Ravasco[1,2,3]
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5-06
Role of Ensure Protein Max on calorie and protein intake, appetite, and body weight in patients with advanced cancer receiving chemotherapy.
Donny Li[1,2,3], Martin Chasen[1,4,5,6,7,8], Ravi Bhargava[4,9], Liliana Astorino[1], Rupdiner Deol[1], Deepanjali Kaushik[1]
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5-07
Leptin, Adiponectin, and Mortality Risk in a Prospective Hemodialysis Cohort
Thuy-Anh Bui, Jerry Yu, Amy S. You, Yoko Narasaki, JiHoon Yoon, Yalitzi Guerrero, Ria Arora, Jasmin Arora, Danh V. Nguyen, Kamyar Kalantar-Zadeh, Connie M. Rhee
University of California Irvine School of Medicine, Orange, CA, USA

5-08
Subjective Global Assessment Scores and Mortality Risk in a Multi-Center Prospective Hemodialysis Cohort
JiHoon Yoon, Yoko Narasaki, Amy S.You, Andrea Daza, Silvina Torres, Lisa Le, Anyssa Dang, Danh V. Nguyen, Kamyar Kalantar-Zadeh, Connie M. Rhee
University of California Irvine School of Medicine, Orange, CA, USA

5-09

High nutritional risk in head and neck cancer radiotherapy: a retrospective analysis of predictors of malnutrition in patients undergoing IMRT

***Adriana Borges*[1], *Antti A. Makitie*[2,3,4,6], *Paula Ravasco* [5,6,7]**

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Poster session 3.3 **Diagnosis of cachexia and sarcopenia III** (posters 1-14 to 1-24)
Chairs: Dimitrios Karampinos, Martina Schweiger

1-14

Associations between muscle ultrasonography, body composition and physical performance in post-menopausal breast cancer survivors

***Vitor Hugo Azevedo*[1,2,3], *Antonio L Palmeira*[1], *Flávio Jeronimo*[1], *Sofia Franco*[1], *Inês Nobre*[1], *Vitor Ilharco*[1], *Bruno Rodrigues*[1], *Andreia Dias*[1], *Marlene Silva*[1], *Eliana V Carraça*[1]**

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1-16

Correcting CT muscle measures for intravenous contrast material

***Jevin Lortie*[1], *Benjamin Rush*[1], *Grace Gage*[1], *Ravi Dhingra*[2], *Tim Szczykutowicz*[3], *Adam Kuchnia*[1]**

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1-17

The relationship between CT-derived sarcopenia, systemic inflammation, physical function and survival in patients with advanced cancer

***Josh McGovern*[1], *Ross D Dolan*[1], *Barry J Laird*[2], *Donald C McMillan*[1]**
On behalf of The Caledonian Cachexia Collaborative

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1-18

Validation of automated whole body skeletal muscle, adipose tissue, bone, and multi-organ segmentation and vertebral level identification from multi-slice CT images: towards extended body Composition

***Da Ma*[1,2,3], *Vincent Chow*[1,2], *Karteek Popuri*[1,2,4], *Mirza Faisal Beg*[1,2]**

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1-19

A systematic review of automated volumetric segmentation from computed-tomography scans: bringing body composition analysis closer to routine clinical practice

***Dinh V C Mai*[1], *Ioanna Drami*[2], *Edward T Pring*[1], *Laura E Gould*[1], *Karteek Popuri*[2], *Vincent Chow*[3], *Mirza F Beg*[3], *John T Jenkins*[1]**

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1-22
The development of a method to assess skeletal muscle mass at the level of the third cervical vertebra in head and neck cancer patients
***Maartje A. van Beers*[1], *Justin E. Swartz*[1], *Najiba Chargi*[1], *Sandra I. Bril*[1], *Ernst J. Smid*[2], *Jan Willem Dankbaar*[3], *Remco de Bree*[1]**
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1-23
Effect of total knee replacement on skeletal muscle mass measurements using dual energy x-ray absorptiometry
***Chang Won Won*[1], *Jaeyoung Jang*[2], *Miji Kim*[2]**
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1-24
Correlations between muscle area and attenuation measurements at L3, T10 and L3 psoas when diagnosing sarcopenia and myosteatosis in oncology patients
Olivia Curtis*, *Nadia Yousaf*, *Katarzyna Abramowicz
Royal Marsden Hospital, London, UK

Poster session 4.1 **Therapeutic development II** (posters 6-11 to 6-19)
Chairs: Yi-Ping Li, Anne-Catherine Maurin

6-11
Inhibition of proteolysis through chloroquine but not bortezomib exacerbates fasting-induced tissue wasting
***Henning T. Langer*[1,2], *Sam R. Taylor*[1,2], *Marcus D. Goncalves*[1,2]**
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6-12
Weight Change and Clinical Outcomes in Heart Failure with Reduced Ejection Fraction: Insights from the EMPEROR-Reduced trial
Wolfram Doehner
Department of Cardiology and Berlin Institute of Health Center for Regenerative Therapies, and German Centre for Cardiovascular Research (DZHK) partner site Berlin; Charité Universitätsmedizin Berlin, Germany

6-13
Pectoralis major flap to compensate for increased risk of pharyngocutaneous fistula in laryngectomy patients with low skeletal muscle mass: study protocol for a randomized controlled trial
***Maartje A. van Beers*[1], *Caroline M. Speksnijder*[1,2], *Carla H. van Gils*[3], *Geert W.J. Frederix*[3], *Jan Willem Dankbaar*[4], *Remco de Bree*[1]**
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6-14

Protocol for a phase II double-blind placebo controlled parallel arm fixed dose multi-site trial of anamorelin for anorexia in small cell lung cancer: The LUANA trial

***Mariana S. Sousa*[1], *Peter Martin*[2], *Miriam Johnson*[3], *Matthew Maddocks*[3,4], *Alex Bullock*[3], *Meera Agar*[1], *Sungwon Chang*[1], *Slavica Kochovska*[1,4], *Irina Kinchin*[5], *David Currow*[1,4]**
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*Michael Lind[3]; Deidre Morgan[6]; Belinda Fazekas[1]; Valentina Razmovski-Naumovski[1]; Linda Brown[1]; John Stubbs[1]; Phillip Lee[1]; Victoria Bray[7]

6-15

Effects of bioarginine c supplementation on functional parameters in adults with long covid: a randomised clinical trial

Matteo Tosato*, *Riccardo Calvani*, *Francesca Ciciarello*, *Vincenzo Galluzzo*, *Francesco Landi
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6-16

Weekly cisplatin versus triweekly cisplatin chemoradiotherapy in head and neck squamous cell carcinoma patients with low skeletal muscle mass: design of the CISLOW randomized clinical trial

***Anouk W.M.A. Schaeffers*[1], *Lot A. Devriese*[2], *Carla H. van Gils*[3], *Jan Willem Dankbaar*[4], *Jens Voortman*[5], *Jan Paul de Boer*[6], *Geert W.J. Frederix*[7], *Remco de Bree*[1]**
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6-17

Cancer appetite recovery study (CAReS): study protocol for a dose-ascending, multicenter, randomized controlled phase 1/2 trial of art27.13 in patients with cancer anorexia and weight loss

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6-18

BIO101 in age-related sarcopenia: results of the SARA Program

***Cendrine Tourette*[1], *Waly Dioh*[1], *Carole Margalef*[1], *Sandrine Rabut*[1], *René Lafont*[1,2], *Pierre Dilda*[1], *Jean Mariani*[1,3], *Sam Agus*[4], *Rob Van Maanen*[1],*Stanislas Veillet*[1]**
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6-19
Neutralization of GDF15 ameliorates muscle weakness and exercise intolerance in Polg^{D257A} mtDNA mutator mice
Bina Albuquerque[1], Anthony Rinald[1], Xian Chen[2], Dinesh Hirenallur Shanthappa[2], Srinath Jagarlapudi[1], Trenton Thomas Ross[1], John Stansfield[3], Abdul Sheikh[1], Bei B. Zhang[1], Zhidan Wu[1]
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Poster session 4.2 **Cachexia - mechanisms II** (posters 3-02 to 3-08)
Chairs: Silvia Busquets, Marco Sandri

3-02
Gut microbiota diversity in cachectic acutely ill geriatric patients
Shirley Steffany Muñoz Fernandez[1], Flavia Barreto Garcez[2], Julio Cesar Garcia de Alencar[3], Heraldo Possolo de Souza[3], Thiago J. Avelino-Silva[2], Laure B. Bindels[4], Sandra Maria Lima Ribeiro[1,5]
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3-03
Iron supplementation is sufficient to rescue skeletal muscle mass and function in cancer cachexia and glucocorticoid induced-atrophy.
Elisabeth Wyart, Myriam Hsu, Roberta Sartori, Erica Mina, Valentina Rausch, Marco Sandri, Alessio Menga and Paolo E Porporato
Department of Molecular Biotechnology and Health Sciences, Molecular Biotechnology Center, University of Torino, Turin, Italy; [2]Department of Biomedical Sciences, University of Padova, Padova, Italy

3-04
Prostaglandins mediate Toll-like receptor-induced hypothalamic inflammation via prostaglandin receptor EP4 in cancer cachexia
Xiaolin Li, Mieke Poland, Renger F. Witkamp & Klaske van Norren
Nutritional Biology, Division of Human Nutrition, Wageningen University, 6708 WE Wageningen, The Netherlands

3-05
Ketogenic diet slows down tumor growth but induces primary adrenal insufficiency that accelerates onset of cachexia in C26 and KPC murine models
Miriam Ferrer[1,2], Thomas R. Flint[3], Nicholas Mourikis[1], Sam O. Kleeman[1], Ashok R. Venkitaraman[2,4,5], Tobias Janowitz[1,6]
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3-06
Overexpression of skeletal muscle PGC1α protects against cisplatin-induced cachexia
Joshua R. Huot[1,2], Fabrizio Pin[2], Rohit Chatterjee[1], Andrea Bonetto[1,2,3,4,5]
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3-07
Understanding BMP signaling in cancer cachexia
***Camilla Pezzini*[1,2], *Roberta Sartori*[1,2], *Adam Hagg*[3], *Paola Costelli*[4], *Fabio Penna*[4], *Giuseppina Caretti*[5], *Vittorio Sartorelli*[6], *Paul Gregorevic*[3], *Marco Sandri*[1,2]**
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3-08
Colon cancer treatment with FOLFIRI exacerbates muscle fiber atrophy and induces a catabolic transcriptional program in skeletal muscle
***Gauhar Ali*[1], *Bhumi Bhatt*[2], *Sambasivarao Damaraju*[2], *Vera Mazurak*[3], *Vickie E. Baracos*[1]**
[1]Department of Oncology, Faculty of Medicine and Dentistry, [2]Department of Laboratory Medicine and Pathology, [3]Division of Human Nutrition, University of Alberta, Edmonton, AB Canada

Poster session 4.3 **Cancer cachexia III** (posters 4-02 to 4-12 + 4-31)
Chairs: Sören Fisker Schmidt, Fabio Penna

4-02
Medium-chain triglycerides as a nutritional supplementation against Cancer Cachexia
Lorena Garcia-Castillo, Marc Beltrà, Fabio Penna, Paola Costelli
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4-03
The impact of cachexia on anorexia, dietary intakes, and quality of life in patients with advanced cancer
***Koji Amano*[1,2], *Vickie E Baracos*[3], *Tatsuya Morita*[4], *Tomofumi Miura*[5], *Naoharu Mori*[2], *Erika Nakanishi*[6,7], *Jun Kako*[8] , *Mitsunori Miyashita*[6]**
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4-04
The relationship between cachexia and inflammatory biomarkers in patients with cancer; initial findings from the REVOLUTION cachexia characterisation study
Robert Paval*[1], *Rebekah Patton*[2], *Judith Sayers*[2,3], *Marie Fallon*[2], *Richard J E Skipworth*[3], *Barry J A Laird*[2], *Iain J Gallagher*[1] *on behalf of the Caledonian Cachexia Collaborative
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4-07

The predictive role of sarcopenic obesity on the overall survival and its association with nutritional parameters in patients with renal cell carcinoma

***Kashia Goto*[1], *Daisuke Watanabe*[1,2], *Kazuki Yanagida*[2], *Takahiro Yoshida*[2], *Akemi Yamashita*[2], *Norikazu Kawae*[3], *Shinobu Mizushima*[1], *Shigeko Okuno*[1], *Hajime Kajihara*[4], *Akio Mizushima*[1]**

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4-08

Identifying cancer patients with cachexia at scale by leveraging self-supervised natural language processing and predictive models on unstructured data in patients' electronic health records

***Atri Sharma*[1], *Jingqing Zhang*[1, 2], *Judith Sayers*[3, 4], *Richard J.E. Skipworth*[3, 4], *Barry J. A. Laird*[3], *Vibhor Gupta*[1], *Yike Guo*[1, 2, 5]**

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4-09

Examining the negative impact of weight loss and cachexia in Chimeric Antigen Receptor (CAR) T-cell therapy

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4-11

Evaluation of weight gain and overall survival of patients with advanced non-small-cell lung cancer (NSCLC) treated with first-line platinum-based chemotherapy

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4-12

A comparison of body composition changes between the FLOT and MAGIC regimes in patients with locally advanced oesophageal cancer

***Mei Sien Liew*[1], *Ahmed Almonib*[1], *Yousif Al-Najjar*[1], *Manjunath Siddaiah-Subramanya*[1], *Benjamin Tan*[1]**

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4-31

Respiratory Muscle Pathology in Esophageal Adenocarcinoma Patients

***Miles Cameron*[1,2], *Alexander Ayzengart*[3], *Olusola Oduntan*[3], *Ziad Awad*[4], *Sarah Judge*[1], *Andy Judge*[1]**

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Poster session 4.4 **Muscle wasting & sarcopenia – mechanisms III** (posters 2-11 to 2-19)
Chairs: Rodney Infante, Sigmar Stricker

2-11

Low levels of 25-hydroxyvitamin D as a risk factor for Sarcopenia in community-dwelling older Chileans

Cecilia Albala, Carlos Márquez, Felipe Salech, Bárbara Angel, Hugo Sánchez
INTA, University of Chile, Clinic Hospital, University of Chile, Chile

2-12

Chronic activation of ALK5/TGFβI signaling in adult mouse skeletal muscle induces severe muscle wasting with concomitant impaired mitochondrial integrity.

Andréa Emerit*[1], Véronique Chauvet*[1], Lola Lessard[1], Damien Roussel[3], Caroline Romestaing[3], Colline Sanchez[1], Thomas Simonet[1], Julien Gondin[1], Girard Emmanuelle[1], Vincent Jacquemond[1], Yann-Gael Gangloff[1], Laurent Bartholin[2], Laurent Schaeffer[1#], Laetitia Mazelin[1#]
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2-13

Mitochondrial degeneration during the progression of sarcopenia in SAMP8 mice model

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2-14

The effect of severe burns on skeletal muscle protein balance in female rats 10 and 40 days post-burn

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2-15

Immobilization combined with caloric restriction as translational mouse model for sarcopenia expressing key pathways of human pathology

Jelle CBC de Jong[1,2], Martien PM Caspers[3], Nanda Keijzer[1], Nicole Worms[1], Joline Attema[1], Christa de Ruiter[1], Simone van der Drift-Droog[1], Arie G Nieuwenhuizen[2], Jaap Keijer[2], Aswin L Menke[1], Robert Kleemann[1], Lars Verschuren[3] and Anita M van den Hoek[1]
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2-17

JQ1 as a possible strategy to improve aging-related sarcopenia and frailty

Alessia Sofia Cento[1], Claudia Fornelli[1], Lorenzo Nevi[2], Paola Costelli[1], Giuseppina Caretti[2], Massimiliano Leigheb[3], Fabio Penna[1]
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2-18

Dipyridamole as a novel therapy for sarcopenia via A2B and AMPK/cAMP signaling.

Miguel Marco-Bonilla, Raquel Herencia, María Fresnadillo, Raquel Largo, Gabriel Herrero-Beaumont, Aranzazu Mediero
IIS-FJD, Bone and Joint Research Unit, Madrid, Spain

2-19

Sex differences in skeletal muscle-ageing trajectory: same processes, but with different magnitudes

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POSTER ABSTRACTS

1-02

An investigation into the impacts of early access to a dietitian-led multimodal cancer cachexia intervention in metastatic cancer (CACHEXIA-CARE): Evaluating Utility of Cachexia Diagnostic Methods

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Introduction: The management of cancer cachexia (CC), remains challenging due to its multifactorial aetiology. Multimodal interventions have been proposed to target the complex aetiology, however, efficacy of interventions is still expected to be poor in advanced CC, but there is no validated means of identifying patients early in the CC trajectory who might benefit from such interventions. This study aims to examine methods to identify patients likely to benefit from multimodal intervention.
Methods: This RCT will recruit 70 patients with incurable pancreatic, oesophageal, gastric or lung cancer due to begin first-line systemic treatment. Patients will be randomised 1:1 (open-label) to intervention or control. The personalised 12-week multimodal intervention delivered by a dietitian includes dietary counselling, symptom management, exercise prescription and 2 daily servings of a novel powdered oral nutritional supplement for reconstitution with a nutrient profile designed to optimise muscle protein synthesis. The control group receive no routine dietetic input. All patients receive standard oncological care and written resources on diet and cancer. Comprehensive nutrition and functional assessments will be conducted at baseline, weeks 2, 4, 8 and 12. The assessments will incorporate routine anthropometry, biochemistry, nutrition focussed physical exam, bioelectrical impedance, timed up and go test and CT body composition analysis (baseline and week 12 only).
Results: The primary outcome is CC prevalence in intervention vs. control at week 12, according to the 2011 International Consensus Criteria, analysed on an intention-to-treat basis. A secondary outcome will be to identify which assessment methods or diagnostic criteria can identify cachexia early in the trajectory and whether these predict which patients respond to the intervention.
Conclusions: This RCT will add to the emerging evidence-base for multimodal interventions in advanced cancer, and will examine the validity of currently available assessment techniques in appropriate selection of patients with potential to benefit from such interventions.

Conflict of Interest Disclosure: ESS is an IRC Enterprise Partnership Scheme Fellow, whose research is funded by the Irish Research Council and Nualtra Ltd. Nualtra Ltd. are providing the oral nutritional supplement for use in this trial at no cost, and the novel ingredient (Amino L40©) is an Ajinomoto product. Nualtra Ltd. is a wholly owned subsidiary of Ajinomoto.

1-03

Investigating the expression pattern of a novel gene in a cancer cachexia biobank

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Background: Cancer cachexia (CC) is a metabolic disorder characterized by muscle and adipose tissue loss, inflammation, and insulin resistance. CC is highly prevalent in gastrointestinal diseases. *COBLL1*, a novel gene located in a type 2 diabetes risk locus, is associated with insulin resistance, and was recently reported to be differentially expressed in subcutaneous adipose tissue (sc) of subjects with PDAC cachexia compared to subjects without cancer. Moreover, *COBLL1* was shown to co-regulate adipogenesis in human sc adipose tissue.
Methods: To investigate the expression pattern of *COBLL1* in tissues of CC patients, we measured the mRNA level of this gene in four different subgroups (number per group ≥ 5) of a biobank using qPCR. The biobank contains liver, muscle, and adipose tissue from gastrointestinal cancer patients with severe (CAC >10%) and moderate cachexia (CAC >5-10%) (weight loss six months before surgery), with cancer without cachexia (-CAC/+ca) and healthy control subjects (-CAC/-ca). In addition, adipose-derived mesenchymal stem cells (AMSCs) from subcutaneous and omental (om) adipose tissue have been isolated and undergone adipogenesis to fully differentiated fat cells (day14).
Results: Only differentiated sc AMSCs showed a significant upregulation of *COBLL1* in CAC >10% compared to the -CAC/-ca group ($p < 0.05$). In addition, we found a significant downregulation of *COBLL1* expression in muscle tissue in the CAC >10% and -CAC/+ca groups compared to the -CAC/-ca group ($p < 0.05$). Finally, in liver tissue, we observed a significant upregulation of *COBLL1* in CAC >10% compared to -CAC/+ca and downregulation of the gene when -CAC/+ca is compared to -CAC/-ca ($p < 0.05$).
Conclusions: Our data suggest that *COBLL1* expression differs between tissues in patients with cancer and with or without cachexia. Further investigations are needed to understand the role of *COBLL1* in cancer cachexia.

1-04

Body composition assessment by artificial intelligence from routine CT scans in colorectal cancer, introducing BodySegAI

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Introduction: Body composition is of clinical importance in colorectal cancer (CRC) patients but is seldom assessed. Routine computed tomography (CT) scans can be used for this purpose, however manual segmentation is very time consuming and automated methods are needed for clinical utility. We developed and tested a deep learning-based

software named BodySegAI for automated quantification of body composition.
Methods: A 2D U-net convolutional network was trained on 2989 abdominal CT slices to segment skeletal muscle mass (SM), visceral adipose tissue (VAT), subcutaneous adipose tissue (SAT), and inter- and intramuscular adipose tissue (IMAT) in multiple slices, from the second lumbar to the first sacral vertebra (L2-S1). Human ground truth was established by combining segmentations from three human readers using Simultaneous Truth and Performance Level Estimation. Body composition assessment by BodySegAI was tested using 154 slices from 32 CRC patients against the human ground truth and also compared to a software named AutoMATiCA. Dice score, Hausdorff distance, sensitivity, specificity, median absolute error, Bland-Altman plots and time-effectiveness were assessed.
Results: Median Dice scores for BodySegAI against human ground truth were 0.969, 0.814, 0.986, and 0.990 for SM, IMAT, VAT and SAT, respectively. The mean difference in segmentation between BodySegAI and human ground truth for SM were -0.09 cm^3, IMAT: -0.17 cm^3, VAT: -0.12 cm^3 and SAT: 0.67 cm^3. Median absolute errors (%) for SM, IMAT, VAT and SAT were 1.35%, 10.54%, 0.91%, and 1.07%, respectively. When analyzing different anatomical levels separately, L3 and S1 demonstrated the overall highest and lowest Dice scores, respectively. BodySegAI presented higher Dice scores for SM, IMAT, SAT and VAT than AutoMATiCA (slices=154). On average, BodySegAI segmented 148 times faster than human readers (4.9 vs. 726.5 seconds, $p<0.001$).
Conclusions: BodySegAI is time-efficient and provides accurate quantifications of body composition in CRC patients in L2 to S1.

1-05

The association of body composition with postoperative complications and length of hospital stay after nephrectomy in patients with renal cell cancer: a multicenter population-based cohort study

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Introduction: Body mass index (BMI) and body composition (BC) have been associated with postoperative outcomes in oncological surgery. Evidence in renal cell cancer (RCC) is limited and inconsistent. Therefore, we examined the association of BMI and BC with postoperative outcomes in patients with RCC.
Methods: We conducted a multicenter population-based historical cohort study including 801 patients with RCC treated with radical (79%) or partial (21%) nephrectomy between 2008-2012. Computed Tomography images at L3 were assessed for skeletal muscle index (SMI), skeletal muscle density (SMD), visceral adipose tissue index (VATI) and subcutaneous adipose tissue index (SATI). Multivariable multilevel logistic regression analyses were used to examine associations of BMI and BC with (major) postoperative complications and extended length of hospital stay (≥7 days) (LOHS). Discrimination of models for major complications was compared using receiver operating characteristics curves.
Results: In total, 19.6% of the patients had postoperative complications (6.2% Clavien grade ≥III) and 24.1% had extended LOHS. A 10-unit increase in SMD was associated with extended LOHS (OR 0.58; 95%CI 0.44-0.78). Associations of high BMI and lower SMD with risk of major complications and of higher VATI with extended LOHS were also observed but statistical significance differed according to surgical procedure. Models predicting major complications with or without BC parameters were not different.
Conclusions: Lower SMD was associated with extended LOHS. High BMI and lower SMD may be associated with major complications and higher VATI with extended LOHS. Validation of these results and investigation of the added value of BC parameters to anatomic classification systems is needed.

1-06

Anogenital distance and body composition in rectal cancer patients

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Introduction: Anogenital distance (AGD) is a sexually dimorphic anatomic landmark that develops in response to hormone signalling during foetal life. Testosterone exposure affects the body composition (BC). The aim of this study was to investigate whether AGD can be a surrogate marker for the BC phenotype.
Methods: Analysis was performed on a prospectively maintained database of male rectal cancer patients (2012-2016). BC analysis was performed on staging CTs, applying the SliceOmatic® software on a single axial abdominal CT landmarked at the 3rd lumbar vertebrae. We calculated sarcopenia, myosteatosis, visceral obesity and sarcopenic obesity, applying internationally used cut off values. AGD was measured on the staging rectal MRI. AGD measurements were performed by a single trained assessor. The AGD was defined as a straight line drawn from the posterior of the scrotum to the middle of the anus, based on the methodology described by *Pedersen et al (2021)*.
Results: 139 male rectal cancer patients with a median age of 67 years old, with available MRI and CT scans were analysed. We excluded 37 patients as the MRI did not include all the important anatomical landmarks for the AGD measurement. The median AGD in our cohort was 79.08mm (min: 44mm, max 146mm). We did not identify a statistically significant correlation between age and AGD (Pearson coefficient -0.052, p 0.545). There was no significant difference in AGD between sarcopenic and non-sarcopenic (p 0.407), myosteatotic and non myosteatotic (p 0.153), those with and those without sarcopenic obesity (p 0.326), those with and those without visceral obesity (p 0.218).
Conclusions: In our population, AGD could not be translated into a surrogate marker for the patient's BC. However, the study has certain limitations including small cohort, limited variation of BC phenotype and potential bias from the single assessor AGD measurement.

1-07

Body composition and volumetric aortic calcification measurement in colorectal cancer patients

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Background: Body composition (BC) affects cancer outcomes and is related to the general inflammatory state. Aortic calcification (AC) is the result of a pro-inflammatory pathway. AC measurement on imaging is performed using semi-quantitative methods manually. Our aim is to identify an association between the BC phenotypes of colorectal cancer (CC) patients and their aortic calcification.

Methods: We used a prospectively maintained CC database from 2012-2015. The body composition analysis was performed on preoperative staging or monitoring CTs, applying the SliceOmatic® software on a single axial abdominal CT landmarked at the 3rd lumbar vertebrae. More specifically we looked at four BC parameters, sarcopenia, myosteatosis, visceral obesity (VO) and sarcopenic obesity (SO), using widely used cut off values. Aortic calcification volume (cm^3) between the first and fifth lumbar vertebrae was calculated using Voronoi's Data Analysis Facilitation Suite *v3.6*. This software harnesses deep learning to automate this process.
Results: We looked at 193 patients, with a median age of 69 years old, of which 54.9% were male. 67.4% were sarcopenic, 82.9% myosteatotic, 6.7% had sarcopenic obesity and 52.8% were characterised by visceral obesity. The median AC was 0.46 cm^3, (min 0, max 6.68). There is a statistically significant weak correlation between AC and myopenia (r_s 0.1, p 0.051), AC and myosteatosis (r_s 0.2, p 0.01), but no statistically significant correlation with SO and VO.
Conclusions: The results suggest that the AC inflammatory pathway might be different to the one driving BC changes. The study's limitations are that of a small cohort, AC is measure is the main vessel while major calcification frequently occurs in the smaller vessel and progresses to the larger size one and finally, we are comparing volumetric 3D aortic calcifications with 2D BC analysis.

1-11

Automated body composition assessment from single vs. multi-slice abdominal Computed Tomography: Concordance and associations with outcomes after colorectal cancer diagnosis

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Background: Computed tomography (CT) scans are routinely obtained in oncology and provide measures of muscle and adipose tissue predictive of morbidity and mortality. Automated segmentation of CT has advanced past single-slice to multi-slice measurements, but the concordance of these approaches and their associations with cancer outcomes have not been compared.
Methods: 2,862 patients with colorectal cancer diagnosed during 2012-2017 at Kaiser Permanente Northern California had sex-specific z-scores calculated for mid-L3 cross-sectional area and multi-slice T12-L5 volumes of skeletal muscle (SKM), subcutaneous adipose (SAT), visceral adipose (VAT), and intermuscular adipose (IMAT) tissues using DAFS, an automated multi-slice segmentation platform. Pearson correlation coefficients and Bland-Altman analysis were used to quantify agreement. Cox models were used to estimate hazard ratios adjusting for age, sex, race/ethnicity, height, and tumor site and stage.
Results: Single-slice area and multi-slice abdominal volumes were highly correlated for all tissues (SKM R=0.92, p<.001; SAT R=0.97, p<.001; VAT R=0.98, p<.001; IMAT R=0.89, p<.001). Bland-Altman plots had a bias of 0 (SE: 0.00), indicating high average agreement between measures. The limits of agreement were narrowest for VAT -0.42 to 0.42 SD and SAT -0.44 to 0.44 SD, and widest for SKM -0.79 to 0.79 SD and IMAT were -0.92 to 0.92 SD. The hazard ratios had overlapping confidence intervals, but similar magnitudes and direction of effects, e.g., 1-SD increase in SKM area was associated with an 18% decreased risk of death (95%CI: 0.73-0.93), vs. 15% for volume from T12-L5 (95%CI:0.75-0.96).
Conclusions: Single-slice L3 areas and multi-slice T12-L5 abdominal volumes of SKM, VAT, SAT and IMAT are highly correlated. Associations between area and volume measures with all-cause mortality were similar, suggesting they are equivalent tools for population studies if body composition is assessed at a single timepoint. Future research should examine longitudinal changes in multi-slice tissues to improve individual risk prediction.

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1-12

Towards artificial intelligence: point-of-care musculoskeletal ultrasound correlates with body composition, muscle strength and physical performance in children with acute lymphoblastic leukemia

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Introduction: Non-invasive and reliable tools to measure muscle mass and muscle quality in children with acute lymphoblastic leukemia (ALL) are limited.
The aim of the study was to explore the association of muscle ultrasound outcomes with standardized assessments of body composition, muscle strength and physical performance in children with ALL.
Methods: In this cross-sectional study we included Dutch ALL patients, aged 3-18 years during maintenance therapy.
Bilateral ultrasound measurements of the rectus femoris (RF) muscles were captured using a portable linear array transducer connected to a tablet. Artificial intelligence image analysis was used to estimate RF muscle thickness, cross-sectional area, intramuscular adipose tissue (IMAT) and raw pixel intensity (RPI), as a proxy for glycogen.
Assessments of body composition (bio-impedance analysis and thigh circumference), muscle strength (hand-held dynamometry) and physical performance (timed up and go test [TUG] and time to rise from floor test [TRF]) were performed during the same appointment.
Spearman's rank correlation analyses (r_s) were calculated to study correlations between ultrasound outcomes and measures of body composition, muscle strength and physical performance.
Results: Muscle ultrasound was performed in 60 patients, 37/60 boys (61.7%), median age 6.1 years (range: 3–18.8 years).
RF thickness and cross-sectional area correlated moderately with muscle mass (r_s=0.58, r_s=0.6), handgrip strength (r_s=0.6, r_s=0.65), knee extension strength (r_s=0.65, r_s=0.68), and highly with thigh circumference (r_s=0.76, r =0.78).
IMAT correlated moderately with TUG (r_s=0.52) and TRF (r_s=0.53), i.e. increased fat infiltration correlated with slower performance.
RPI correlated moderately with handgrip strength (r_s=-0.48), knee extension strength (r_s=0.51), and TUG (r_s=0.5), lower

glycogen correlated with lower strength and slower performance. All p-values were <0.001.
Conclusions: Muscle ultrasound may be useful for measuring muscle mass and muscle quality in children with ALL, allowing rapid and non-invasive assessments. Further validation using golden standard assessments in children is needed to determine the accurateness in pediatric populations.

1-14

Associations between muscle ultrasonography, body composition and physical performance in post-menopausal breast cancer survivors

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Introduction: Muscle ultrasonography has been proposed as an accessible, accurate and reliable tool to assess muscle architecture in conditions such as sarcopenia and cachexia. Ultrasound muscular assessment is correlated with complex and less accessible imaging data such as DXA, MRI and CT. This study sought to analyse the associations between muscle ultrasonography, body composition and physical performance in post-menopausal breast cancer survivors.
Methods: PAC-WOMAN is a multi-centric randomized controlled trial focusing on physical activity behavior change for post-menopausal breast care survivors on aromatase inhibitors. Initial assessment (n=23, aged 39-64) screened for, but not exclusively, body composition with multi-frequency bioimpedance analysis (MF-BIA), handgrip strength, leg strength and endurance with 30 seconds sit to stand test, cardiorespiratory fitness with Ebbeling Treadmill Test, and rectus femoris (RF) , biceps brachii (BB) and vastus intermedius (VI) muscle thickness (MT) / cross-sectional area (CSA) via ultrasonography.
Results: Pearson correlations were used to assess the relationship between ultrasound measurements, body composition and physical performance. There was a moderate positive relationship between 30 seconds sit to stand test and RF MT (r (21) = .65, $p \leq 0.001$), and RF CSA (r (21) = .63, p = 0.001). Handgrip strength is correlated to BB CSA (r (21) = .59, p = .003. Fat free mass via MF-BIA is correlated with RF+VI MT (r (21) = .43, p = .042). VO_2max is correlated with RF MT (r (21) = .46, p = .027) and RF CSA (r (21) = .44, p = .036). Fat mass by MF-BIA is correlated with subcutaneous adipose tissue at the thigh (r (21) = .64, p = .001).
Conclusions: Muscle ultrasonography assessment is significantly correlated to body composition, muscle strength and physical performance parameters in the current sample of post-menopausal breast cancer survivors, potentially being a valid and cost-effective tool.

1-16

Correcting CT muscle measures for intravenous contrast material

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Introduction: Computed tomography (CT) can assess muscle density, which is useful to diagnose muscle wasting syndromes. However, the use of intravenous contrast material is underreported in research, despite affecting muscle density (Hounsfield Units, HU). Correcting CT muscle density for contrast would improve opportunistic CT muscle analysis. The purpose of this study was to develop a correction factor for contrast-enhanced CT data for integration with non-contrast data.
Methods: We retrospectively analyzed T12 axial CT scans of 240 patients with weight-adjusted contrast. We collected HU of regions of interest in the right and left erector spinae muscles at pre-injection, arterial, and venous phase scans. The first 140 patients formed the calibration sample for creation of correction factors. The next 100 patients formed the validation sample and tested the correction factors.
Results: The calibration sample was 60% female, mean age 52.1 years, and BMI 26.4. Arterial phase muscle density was 8.7 HU higher than baseline (women, 10.3 HU; men, 6.0 HU) and venous phase muscle density was 6.4 HU higher than baseline (women, 7.9; men, 4.0). After corrections were applied to our validation sample, the corrected contrast muscle density and non-contrast muscle density were equivalent within 3 HU for all corrections. When the simplest correction factor (-7.5 HU, disregards sex and contrast phase) was used on validation sample data, corrected contrast muscle density differed from non-contrast muscle density by 0.81 HU for arterial phase (CI -0.18, 1.80) and 0.27 HU for venous phase data (CI -0.88,1.41).
Conclusions: Arterial and venous phase contrast scans have higher muscle density values than non-contrast scans. Our correction factors successfully corrected contrast muscle density to be equivalent to non-contrast density. This correction method helps the integration of contrast and non-contrast data to synchronize muscle measures and allows for optimal utilization of opportunistic CT exams.

1-17

The relationship between CT-derived sarcopenia, systemic inflammation, physical function and survival in patients with advanced cancer

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Background: Sarcopenia is defined as a loss of muscle mass and function. Taken together, CT-derived skeletal muscle index (SMI) and density (SMD), may provide an objective measure of sarcopenia. However, the relationship with commonly utilised assessments of physical function in patients with advanced cancer is unknown. Therefore, the aim of the present study was to examine the relationship between CT-derived sarcopenia score (CT-SS), measures of physical function and systemic inflammation in patients with advanced cancer.
Methods: The study included 518 patients with advanced cancer, undergoing anti-cancer therapy with palliative intent, across nine sites in the UK and Ireland between 2011–2016. Presence of low SMI and SMD were determined from pre-treatment staging CT scans using recognised threshold values and combined as follows to form the CT-SS: a normal/high SMI irrespective of SMD=0, low SMI and normal/high SMD =1 and low SMI and low SMD =2. Measures of physical function included timed up-and-go test, two-minute walk test and hand-grip strength. Systemic inflammation was determined by mGPS. Categorical variables were analysed using χ^2 test for linear-by-linear association.
Results: Of the 518 patients included, 54% (n=277) of patients were CT-SS 0, 17% (n=88) CT-SS 1 and 30% (n=153) were CT-SS 2. 63% (n=325) had an ECOG-PS>0/1. Of the 192 patients who underwent timed up-and-go testing and two-minute walk testing, 72% (n=138) and 96% (n=185) of patients categorised as a failure, respectively. Of the 114 patients who undertook hand-grip strength assessment, 36% (n=41) of

patients were categorised as having a low hand-grip strength. On univariate analysis, the CT-SS was significantly associated with mGPS ($p<0.05$), ECOG-PS ($p<0.001$), timed up-and-go test failure ($p<0.05$) and two-minute walk test failure ($p<0.05$).
Conclusions: CT-SS was negatively associated with measures of physical function and systemic inflammation in patients with advanced cancer.

1-18

Validation of automated whole body skeletal muscle, adipose tissue, bone, and multi-organ segmentation and vertebral level identification from multi-slice CT images: towards extended body Composition

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Background: Body composition is an important driver and risk factor for a wide variety of diseases, and a predictor of individual patient-specific clinical outcomes. CT images are routinely acquired in the oncological workflows and deliver accurate rendering of internal anatomy and therefore can be used to assess the amount of skeletal muscle and adipose tissue compartments.
Objectives: We aim to build and evaluate automated tools to enable harvesting of multi-slice and whole-body measurements from 3D CT images, by segmenting skeletal muscle, adipose tissue, bone, multiple organs, and vertebral level identification, to enable the discovery of various diseases based on individual tissue, organ volume, shape, and functional status.
Methods: We developed a multi-slice CT segmentation method that can provide body composition analysis from the whole body, from head to toe. This method delivers accurate segmentation of the bony tissue, the skeletal muscle, subcutaneous (SAT) and visceral (VAT) fat, multiple organs such as liver, spleen, pancreas, kidney, gallbladder, lung, and aorta, as well as accurate predictions and annotations of vertebrate body levels.
Results: Evaluation of the dataset achieved average dice coefficients of 0.980 for bone, 0.974 for skeletal muscle, 0.986 for SAT, and 0.960 for VAT, over 0.9 for most of the organs. Most of the error distance in predicting the mid-vertebrate slices is close to 0. The comprehensive evaluation results demonstrate the accurate performance of the proposed multi-slice whole-body 3D tissue segmentation algorithm.
Conclusions: This paper confirms the feasibility of going beyond single-slice-based tissue area measurements to multi-slice measurements of volumes and texture for these tissues from multiple slices, as well as other internal organ volumes, shape, location, texture, and radiomic texture features in the body. This is a necessary step to unleash the full power of AI into supporting new and personalized treatment approaches in the domain of precision medicine.

1-19

A systematic review of automated volumetric segmentation from computed-tomography scans: bringing body composition analysis closer to routine clinical practice

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Introduction: Skeletal muscle (SKM) surface area obtained from a lumbar computed tomography (CT) slice has been used successfully in sarcopenia research. However, accuracy is compromised compared to the reference standard for measuring body composition (BC), i.e. segmentation of whole CT or magnetic resonance [MR] scans. Segmentation describes labelling of individual voxels (3D pixels) to SKM or adipose tissue (AT). Advances in computing can automate this process. We evaluated these advances, translated into feasible volumetric BC analysis.
Methods: Our systematic review evaluated automated segmentation of CT scans for volumetric BC analysis. OVID Medline, Embase and grey literature databases up to October 2021 were searched. Original studies investigating automated segmentation of SKM, visceral and subcutaneous AT from CT were included.
Results: Seven of 92 studies were selected. All scans were manually segmented by radiologists according to BC for algorithm training and testing. There was inter-study variation in patient features, pathology and CT phases, as well as anatomical CT coverage: from "abdomen" to "whole body".
The first two studies used conventional computer algorithms. The latter five used deep learning (DL), an artificial intelligence technique where algorithms are similarly organised to brain neuronal pathways. Six of seven studies reported excellent segmentation performance (Dice coefficients > 0.9 per tissue). Internal testing on unseen scans was performed for only four of seven algorithms, whilst only one was tested externally. Trained DL algorithms achieved full CT segmentation in 1.25 minutes versus 25 minutes for non-DL techniques.
Conclusions: Opportunistic, rapid, and automated volumetric BC analysis from CT is feasible, potentially enabling BC to become a routinely obtainable clinical metric. However, external testing is crucial to ensure algorithms can handle the diversity of real-world scans. Further research is also required to define and validate novel metrics based upon volumetric measures of SKM and AT.

1-22

The development of a method to assess skeletal muscle mass at the level of the third cervical vertebra in head and neck cancer patients

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Introduction: Low skeletal muscle mass (SMM) has become an important predictive and prognostic biomarker in oncological patients. The most commonly used method for SMM assessment is on abdominal CT imaging, which is unfortunately not routinely performed in head and neck cancer (HNC) patients. The aim of this study is to describe the development of SMM measurement on routine diagnostic CT and MRI

imaging at the level of the third cervical vertebra (C3) for use in clinical studies.
Methods: Cross-sectional muscle area (CSA) was measured in axial CT-images. At the level of C3 the paravertebral and sternocleidomastoid muscles were delineated. At the level of the third lumbar vertebra (L3) all muscles were delineated. Using linear regression, a multivariate prediction rule was established to correlate CSA at the levels of C3 and L3 in pretreatment whole-body CT-scans of 103 HNC patients. This prediction rule was externally validated in 200 HNC patients. The interobserver agreement for C3 CSA measurements was evaluated in 44 HNC patients by 6 observers using intra-class correlation coefficients (ICC). The correlation of C3 CSA measurements on CT and MRI was investigated in 50 HNC patients.
Results: The univariate correlation between CSA at C3 and L3 was strong (r=0.79). The multivariate prediction rule to estimate CSA at L3 from C3 showed an even stronger correlation between measured and estimated CSA at L3 (r=0.90). In the external validation study correlation-coefficients of r=0.75 and r=0.82 were observed, respectively. The interobserver agreement for CSA measurements at C3 was good (ICC=0.76–0.97). The correlation between CSA measurement on CT and MRI at C3 was excellent (r=0.97).
Conclusions: Assessment of SMM on routinely performed head and neck CT and MRI scans is robust and can reliably be used in clinical studies on the predictive and prognostic value of low SMM in HNC patients.

1-23

Effect of total knee replacement on skeletal muscle mass measurements using dual energy x-ray absorptiometry

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Background: Sarcopenia and osteoarthritis often accompany and increasing number of older sarcopenic adults are undergoing total knee replacement (TKR) surgery. The metal implants of TKR may overestimate lean mass measured by using dual-energy x-ray absorptiometry (DXA), but scarce studies have been considering metal implants when measuring lean mass using DXA. DXA producing company is providing automatic metal detection (AMD) and difference in lean mass measurements between with and without AMD is also important. Therefore, the aim of this study is to examine the effect of TKR and AMD device on lean mass measurements.
Methods: A total of twenty-four subjects who underwent TKR were selected from the Korean Frailty and Aging Cohort Study. DXA was used to measure lean mass twice, one without AMD and the other with AMD application. ,
Results: The segmental lean mass was significantly overestimated in both sides of right and left legs with TKR. The lean mass of right leg without and with AMD was 6.0±0.2kg vs. 5.5±0.17kg (p <0.001), and left leg without and with AMD was 5.7±0.22kg vs. 5.2±0.20kg (p <0.001).Height adjusted appendicular skeletal muscle mass(ASMI) without and with AMD was 6.5 ± 0.6kg/m^2 vs. 6.1 ± 0.6kg/m^2 (p <0.001). Only one(4.2%) subject was classified as low muscle mass without AMD application, but it increased to four(16.7%) after AMD application.
Conclusions: The metal implants of TKR overestimated LM measured by DXA and the overestimation decreased with AMD application. Furthermore, AMD application increases the rate of low appendicular lean mass for the diagnosis of sarcopenia. Therefore, considering metal implants may be necessary to accurately measure lean mass using DXA.

1-24

Correlations between muscle area and attenuation measurements at L3, T10 and L3 psoas when diagnosing sarcopenia and myosteatosis in oncology patients

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Introduction: Sarcopenia is a muscle disorder that causes generalised, progressive loss of muscle mass and function. It is associated with poorer outcomes and, in patients with cancer, higher rates of chemotherapy toxicity. Increased muscular fat infiltration, known as myosteatosis, is detected when muscle radiation attenuation (MRA) is low and is also associated with poorer outcomes.
Validated methods for measuring muscle parameters have established clinically significant thresholds for sarcopenia and myosteatosis, taking measurements from L3 spinal level as a validated surrogate for whole body muscle mass. The accuracy of measurements from other sites have not been validated.
Methods: Skeletal muscle mass and attenuation were retrospectively measured on routine baseline CT images in a cohort of advanced non-small cell lung cancer patients receiving first-line treatment with a tyrosine kinase inhibitor. Total muscle measurements were taken at L3 and T10 spinal levels, and psoas only measurements taken at L3 level. Data were analysed using descriptive statistics and correlation analyses.
Results: 90 patients were identified (mean age 64, 65 (72%) female). None had skeletal muscle index (SMI) below validated thresholds for sarcopenia at baseline but a greater proportion (43%) had low MRA.
Comparing total SMI and MRA values at L3 with measurements at T10 and L3 psoas demonstrated strong, positive correlations (L3 total muscle and L3 psoas correlations: SMI r=0.82; MRA r=0.78. L3 and T10 correlations: SMI r=0.84; MRA r=0.86).
Conclusions: Strong correlations between muscle parameter measurement sites suggest that T10 and L3 psoas values could offer an alternate to the gold standard L3 total muscle measurement. This has clinical relevance as simpler muscle measurement sites, such as psoas, could offer a more attractive target for artificial intelligence algorithms designed to automate the detection of sarcopenia and myosteatosis.
Further work is needed to determine if this imaging correlation also correlates with clinical outcomes.

1-25

A standardized approach for the assessment of skeletal muscle index depletion based on T-scores in patients with cancer

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Introduction: Skeletal muscle index (SMI) depletion is prognostic for overall survival (OS) in head and neck cancer patients (HNC). Heterogeneous thresholds and lack of a standardized approach defining SMI depletion however, affects the ability to define association with mortality. We aimed to (1) determine the gradient risk of mortality based on SMI T-score

(i.e. SMI values in individuals expressed in relation to healthy young reference population (https://pubmed.ncbi.nlm.nih.gov/30054580/) in units of standard deviation [SD]), and (2) test for thresholds defining moderate and severe SMI depletion.
Methods: Measurement of SMI by cross-sectional abdominal imaging of 1231 consecutive HNC patients (01/2008-11/2018) referred to the cancer-care center serving northern-Alberta, Canada. SMI T-scores tested for association with gradient risk of mortality. Primary outcome was OS. Validation cohort (N=467) included patients with HNC from USA.
Results: Continuous SMI T-scores associated with mortality in the Alberta cohort (hazard ratio [HR], **1.47**; 95% CI, 1.36-1.58; P <.001) per each 1 SD decrease and validation cohort (HR, **1.49**; 95% CI, 1.28-1.72, P <.001). SMI T-score thresholds ascertained through optimal stratification demonstrated significant increase in mortality associated with SMI depletion at 2 levels (male -2.0 SD and -3.0 SD; female -1.0 SD and -2.0 SD). Median OS associated with these thresholds were: Normal SMI (114 months, 95% CI, 97.1-130.8); Class I SMI Depletion (42 months, 95% CI, 28.5-55.4), and Class II SMI Depletion (15 months, 95% CI, 9.8-20.1). In multivariable analysis adjusted for tumor site, stage, performance status, age, sex dietary intake and weight loss, compared with Normal SMI (reference), Class I SMI Depletion (HR, **1.49**; 95% CI, 1.18-1.88; P <.001), Class II SMI Depletion (HR, **1.91**; 95% CI, 1.42-2.58; P <.001) associated with death.
Conclusions: Proposed sex- and ethnicity- normalized T-scores may lead to characterization of definitive criteria for the classification of reduced SMI in oncology patients.

1-26

Two years of aging – initial results on changes in muscle composition in the UK Biobank imaging study

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Introduction: Adverse muscle composition (low muscle volume with high muscle fat infiltration) assessed with magnetic resonance imaging (MRI) is common in general population (10%) and has been linked to poor functional performance and comorbidity in non-alcoholic fatty liver disease (NAFLD) as well as increased hospitalization and all-cause mortality in general population[1,2,3]. The aim of this study was to describe changes in muscle composition in healthy individuals and common metabolic disorders.
Methods: 1,265 participants from the UK Biobank imaging study were scanned twice approximately 2 years apart using a 6-minute MRI protocol. Images were analyzed for thigh fat-free muscle volume (FFMV) and muscle fat infiltration (MFI) using AMRA® Researcher, Linköping, Sweden. For each participant, a sex-, weight- and height invariant FFMV z-score was calculated[1]. Muscle composition changes were described in participants that were metabolic disease free (MDF) at both timepoints and for participants with NAFLD, type 2 diabetes (T2D) and cardiovascular disease (CVD) at baseline.
Results: The cohort consisted of 51% females, with mean (SD) age 63.3 (7.3) years and BMI 26.3 (4.2) kg/m^2 at baseline. No group had a significant weight change over two years while significant changes in muscle composition and hand grip strength were observed (Table 1). The smallest average change in muscle composition variables were found in the MDF group [FFMV z-score -0.12 (0.25) SD, MFI +0.24 (0.32) pp] and the largest within participants with CVD [FFMV z-score -0.19 (0.26) SD, MFI +0.36 (0.47) pp] (Figure 1).

Conclusion: Significant changes in muscle composition measurements (thigh FFMV and MFI) can be observed across 2 years. Results indicate that individuals with metabolic disorders experience more rapid wasting and that different diseases may be associated with

		Metabolic disease free	Non-alcoholic fatty liver disease	Type 2 Diabetes	Cardio-vascular disease
N		231	171	66	59
% female		53.7	39.2	33.3	25.0
Age (years)	Baseline	60.1 (6.8)	63.9 (7.6)	65.5 (7.2)	66.4 (6.7)
Weight (kg)	Baseline	72.0 (12.7)	85.2 (15.6)	81.1 (14.0)	83.3 (14.3)
	Change	0.3 (3.2) p=0.121	-0.4 (3.9) p=0.237	-0.4 (3.8) p=0.421	-0.8 (5.0) p=0.181
FFMV (L)	Baseline	10.20 (2.53)	11.01 (2.61)	10.56 (2.43)	11.20 (2.03)
	Change	-0.11 (0.31) p<0.001	-0.20 (0.40) p<0.001	-0.23 (0.43) p<0.001	-0.24 (0.49) p<0.001
FFMV z-score (SD)	Baseline	0.29 (0.96)	0.00 (1.00)	-0.40 (1.13)	-0.15 (0.91)
	Change	-0.12 (0.25) p<0.001	-0.16 (0.25) p<0.001	-0.18 (0.27) p<0.001	-0.19 (0.26) p<0.001
MFI (%)	Baseline	6.66 (1.55)	7.71 (1.92)	7.74 (1.79)	7.64 (1.76)
	Change	0.24 (0.32) p<0.001	0.29 (0.36) p<0.001	0.30 (0.38) p<0.001	0.36 (0.47) p<0.001
Hand grip strength (kg)	Baseline	33.12 (10.84)	32.06 (10.75)	31.44 (10.92)	34.54 (10.05)
	Change	-2.74 (7.26) p<0.001	-1.97 (7.83) p=0.001	-2.15 (7.78) p=0.032	-3.11 (7.56) p=0.001

Table 1 *Baseline characteristics and changes across 2 years. Values are mean (SD). p-values from paired t-test comparing baseline and follow-up values. FFMV (fat-free muscle volume), MFI (muscle fat infiltration).*

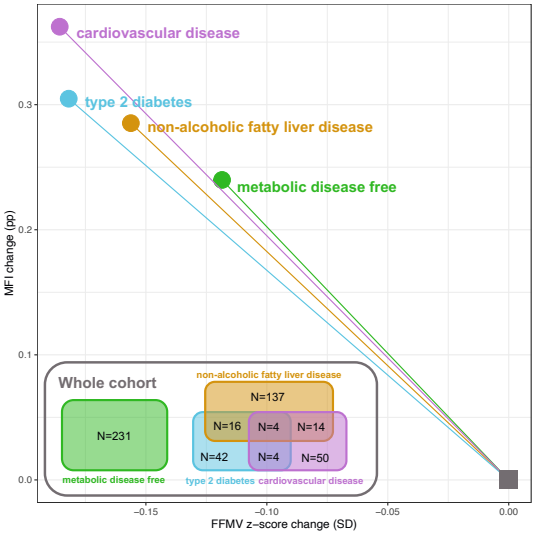

Figure 1 *Changes in thigh muscle composition across 2 years. FFMV (fat-free muscle volume), MFI (muscle fat infiltration).*

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1-28

Sarcopenic gastrointestinal cancer patients have higher plasma levels of ST2

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Introduction: Cachexia is a wasting syndrome caused by multiple chronic diseases including cancer with a high prevalence in gastrointestinal tumors. Cachexia is characterized by metabolic dysfunction and inflammation and leads to substantial loss of fat and skeletal muscle tissue.
IL-33 is part of the IL-1 family and plays a role in metabolic homeostasis in fat and muscle tissue. Its activity is regulated by its decoy receptor sST2 (soluble suppressor of tumorigenicity 2).
Methods: Plasma levels of IL-33 and ST2 were measured in a cohort of 188 patients. Blood samples were taken prior to oncological treatment and analyzed using ELISA (Human IL-33 and ST2/IL-33R DuoSet ELISA R&D Systems). Clinical data were obtained from patient records and questionnaires. Measurements of body composition were conducted using CT scans of the lumbar region.
Results: Plasma levels of ST2 are higher in cancer patients with sarcopenia. A therefore conducted correlation analysis shows a negative correlation between ST2 and skeletal muscle area index, and a positive correlation between ST2 and loss of muscle tissue in a subgroup of patients with pancreatic cancer. Plasma levels of IL-33 are mostly below detectable limits.
Conclusions: The results suggest that plasma ST2 levels reflect muscle loss and might be a prognostic marker for further muscle loss in patients suffering from pancreatic cancer. Further research is needed to investigate the effects of IL-33 and sST2 on muscle tissue homeostasis.

1-29

MicroRNA-22 as a potential diagnostic tool in males with sarcopenic heart failure: Results from the Studies Investigating Co-morbidities Aggravating Heart Failure (SICA-HF)

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Background: Accelerating loss of skeletal muscle mass and strength (sarcopenia) is a frequent comorbidity of heart failure (HF). MicroRNA-22 (miR-22) was reported as a regulator of skeletal muscle differentiation *via* TGF-β/SMAD pathway. The study aimed to investigate the diagnostic capabilities of circulating miR-22 in male sarcopenic HF.
Methods: We conducted a retrospective analysis of 139 ambulatory HF male patients enrolled in the multicentric, observational SICA-HF study (Studies Investigating Comorbidities Aggravating Heart Failure). The diagnosis of sarcopenia was extracted from medical records, based on a reduction in appendicular skeletal muscle mass. Body composition was assessed by DEXA-Scan. MiR-22 serum concentrations were measured by miR-specific PCR analyses. Determinants of sarcopenia were analyzed using multivariate logistic regression analysis.
Results: The overall prevalence of sarcopenia was 19.4%. Sarcopenic HF patients were older compared to non-sarcopenic HF patients (74.7 [68.7-80.2] vs. 68.4 [60.3-74.3]; p=0.002), had a lower BMI (25.3 [22.8-26.9] vs. 29.2 [26.0-32.8] kg/m^2; p<0.001), higher NTproBNP levels (1150.3 [513.7-3134.5] vs. 519.1 [161.8-1328.8] pg/ml; p=0.002), lower heart rate reserve during exercise (51.0 ± 22.0 vs. 65.0 ± 23.0 bpm; p=0.007), lower peak VO_2 (14.5 ± 4.6 vs. 19.2 ± 4.7 mL/min/kg; p<0.001) and a lower 6-minute walk test distance (381.1 ± 133.5 vs. 481.6 ± 118.6 m; p=0.003). Serum level of miR-22 was significantly upregulated in sarcopenic HF patients (5.1 [4.7-5.6] vs. 5.6 [4.9-6.2] CT value; p=0.031). In the multivariate logistic regression model adjusted for age, left ventricular ejection fraction, NTproBNP levels and heart rate reserve during exercise, miR-22 levels (OR 0.271, 95%CI 0.091-0.802, p=0.018), BMI (OR 0.612, 95%CI 0.463-0.810, p=0.001) and peak VO_2 (OR 0.732, 95%CI 0.591-0.906, p=0.004) remained associated with presence of sarcopenia in male HF patients.
Conclusions: Sarcopenia in HF patients was independently associated with miR-22 profile, proposing a potential novel epigenetic biomarker of alteration of skeletal muscle in HF patients.

1-31

Verification of an effective grip-strength order for the diagnosis of possible sarcopenia in Korean population

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Introduction: The Korean National Health and Survey has been investigating the effectiveness of grip strength measurement whether it should be measure as two times or three times. Therefore, the purpose of this study was to examine the verify the effective grip-strength order for the diagnosis of possible sarcopenia.
Method: For the purpose, we investigated data of the handgrip strength tests of older people (>=60yrs, N=9,748) from the Korean National Health and Survey.
Results: the 3rd measurement with the dominant hand showed the highest distribution of the maximum handgrip strength value among the dominant (D) and non-dominant (ND) handgrip strength tests (28.5%(D3) in men, 30.4%(D3) in women, *p*<.001]. the maximum grip strength value in the third order was significantly higher than that in the second order (men: 30.8±6.9kg vs. 31.6±6.9kg; women: 18.5±4.8kg vs. 19.1±4.7kg, p<.001). In measuring the maximum handgrip strength twice, the prevalence of 'possible sarcopenia' is higher than measuring the maximum handgrip strength three times, and 384,634 additional elderly people (>=70yrs) in Korea are diagnosed with 'possible sarcopenia'.
Conclusions: the maximum handgrip strength in the elderly should be validated by the grip strength test three times at both

hands. In particular, 'possible sarcopenia' can be overestimated by the handgrip strength test in the elderly, the maximum grip strength value can be reasonably obtained only when the grip strength test at both hands. Therefore, for an accurate grip strength test, the current procedure of grip strength test for three times with both hands was effectively valid.

1-32

Case-findings from the ESPEN EASO 2022 diagnosis procedure to detect sarcopenic obesity among community-dwelling older adults: insights from an observational study designed within a prevention care-path

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Introduction: Recently, the ESPEN EASO expert panel has defined sarcopenic obesity (SO) and has agreed upon a diagnostic procedure to enhance patient identification and implement preventive strategies. It remains essential to assess this SO diagnosis procedure from existing data sets and determine reference values. The purpose of this cross-sectional observational study was to investigate the ability of the ESPEN EASO diagnosis to detect SO in community-dwelling older adults (CDOA) in order to determine sensibility/specificity of strength measurements.
Methods: SO diagnosis procedure was performed, under the guidance of doctors and kinesiologists, on a cohort of 684 CDOA (age>70), assessed during a multidimensional day hospital consultation of a mobility prevention care-path. Strength assessments included grip strength (GS) and 5-chair stand test (CST). Muscle mass assessment was performed by bio-impedance analysis. Then, 3 ROC curves were performed on participants screened at risk of SO with GS values, in men and women, and with CST values.
Results: 171 participants were screened at risk of SO and 136 (age 77.9±6.4) were included for diagnosis procedure. 89 participants (65%) were diagnosed with SO from whom 86 at stage II (97%), considering 53 (61%) with functional disabilities (SPPB ≤9). High sensibility was obtained for GS in men (0.85) and women (0.79) but showed poor specificity (0.58; AUC: 0.704 and 0.48; AUC: 0.611 respectively). CST had a higher specificity (0.66) than sensibility (0.61) but with an overall poor performance (AUC: 0.600). Indicative cut-off points were found at 19.735kg for GS in women, 33.8kg for GS in men, and 12.915s for CST.
Conclusions: The ESPEN EASO diagnosis procedure is effective and feasible to detect cases of SO in CMDOA in clinical practice. A high sensibility was found for GS but with an overall poor specificity. Thus, GS may represent an interest to rule out SO in this population although requiring further investigation in a larger cohort to develop cut-off values.

1-33

Novel adaption to the pediatric SARC-F score to classify pediatric hemato-oncology patients with functional sarcopenia

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Introduction: The SARC-F questionnaire is recommended as a screening tool for sarcopenia in elderly, and consists of five self-reported questions addressing strength, walking, rising, stairclimbing and falling.
The aim of this study was to investigate the accuracy of the pediatric SARC-F (PED-SARC-F), for identifying sarcopenia in pediatric hemato-oncology patients, including determination of a cut-off for clinical use.
Methods: Patients 3-20 years, under active treatment or within 12 months after treatment cessation at the hemato-oncology department of the Princess Máxima Center for Pediatric Oncology, were eligible. Patients had a physiotherapy assessment including PED-SARC-F, as part of standard of care.
The physiotherapy assessment consisted of muscle strength measures (handheld dynamometry), physical performance (various tests) and muscle mass (bio-impedance analyses).
Structural sarcopenia was defined as low muscle mass in combination with low muscle strength and/or low physical performance. Functional sarcopenia indicated low muscle strength combined with low physical performance.
Multiple logistic regression models were estimated to study the associations between PED-SARC-F, and the endpoints: structural and functional sarcopenia.
To evaluate which PED-SARC-F cut-off point (0-10) provides the most accurate classification of functional sarcopenia, the area under the receiver operating characteristic curve (AUCs), sensitivity and specificity per point were calculated.
Results: In total, 215 assessments were included, 62% were performed in boys and median age was 12.9 years (IQR: 8.5-15.8).
The PED-SARC-F had an AUC of 0.90 (95%CI = 0.84-0.95) for functional sarcopenia and 0.69 (95%CI = 0.57-0.80) for structural sarcopenia.
A cut-off point of ≥5 had the highest specificity of 96% and sensitivity of 74% for functional sarcopenia.
Conclusions: We adapted the SARC-F to a pediatric version and confirmed its excellent accuracy for identifying functional sarcopenia and defined a clinically useful cut-off in a pediatric hemato-oncology setting. This easy self-report score can identify children that may need physiotherapy interventions during and shortly after treatment.

2-01

Dynapenic abdominal obesity as a risk factor for cardiovascular mortality

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Introduction: Dynapenic abdominal obesity has been shown as a risk factor for all-cause mortality in older adults. However, there is no evidence of the association between this condition and cardiovascular mortality. We aimed to investigate whether dynapenic abdominal obesity increases the risk of cardiovascular mortality in individuals aged 50 and older.
Methods: A longitudinal study with an eight-year follow-up was conducted involving 7,030 participants of the English Longitudinal Study of Ageing (ELSA Study). Abdominal obesity and dynapenia were respectively defined based on waist circumference (> 102 cm for men and > 88 cm for women) and grip strength (< 26 kg for men and < 16 kg for women). The sample was divided into four groups: non-dynapenic/non-abdominal obesity (ND/NAO), non-dynapenic/abdominal obesity (ND/AO), dynapenic/non-abdominal obesity (D/NAO) and dynapenic/abdominal obesity (D/AO). The outcome was cardiovascular mortality. The Fine-Gray regression model was used to estimate the risk of cardiovascular mortality as a function of abdominal obesity and dynapenia status in the presence of competing events controlled by sociodemographic, behavioral and clinical conditions. Four sensitivity analyses were performed: First, excluding individuals younger than 60 years, second, including only non-smokers, third, excluding individuals with heart disease at baseline and fourth, excluding participants younger than 60 years, smokers and individuals with heart disease at baseline.
Results: The risk of cardiovascular mortality was significantly higher in the D/AO group compared to the ND/NAO group (SHR: 1.61; 95% CI: 1.01 – 2.56). ND/AO and D/NAO individuals were not at greater risk of cardiovascular mortality. All sensitivity analyses showed similar results to our main analysis.
Conclusions: Dynapenic abdominal obesity increases the risk of cardiovascular mortality in individuals older than 50 years of age. Thus, prevention strategies and clinical interventions that enable mitigating the harmful effects of this condition should be adopted to diminish such risk.

2-02

Cross-sectional and longitudinal impact of congestion on body composition analysis in patients with heart failure

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Introduction: Heart failure (HF) patients present with a series of co-morbidities that have an impact on mobility, particularly concerning changes in body composition. A main concern in the past decades has been the accuracy of the measurement of lean mass in the presence of oedema. We aimed to analyze the relationship between two standard assessments of body composition, dual X-ray absorptiometry (DEXA) and bioelectrical impedance analysis (BIA), and the influence of congestion in their accuracy among HF patients.
Methods: We investigated 129 HF patients from Studies Investigating Co-morbidities Aggravating Heart Failure (SICA-HF) cohort presenting with both body component assessments. The presence of peripheral oedema was assessed during clinical examination. Bland-Altman plot and Pearson's correlation were used as measurements of agreement between methods.
Results: A comparison of patients without oedema (n=41) vs. with oedema (n=88) showed no statistically significant difference with regards to age, gender, creatinine, presence of sarcopenia and survival (all p>0.1). Weight and body mass index (BMI) were higher in the oedematous subgroup (81.1±15.7 vs. 91.7±17.2 kg; 27.5±4.5 vs. 30.8±5.4 kg/m2, both p=0.001). Fat mass (FM) showed a small difference by Bland-Altman analysis (mean difference [M_{diff}] = 1.38) while fat free mass (FFM) was estimated higher on BIA analysis (M_{diff}=-4.04). The difference was slightly reduced within the subgroup without oedema (M_{diff}=0.68 for FM; M_{diff}=-3.24 for FFM) and slightly increased within the group with oedema (M_{diff}=1.70 for FM; M_{diff}=-4.41 for FFM). Body components were all higher in the oedematous subgroup with respect to both methods: FM: 26.5±10.5 vs. 32.7±10 kg, p=0.001; FFM: 52±9.8 vs. 56.2±12.2 kg, p=0.054 by DEXA, as well as FM, FFM and water in litre by BIA (25.8±8.4 vs. 31±10.2 kg, p=0.005; 55.2±12.6 vs. 60.6±12.7 kg, p=0.027; 42.5±7.9 vs. 46.5±9.4 L, p=0.019). We analyzed paired mean difference (pM_{diff}) on 25 patients from an oedema status to a no oedema status in a period of six months. From all body components only water on BIA assessment was significantly different (pM_{diff} [CI]: -2.31 [-4.24;-0.39], p = 0.022).
Conclusions: There is a good correlation between measurements of fat mass and fat free mass done by DEXA scan vs. BIA analysis, regardless of the presence of oedema. No statistically significant difference was found in patients developing oedema with respect to any of the methods and components. The only significant difference found was at water level, whose clinical relevance requires further investigation.

2-04

Metabolites of gut microbiota and nutritional status in kidney transplant recipients and hemodialysis patients

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Background: Protein-energy wasting (PEW) is common among patients with chronic kidney disease. The occurrence of PEW may also be influenced by disturbances in the intestinal microbiota and its metabolites.
The study aimed to assess the association between of the metabolites of gut microbiota (trimethylamine-N-oxide ¬— TMAO, p-cresyl sulfate ─ pCS, and indoxyl sulfate ─ IS) and body composition of kidney transplant recipients (KTRs) and hemodialysis (HD) patients.
Methods: The study involved 43 KTRs (24 m) aged 52.4 ± 10.4 years and 79 HD patients (45 m) aged 62.4 ± 16.1 years. Nutritional status was assessed by Subjective Global Assessment, body composition and handgrip strength. TMAO, pCS, and IS were measured by LC-MS/MS.
Results: It was observed that TMAO, pCS, and IS was significantly higher in HD patients than in KTRs (TMAO 149.3 vs. 27.5 μM/L; pCS 174.2 vs. 58.4 μM/L; IS 46.8 vs. 5.4 μM/L). In HD patients, negative correlations between pCS, BMI, MAMC, and fat tissue index (FTI) were observed. IS negatively correlated with FTI and positively with lean tissue index (LTI). IS and pCS were correlated with the percentage of adipose tissue ($p<0.05$).
Conclusions: The concentration of pCS and IS was related to FTI and LTI in HD patients.

2-05

Frailty in the elderly after CoViD-19 – a pilot study

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Introduction: Frailty is a better predictor of CoViD-19 evolution and outcome than age or comorbidities, however it is unclear whether frailty is a risk factor or a consequence in elderly after CoVid-19.
Objective: To compare frailty levels between elderly after CoViD-19 and with unknown CoViD-19 diagnosis.
Methods: A Cross-sectional study was carried out in the community. Handgrip strength and the Frailty Index (Clinical Fragility Scale) were assessed in 25 community-dwelling individuals aged ≥65 years who had been diagnosed with CoViD-19 for less than 6 months, and in an equal number of elderly participants with the same characteristics without a known diagnosis of CoViD-19.
Results: Elderly with a diagnosis of CoViD-19 for less than 6 months presented increased Frailty Index ($p=0.026$). No differences regarding handgrip strength were found.
Conclusions: Significant changes were found in frailty levels in elderly patients diagnosed with CoViD-19 for less than 6 months, when compared with elderly individuals without a diagnosis of CoViD-19. These results may indicate that CoViD-19 could increase frailty levels in elderly patients.

2-07

Long-haul COVID-19 is related to lower pectoralis muscle mass at hospital admission for treatment of acute infection

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Long-COVID-19 has been described as the presence of persistent symptoms in patients who recovered from SARS-Cov-2 infection, of which fatigue and muscle weakness are the most common symptoms. ´
Objectives: To evaluate the relationship of muscle mass to disease severity and long-lasting symptoms of COVID-19.
Methods: Pectoralis muscle index (PMI, cm^2/m^2) from patients who recovered from COVID-19 was measured using computerized tomography images taken at the level of the fourth thoracic vertebra at hospital stay and at the follow-up period (9-11 months after hospital discharge).
Results: 70 women and 74 men were included in this study. At hospital admission, women with low PMI had higher C-reactive protein compared to the 3rd tertile ($p=0.0013$) and higher troponin compared to those in the 2nd and 3rd tertiles ($p=0.0081$ and $p=0.0009$, respectively). Women in the 3rd tertile had lower need for intubation ($p<0.0001$). Women in the 1st and 2nd tertiles presented with persistently lower PMI at the time of follow-up assessment, compared to those with high muscle mass ($p<0.0001$ and $p=0.0005$, respectively). There was a higher frequency of fatigue reported by women in the 1st tertile ($p=0.0003$). Men in the 1st tertile showed a higher troponin at the time of hospitalization ($p=0.0440$) and longer length of hospital stay ($p=0.0339$) compared to those in the 3rd tertile. Moreover, those in the 1st tertile presented with lower muscle attenuation compared to those in the 2nd and 3rd tertiles ($p=0.0064$ and $p<0.0001$, respectively) and the difference between the 1st and 3rd tertiles was also observed at follow-up ($p=0.0017$). At the follow-up period, men in the 1st tertile reported higher frequency of weakness, walk impairment and fatigue.
Conclusions: Lower PMI at the time of hospitalization for treatment of acute infection had worse in-hospital outcomes and greater long-COVID-19 symptoms.

2-09

Chronic mild stress and diabetes lead to muscle atrophy and osteopenia

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Background: Muscle atrophy is a condition characterized by the loss of muscle mass, strength, and function. Depression and diabetes share several common risks with muscle wasting which could negatively affect various aspects of muscle and bone health. The aim of this study was to evaluate the concomitant effects of chronic psycho-physical stress and diabetes on skeletal muscle and bone.
Methods: Animals were randomized in control, stressed, diabetic, and diabetic/stressed experimental groups. Unpredictable chronic mild stress (UCMS) was induced exposing mice to different stressors daily for 9 weeks. Behavioral tests were assessed from week 7. Body weight and body composition were assessed weekly. Muscle atrophy markers were assessed by western blot analysis, inflammatory status through Bio-Plex cytokines assay, and analysis of cross-sectional area of muscle fibers by Hematoxylin & Eosin staining. Micro-computed tomography was performed on femour bone.
Results: UCMS and diabetes led to a muscle wasting phenotype and the comorbidity accentuated this aspect. We observed a reduction of lean mass in diabetic and diabetic/stressed groups, a reduction in GC muscle weight, and an increase of some atrophic markers, such as Beclin-1, p-62, TRAF-6, Pax-7, NGAL, IL-6, while the anabolic marker Akt showed a reduction. The histological analysis showed a reduced cross-sectional area in GC fibers. Furthermore, variations in cortical and trabecular parameters were observed. Analysis of inflammatory markers showed an upregulation of specific cytokines. The obtained results were significant in stressed and diabetic groups and greater in the diabetic/stressed group.
Conclusions: Here we showed that depression and diabetes have a negative impact on muscle and bone health but most importantly, we demonstrated that the comorbidity of these pathologies led to an exacerbation of muscle atrophy driven by the upregulation of inflammatory and atrophic markers which determine a synergistic effect on the musculoskeletal system.

2-11

Low levels of 25-hydroxyvitamin D as a risk factor for Sarcopenia in community-dwelling older Chileans

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Introduction: 25-hydroxyvitamin D (25OHD) exerts its effects in multiple organs and systems among which muscle has been proposed as an important target in older people. Considering the high frequency of both sarcopenia and vid D deficiency and its adverse consequences on health, our objective was to study vit D deficiency as a risk factor for sarcopenia in older Chileans.
Methods: Longitudinal study in 643 subjects, mean age 66.2±5.0 (68.4% women), community-dwelling people participating in the ALEXANDROS cohorts, designed to study disability associated with obesity in community-dwelling people 60y and older living in Santiago/Chile, having 25(OH)D measurements at baseline. Sarcopenia was identified using the EWGSOP 2010 algorithm validated for Chile. Plasma levels of 25OHD, were measured through radioimmunoassay technique defining Normal status as 25(OH)D ≥30 ng/mL, Insufficiency as 20-29.9 ng/mL, Deficiency as 12-19.9 ng/mL and Severe Deficiency as <12 ng/mL.
Results: At baseline 11.3% (100) of subjects were diagnosed as sarcopenic (women 15.2%; men 16.3%); 25(OH)D levels were normal in 34.2%, insufficient in 27.5%, deficient in 27.1% and severely deficient in 11.2% of the sample, similar in men and women. Only Severe deficiency was associated with sarcopenia at baseline (OR=1.48; 95%CI:1.18-2.79, p=0.045). After 4971.9 person/y of follow-up, 60 new sarcopenia cases were identified. Mean 25(OH)D levels were lower in people with sarcopenia (23.2 vs.27.2 ng/mL p=0.028) The sex, age and BMI adjusted logistic regression analysis of 25(OH)D levels as continuous variable, showed it as a protective factor for sarcopenia (RR=0.97; 95%CI:0.95-0.99 p=0.041), but when analyzed as a categoric variable, only severe deficiency was identified as a risk for sarcopenia (RR=1.42;95%CI:1.15-3.75, p=0.039)
Conclusions: The results demonstrate that severe deficiency of 25(OH)D, besides its negative effects in other organs and systems, is an important risk factor for sarcopenia in older people, supporting the importance of 25(OH)D monitoring and supplementation when needed.

2-12

Chronic activation of ALK5/TGFβI signaling in adult mouse skeletal muscle induces severe muscle wasting with concomitant impaired mitochondrial integrity

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Background: Transforming Growth Factor β (TGFβ) pathway is a major negative regulator of skeletal muscle mass. Dysregulation of TGFβ signaling is increasingly being implicated in muscle wasting in chronic diseases (myopathies, cancer...) and sarcopenia. Studies conducted so far mostly relied on loss-of-function and ligand gain-of-function approaches, resulting in intricated effects not restricted to muscle cells. However, the impact of chronic TGFβ activation restricted to skeletal muscle has not yet been examined.
Methods: We have generated a new conditional mouse model to activate TGFβ signaling in adult myofibers through the muscle-specific and inducible expression of a constitutively active ALK5/TGFβRI receptor, also called TGFβRI-CA (RCA). The pathophysiology of dysregulated TGFβ signaling in skeletal muscle was investigated.
Results: We observed that expression of a constitutively active ALK5 receptor in adult myofibers promoted activation of Smad2/3 signaling leading to severe muscle wasting, fiber type shift and progressive reduction in muscle force. We show that muscle atrophy was due to reduced myofiber size induced by decreased protein synthesis associated with upregulation of protein degradation. Indeed, following ALK5 activation, mTORC1 downstream signaling was rapidly downregulated while the expression and activity of FoxO transcription factors were upregulated and linked to activation of the Ubiquitin-Proteasome-System catabolic pathway. Interestingly, changes in Akt/FoxO signaling underlied the muscle remodeling over time in these mice. Our results indicate moreover that muscle

atrophy is accompanied with progressive impairment of mitochondrial respiration.
Conclusions: Our study provides the first transgenic mouse model to investigate the impact of cell-autonomous, inducible and chronic activation of TGFβ signaling in skeletal muscle. Altogether, our data show that chronic activation of ALK5 signaling in adult muscle fibers leads to severe muscle wasting and concomitant loss of mitochondrial function.

2-13

Mitochondrial degeneration during the progression of sarcopenia in SAMP8 mice model

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Introduction: Sarcopenia is a hallmark of ageing process, which is characterized by the declined muscle mass and strength. Peroxisome proliferative activated receptor gamma coactivator 1 alpha (PGC-1α) is a major factor in mitochondrial biogenesis, while mitofusin 2 (Mfn2) is a key mitochondrial membrane protein in mitochondrial fusion. Additionally, ATP5A1 and cytochrome c represent the level of mitochondrial ATP production. This study aims to investigate the changes of mitochondria in skeletal muscle during sarcopenia in SAMP8 mice model.
Methods: Senescence-accelerated mouse P8 (SAMP8) male mice were used in this study, meanwhile, senescence-accelerated mouse resistant-1 (SAMR1) male mice were used as age-matched non-sarcopenic group. The levels of mitochondrial biogenesis, fusion, ATP production at month 3, 6, 8, 10, 12 were assessed by western blotting. *Ex-vivo* functional assessment, grip strength and morphological analysis of mitochondria in skeletal muscle by transmission electron microscopy were performed. Data analysis was done with one-way ANOVA, and the significant level was set at $p \leq 0.05$.
Results: Grip strength, tetanic force and twitch force of gastrocnemius reached the peak in SAMP8 mice at month 8 and decreased from month 8 to 12 ($p<0.05$, Figure 1), while those in SAMR1 mice had no significant changes. The number, density, and relative area of mitochondria in SAMP8 mice reached the peak at month 6 and decreased from month 6 to 12 ($p<0.05$, Figure 2), while those in SAMR1 mice had no significant changes. The expression levels of PGC-1α, Mfn2, ATP5A1 and cytochrome c in SAMP8 mice reached the peak at month 6 and decreased from month 6 to 12, while those in SAMR1 mice had no significant changes ($p<0.05$, Figure 3).
Conclusions: The expression levels of PGC-1α in cytoplasm, Mfn2, ATP5A1 and cytochrome c in mitochondria decreased along with mitochondria deterioration during sarcopenia in SAMP8 mice model. Furthermore, mitochondria deterioration onset earlier than muscle deterioration in SAMP8 mice model.

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2-14

The effect of severe burns on skeletal muscle protein balance in female rats 10 and 40 days post-burn

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Introduction: During the hypermetabolic state after a burn injury losses of skeletal muscle mass are caused by a negative protein balance, however the specific pathways involved are incompletely understood. We examined, in a rat burn model, the effects of severe burns on pathways regulating skeletal muscle protein synthesis and breakdown 10 and 40 days postburn.
Methods: 38 rats (6 weeks) were assigned to a sham (S) or severe burn (SB) group with a follow-up of 10 or 40 days. Rats of the SB group received a 40% TBSA burn according to the Walker-Mason model. After 10 or 40 days, rats were sacrificed, weighed and soleus (SOL) and extensor digitorum longus (EDL) muscles were harvested. Western blotting was used to measure expression of Akt and eEF2 for protein synthesis, and MURF and Atrogin-1 for proteolysis. Differences between burn groups were tested with linear mixed models and considered significant when $p<0.05$(*).
Results: SB rats showed significantly less body weight gain at 10* and 40* days postburn due to differences in muscle mass, as shown by lower muscle weight/body weight ratios for SOL* and EDL*. In SOL of SB animals, we observed a protein imbalance at 10 and 40 days postburn, with decreases in Akt* and eEF2* and increases in MURF* and Atrogin-1*. In EDL, no negative protein balance could be found. 10 days postburn a decrease in Akt* and eEF2*, but also a decrease in MURF* was observed. At 40 days postburn Akt* increased again, whilst also Atrogin-1* decreased.
Conclusions: This study revealed the presence of skeletal muscle wasting at 10 and 40 days postburn, dependent on muscle type. A negative protein balance is seen at 10 continuing to 40 days postburn in SOL of burned animals, whereas in EDL no clear protein imbalance can be concluded.

2-15

Immobilization combined with caloric restriction as translational mouse model for sarcopenia expressing key pathways of human pathology

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Introduction: The prevalence of sarcopenia is increasing and translational animal models that are adequately mimicking the underlying physiological pathways are scarce. Strong predictors for the incidence of sarcopenia include a sedentary life-style and malnutrition. Therefore, our objective was to test the translational value of three potential mouse models for sarcopenia, namely partial immobilized, caloric restricted (CR) and a combination (immobilized & CR) model.
Methods: C57BL/6J mice were calorically restricted (40%) and/or one hindleg was taped and immobilized for two weeks

to induce muscle atrophy. Muscle mass, function and type 1 and 2 myofiber diameters were compared to those of young control (4 months) and aged mice (21 months). Transcriptome analysis of *quadriceps* muscle was performed to identify the underlying pathways and were compared with those of human aged *vastus lateralis* muscle biopsies using five different human studies.
Results: CR induced overall loss of lean body mass (-15%, p<0.001), whereas immobilization decreased grip strength (-28%, p<0.001) and muscle mass of hindleg muscles specifically (on average -25%, p<0.001). Type 1 and 2 myofibers decreased in diameter in immobilized mouse models, while in CR and aged mice only type 2 myofibers decreased in size. Notably, on transcriptional level, the underlying pathways of the combination model revealed more similarity with human underlying pathways than aged mice and recapitulated 73% of pathways that were differently expressed in aged human *vastus lateralis* muscle (*vs.* 45% in aged mice).
Conclusions: We demonstrate that a two-week period of CR is an effective way to induce muscle atrophy, while immobilization is required to induce loss of muscle strength. The combination model exhibited loss of both muscle mass and function and illustrated substantial similarity with human pathways. We conclude that the combination model can be a suitable model for testing the effectiveness of muscle-ageing related interventions.

2-17

JQ1 as a possible strategy to improve aging-related sarcopenia and frailty

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Introduction: Sarcopenia is the decline of skeletal muscle mass and function and despite its significance, the molecular mechanisms underlying these impairments are only partially deciphered. Preliminary experiments in *in vivo* models of skeletal muscle diseases associated to wasting, including cancer cachexia and Duchenne dystrophy, showed that pharmacological blockade of bromodomain protein BRD4 with inhibitor JQ1 has a beneficial effect on muscle function. Aim of this study was to correlate alterations observed in old mice treated or not with JQ1, on key processes involved in skeletal muscle aging, including inflammation, oxidative stress and fibrosis, with alterations observed in sarcopenic older individuals.
Methods: Muscle biopsies derived by recruitment of volunteers within the range of interest (adult (<65 yo) (n=11), old (65-85 yo) (n=71), very old (>85 yo) (n=33)). RT-PCR analyses were performed on muscles. 24-months old C57Bl/6 mice were treated or not with JQ1 (IP 20 mg/kg/day) for 45 days (n=12 per group).
Results: Analyses on muscles of old mice showed increased levels of inflammation, oxidative stress and fibrosis. JQ1 treatment beyond improving muscle function, rescued in part histological and molecular alterations. In order to validate the targets modulated by JQ1 in the pre-clinical setting, we attempted to validate the alterations in sarcopenic individuals. Indeed, RT-PCR analyses revealed that muscles from old individuals show increased mRNA levels of specific genes modulated by JQ1 and not previously reported to be altered in aging sarcopenia.
Conclusions: Since molecular mechanisms underlying sarcopenia are elusive and the development of optimal therapeutic interventions remains obscure, defining common muscle-specific alterations between aged mice and humans could be useful in order to identify functional clinical parameters, new markers for frailty prevention as well as novel targets for treatment. The ability of JQ1 in preventing some of these alterations provides the proof of concept of the effectiveness of such strategy.

2-18

Dipyridamole as a novel therapy for sarcopenia via A2B and AMPK/cAMP signaling

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Introduction: Sarcopenia, loss of muscle mass and strength, is a condition recognized within the frailty syndrome, but also associated with chronic inflammatory diseases. During myogenesis the regulation of cellular energy homeostasis by ATP is critical. We aim to determine how purinergic system modulates myogenesis using dipyridamole (blocks adenosine uptaken by the cells) and tenofovir (inhibits Pannexin-1-mediated ATP release) in C2C12 murine myoblast cell line.
Methods: Differentiation of C2C12 cells is done with 2% horse serum for 4 days in the presence/absence of tenofovir +/- dipyridamole 1μM. Muscle differentiation proteins (Pax7, Mif5, MyoD, MyoG and MHC) are studied by immunofluorescence and Western Blot (WB). Adenosine receptors (A1R, A2AR, A2BR, A3R), ATP-channel Pannexin-1 and P2X7 receptor expression are analyzed by WB and RT-PCR. Nucleotides are examined with HPLC. AMPK activation and cAMP concentration are also measured. The PKA/CREB pathway is studied by WB.
Results: Tenofovir maintain a not proliferative state of myoblast with reduced Pax7 expression which is reverted by dipyridamole. All adenosine receptors are expressed during differentiation but A2AR decreased during differentiation. Pannexin-1 and P2X7 also increased during differentiation. Tenofovir decreases Pannexin-1/P2X7 expression, while dipyridamole reverts this effect as well as increases the expression of A2BR. Tenofovir increases intracellular ATP meanwhile dipyridamole increases intracellular AMP and extracellular adenosine. Tenofovir maintain inactive AMPK and low levels of cAMP, which are recovered using dipyridamole. The use of dipyridamole activates PKAα as well as pCREB in an A2B dependent manner.
Conclusions: Adenosine and ATP act as mediators in muscle myogenesis. Modulation of the purinergic system with compounds that increase extracellular adenosine levels, activates adenosine A2B receptor and increases cAMP and AMPK pathways, meanwhile blockade of ATP transport exert the opposite effect. Therefore, Dipyridamole might be interesting as a therapeutically approach in sarcopenia.

2-19

Sex differences in skeletal muscle-ageing trajectory: same processes, but with different magnitudes

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Introduction: Sex differences in muscle-ageing are incompletely understood, therefore, we performed a cross-sectional trial to gain insight in potential sex differences in the etiology of muscle-ageing by analysis of underlying processes.
Methods: Young (13 males and 13 females; 23 ± 2 yrs) and old subjects (26 males and 28 females; 80 ± 3.5 yrs) were recruited. Males and females were highly matched and muscle biopsies taken from *vastus lateralis* muscle were used for RNA-seq analysis. Old versus young subjects were compared for each sex separately, and most noticeable findings were studied in detail using alternative methods.
Results: Overall gene expression separated the sexes, with parallel age-related changes. Analysis of differentially expressed genes (DEGs) revealed 1367 DEGs specific for males, 3146 DEGs specific for females and 2354 shared DEGs. Nearly all (99.8%) shared DEGs were regulated in the same direction in males and females, revealing that some features of muscle-ageing were highly similar in either sex. Top male pathways were involved in oxidative phosphorylation (OXPHOS) and (mitochondrial) metabolism, but similar changes were found in females and both sexes lost comparable amounts of protein levels of COX4. Top female pathways were involved in cell growth mediated by Akt signalling. Males displayed less DEGs involved in Akt signalling, but notably the direction of regulation (up or down) was highly similar for the majority (73%) of these genes. No sex specific effects were found on intramuscular p-Akt^{thr308} or serum IGF-1 levels.
Conclusions: Males and females displayed similar loss of OXPHOS subunits. More DEGs related to Akt signalling were found in females, although Akt signalling tended to be regulated in males in similar direction. Therefore, we conclude that processes involved in the ageing of *vastus lateralis* muscle are shared by the two sexes, but that the magnitude of regulation is sex specific.

2-20

Hyperphosphatemia and chronic inflammation are associated with aging and could be involved in the development of sarcopenia

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Introduction: Hyperphosphatemia and chronic inflammation have been related to aging. We analyze whether factors involved in phosphate homeostasis are associated with markers of inflammation and if both are correlated with the appearance of signs of sarcopenia.
Methods: Geriatric patients older than 75 years (n=175) and a control group of young people under 40 years (n=45) were included in the study. The levels of C-reactive protein (CRP), vitamin D, PTH and phosphate were analyzed by biochemistry, FGF23 and Klotho by commercial ELISA, and the cytokines IL-6, IL-18, TNF-α and MCP-1 by Milliplex ELISA. As markers of sarcopenia, strain force, gait speed-6m, equilibrium, speed, strength and the percentage of lean mass by bioimpedance were evaluated.
Results: The elderly had higher serum phosphate concentration and proteins related to phosphate metabolism such as vitamin D, PTH and FGF23, with a significant reduction in Klotho levels. Pro-inflammatory cytokines levels such as CRP, IL-6, IL-18, MCP-1 and TNF-α were significantly increased in the elderly compared to the young. Signs of sarcopenia appear in the elderly and affect strength, gait speed, balance, and percent lean mass. PTH correlates positively with IL-6 (r=0.2240; p=0.0022) and age (r=0.2423, p=0.0004), and negatively with signs of sarcopenia: strain force (r=-0.1529, p=0.0263), gait speed (r=-0.1598, p=0.0205), and lean mass (r=-0.1457, p=0.0391). In addition, a significant correlation was found between IL-6 and age (r=0.1755, p=0.0149), strain force (r=-0.1925, p=0.0075), and gait speed (r=-0.1677, p=0.0204).
Conclusions: We conclude that geriatric patients shown impaired phosphate homeostasis, leading to hyperphosphatemia, and chronic inflammation. A relationship could be stablished with age-related sarcopenia, since PTH levels positively correlated with age and the inflammation marker IL-6, and both parameters were negatively correlated with muscle strength, gait speed and lean mass.

2-21

Mechanosignaling through YAP/TAZ drives fibroadipogenic progenitors activation and promotes paraspinal muscle fibrosis in degenerative scoliosis

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Introduction: Degenerative scoliosis (DS) is a three-dimensional spinal deformity that accompanies by abnormal mechanical loading. Paravertebral muscle degeneration featured by fibrosis is believed to be involved in the onset and development of DS. YAP1 and TAZ are homologous mechanosensing transcription cofactors which regulates stem cell commitment. However, there is scarce information on whether and how the YAP/TAZ regulates the pathological change of paraspinal muscle in patients with DS. We aimed to study the molecular role of YAP/TAZ in the pathological process of DS.
Methods: Biopsies of paraspinal muscle from healthy and DS patients were obtained during surgery. H&E staining, Masson's staining, and immunofluorescence were used to evaluate the pathological change of paraspinal muscle. RNA-seq was performed to identify differently expressed genes between two groups. RT-PCR and western blotting were conducted to confirm the RNA-seq results. Primary fibro/adipogenic progenitors (FAPs) isolated and RNA interference, immunofluorescence were utilized to study the role of YAP/TAZ in FAPs commitment and the propensity of fibrotic differentiation. Verteporfin was used to investigate the therapeutic potential of YAP/TAZ inhibition in the development of DS.
Results: Histological evaluation revealed severe fibrosis in the paraspinal muscle of DS compared to age-matched controls. Enriched FAPs cells were embedded in the fibrotic area of the paraspinal muscle in DS patients. RNA-seq demonstrated a total of 1550 genes were differentially expressed among which 1270 genes were upregulated and 280 genes were downregulated with a foldchange of 2 and p value≤0.05. Both GO and KEGG analyses revealed that extracellular matrix organization, skeletal muscle contraction, collagen biosynthetic process were markedly affected by the differentially expressed genes. TGFβ signaling pathways (p=0.008) and hippo signaling pathways(p=0.048) were highly enriched in DS patients. qPCR and western blot showed that profibrogenic genes and YAP1 and TAZ were upregulated while p-YAP1 were downregulated in DS patients. Immunofluorescence staining also confirmed translocation of YAP1 and TAZ in nuclear. FAPs cells isolated from DS demonstrated a higher propensity to differentiate to fibroblast and knockdown of YAP1 or treatment with verteporfin resulted in a reduction of fibrosis and downregulation of Samd2/3.
Conclusions: The severe paraspinal muscle fibrosis in DS patients may be attributed to the increased YAP/TAZ activity

and its interaction with Samd2/3 in FAPs cells. Verteporfin can be a novel therapy for DS patients.

2-23

Hemichannels upregulation and inflammasome activation is associated with instability of the neuromuscular junction during unilateral lower limb suspension in humans

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Introduction: Disuse muscle atrophy comes from spaceflight, bed rest or limb immobilization. If prolonged, disuse can lead to severe muscle loss resulting from the activation of the atrophic gene-program and from the depression of protein synthesis. Recent findings by our group and others showed that neuromuscular junction (NMJ) instability occurs within 10 days of bed rest in young males. Using the unilateral lower limb suspension (ULLS) human model, we investigated other molecular players, possibly involved in the early stages of NMJ instability.
Methods: Healthy young males (n=11, 22.1±2.9 years, BMI 20 - 28 kg m^{-2}) underwent 10 days of ULLS. Biopsies from vastus lateralis (VL) muscle and blood sampling were collected prior and post ULLS, to analyse local and systemic biomarkers of NMJ instability: serum level of c-terminal agrin fragment (CAF), neural cell adhesion molecule (NCAM) positive myofibers, connexin 43 (Cx43) and pannexin-1 (Panx-1) hemichannels, neurofilament light chains (NFL) by SIMOA analysis, alongside deep transcriptomic analysis of VL.
Results: We showed that during the initial phase of disuse there is upregulation of biomarkers of denervation: increased serum level of CAF (+6%, $p<0.05$) and NFL (+46%, $p<0.01$), appearance of NCAM positive myofibers and transcriptional upregulation by RUNX1. The suggested NMJ instability appears alongside changes in the sarcolemma physiological permeability due to increased expression of Cx43 and Panx-1 hemichannels. The latter accompanied by an upregulation of transcriptomic evidence of robust inflammation and gene-reprogram.
Conclusions: Impairment of the NMJ physiology, axonal damage and inflammatory transcriptional activation is significant after 10 days of ULLS. The upregulation of Cx43 and Panx-1 suggests NMJ instability maybe due to chronic pre-junctional NMJ depression. The possible leakage of Ca^{2+} by sarcoplasmic reticulum and the possible extracellular release of ATP with autocrine properties could directly trigger the inflammatory transcriptional activation. The Cx43 and Panx-1 hemichannels upregulation may represent a possible molecular target.

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2-24

In vitro and In vivo effects of cigarette smoke on adipose and skeletal muscle tissue

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Introduction: Chronic obstructive pulmonary disease (COPD) is a chronic lung disease with systemic manifestations, including metabolic comorbidities involving altered adipose and skeletal muscle tissue. This study investigates alterations in adipose and skeletal muscle tissue in a cigarette smoke-induced COPD murine model.
Methods: Mice were exposed to cigarette smoke or air for 72 days. In white adipose tissue, morphology and inflammation were determined and for skeletal muscle tissue, muscle weight, muscle function (fore-limb grip strength), and mitochondrial and protein turnover markers were measured. 3T3-L1 pre-adipocytes were exposed to TPM from cigarette smoke to further understand the effect of cigarette smoke exposure on lipolysis.
Results: Cigarette smoke exposure decreased body weight, and the proportional loss in fat mass was more pronounced than the loss in lean mass in cigarette smoke-exposed mice. Fat mass was positively correlated with serum leptin levels. Cigarette smoke exposure reduced adipocyte size of and increased adipocyte numbers in both para-ovary and inguinal adipose tissue. Adipose macrophage numbers and associated cytokine levels (IL-1β, TNF-α and IL-6) were elevated in cigarette smoke-exposed mice. Muscle strength was decreased after cigarette smoke exposure, however, no changes in muscle weight and protein turnover markers were observed. *In vitro* studies demonstrated that lipolysis and fatty acid oxidation were upregulated in TPM-exposed pre-adipocytes.
Conclusions: Our findings indicate that cigarette smoke exposure induces loss of whole-body fat mass and adipose tissue atrophy which is likely due to enhanced lipolysis. Though skeletal muscle function deteriorated, no change in muscle weight and protein turnover markers were observed.
Therefore, it seems that fat mass loss and adipose tissue atrophy precedes muscle wasting.

2-25

Ethanol causes temporally clustered perturbations across the skeletal muscle multiome

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Introduction: Ethanol causes multiple signaling, metabolic and functional perturbations in the skeletal muscle. Unbiased approaches to determine molecular and metabolic changes in myotubes and skeletal muscle during ethanol exposure were

performed to identify novel mechanistic and therapeutic targets in sarcopenia of alcohol-related liver disease (ALD).
Methods: Studies were performed in differentiated murine myotubes and treated without (UnT) or with 100mM ethanol for 6h and 24h. Physiological relevance was established in gastrocnemius muscle from C57BL/6J ethanol-fed (EF) or pair-fed (PF) mice. Translational relevance was established in vastus lateralis muscle from human subjects with ALD and control subjects. Multiomics datasets across models included assay for transposase accessible chromatin sequencing (ATACseq), RNAseq, proteomics, phosphoproteomics, acetylomics and metabolomics. Vertical and horizontal integration of the multiome was performed including quality measures, heatmaps of differentially expressed molecules (DEM), upset plots, correlation plots, and labeled volcano plots (R version 4.2.0 (2022-04-22)). Functional enrichment analysis using g:Profiler and Ingenuity Pathway Analysis (QIAGEN, INC.) were performed. STRING (version 11.5) database was used to identify protein-protein interaction networks. Temporal clustering was determined by a priory cutoff criteria for DEM.
Results: There were significant differences in ethanol-treated samples compared to control samples in each dataset. The greatest number of shared DEM were between the mouse and C2C12 RNAseq datasets (n=748, p<0.05 mouse and padj<0.05 cells) with the next most shared between cell RNAseq and cell phosphoproteomics (n=553). Early responses to ethanol included perturbations in tRNA charging, ubiquitination, and Ephrin (receptor tyrosine kinases) signaling. Persistent perturbations (genes that are changed at both early and late treatment timepoints) include changes in protein kinase A signaling, senescence, and HIPPO signaling.
Conclusions: Integration of multiomic analyses defined new targets in the skeletal muscle that are upregulated or downregulated during ethanol exposure. Ephrin receptors and HIPPO signaling are novel targets for restoring skeletal muscle protein homeostasis.

2-27

Comparison of skeletal muscle changes at three vertebral levels following radiotherapy in patients with oropharyngeal carcinoma

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Introduction: Assessment of skeletal muscle (SM) depletion, or sarcopenia, using computed tomography (CT) scans, has emerged as an effective tool in body composition analysis. The gold standard technique utilises cross-sectional area (CSA) measures at the third lumbar vertebra (L3), however, alternate vertebral landmarks are used for muscle evaluation in patients with head and neck cancer due to scan unavailability. We aimed to investigate muscle changes following radiotherapy at the third cervical (C3) and second thoracic (T2) levels, to determine whether this is proportionate to SM changes detected at L3 in patients with oropharyngeal carcinoma (OPC).
Methods: Muscle density data were derived retrospectively from diagnostic PET-CT scans of patients with OPC who completed treatment between 2014 and 2021. SM was delineated at C3, T2 and L3 pre-treatment, and up to six months post. Changes in CSA were explored at each level and compared to L3. Sarcopenia and weight loss were also investigated.
Results: Scans of 33 patients were analysed (88% male, mean age 61 (SD 8.5) years). Sarcopenia was detected in 36% at baseline, 42% post-treatment. On matched pair analysis at each vertebral level; mean L3-CSA change -12.1 cm^2 (SD 9.7, 95%CI -15.5 to -8.6, p<0.001), T2-CSA -30.5 cm^2 (SD 34.8, 95%CI -42.8 to -18.1, p<0.001) and C3-CSA +2.1 cm^2 (SD 4.1, 95%CI 0.63 to 3.5, p<0.00). No difference found in percentage change of T2-CSA with L3-CSA (mean -2.2%, SD 10.6, 95%CI -6.0 to 1.6, p=0.240), however, was significantly different to C3-CSA (mean 13.2%, SD 11.6, 95%CI 9.1 to 17.3, p<0.001).
Conclusions: SM changes post treatment at T2 are not significantly different to L3. However, our results suggest that SM at C3 does not change proportionately, and therefore is not a reliable representation of whole body SM change over time in patients with OPC.

2-28

The change in skeletal muscle mass during (chemo)radiotherapy of head and neck cancer patients

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Introduction: Head and neck cancer (HNC) patients with low skeletal muscle mass (SMM) are at higher risk for adverse events during (chemo)radiotherapy. For other types of cancer it is known that SMM decreases during therapy predicts adverse events and worse survival. The goal of this study is to identify patient, tumor, treatment and survival characteristics associated with SMM decline in HNC patients during (chemo)radiotherapy.
Methods: For 47 HNC patients MRI-scans before, and 2, 3, 4 and 5 weeks after start of radiotherapy were used to assess SMM. SMM was assessed by delineating the skeletal muscle area at the level of the third cervical vertebra. Data collection consisted of patient, tumor and treatment parameters, and occurrence of adverse events. Low SMM was defined as a lumbar skeletal muscle index of ≤ 43.2 cm^2/m^2. Mixed effects models were performed to assess the SMM trend. A percentual SMM loss of more than one standard deviation (SD) during treatment was considered as SMM decline. Logistic regression and Kaplan-Meier curves were used to respectively identify predictors and effects of SMM decline on survival.
Results: Eleven patients (23%) experienced SMM decline and SD was 4%. SMM decreased from 41.5 to 40.8 cm^2/m^2 on average and showed a decreasing trend (p=0.036) over time. Adverse events were associated with SMM decline (OR 10.0 [95% CI 1.1-88.9]; p=0.039). Low SMM prior to therapy was not associated with SMM decline. The median disease-specific survival was shorter in patients with SMM decline compared to patients with a stable SMM (99 vs. 173 months; p=0.051).
Conclusions: SMM declines during (chemo)radiotherapy in HNC, and adverse events were associated with SMM decline. There was no association between low SMM prior to treatment and SMM decline. Disease-specific survival seems to be shorter for patients with SMM decline compared to patients with no SMM decline.

2-29

Associations between body composition variables and tumor features in male clear cell renal cell carcinoma (ccRCC) patients

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Introduction: ccRCC is a male predominant disease where low skeletal muscle index (SMI) and density (SMD) are associated with poor cancer-specific and overall survival. Visceral adipose tissue index (VATI) and subcutaneous adipose tissue index (SATI) are inconsistently related to clinical outcomes. Mechanisms underlying these associations are unclear. We examined how body composition relates to tumor features among non-metastatic male ccRCC patients ≥50 years undergoing nephrectomy from Memorial Sloan Kettering Cancer Center.
Methods: Pre-surgical CT scans from 606 patients were interpreted for body composition using automated analysis. Tumor stage and grade were determined by pathological review. SMI and SMD were dichotomized using published cutpoints, whereas VATI and SATI were analyzed continuously. Joint effects of SMI and SMD were also examined. Odds ratios and 95% confidence intervals (OR [95% CI]) from logistic regression models estimated associations between body composition and tumor features. P-values<0.05 were considered statistically significant.
Results: Median age was 61, 36% presented with advanced stage (T3), 61% had high grade tumors; 28% and 30% were classified as low SMI and low SMD, respectively. In age-adjusted models, low vs. adequate SMI was associated with advanced stage (OR 1.7 [1.1-2.4]) and with high grade (OR 1.6 [1.1- 2.4]). Low vs. adequate SMD was also associated with advanced stage (OR 2.2 [1.5-3.1) and high grade (OR 2.0 [1.4-3.0]). Compared to patients with both adequate SMI and SMD, those with both low SMI and low SMD were ~three times more likely to present with advanced stage (OR 3.0 [1.7-5.1]) and high grade (OR 2.8 [1.6-5.3]). VATI and SATI were not significantly associated with either tumor feature.
Conclusions: Poor muscle health, but not adiposity, are associated with advanced tumor features which may explain why they are poor prognostic factors. Whether low SMI and SMD are a cause or consequence of aggressive tumors is not clear.

3-02

Gut microbiota diversity in cachectic acutely ill geriatric patients

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Introduction: Cachexia is a multifactorial syndrome associated with acute and chronic diseases. It affects treatment efficacy, quality of life, prognosis, and survival, and its occurrence increases with age. Considering the proposed gut-muscle axis, we hypothesise that gut microbiota diversity may play a part in the development of cachexia.
Methods: In this cross-sectional analysis, we included 90 acutely ill older adults in the emergency ward of a Brazilian hospital. We defined cachexia according to Evans et al. We characterised the gut microbiota using 16S rRNA gene amplicon sequencing from rectal swab samples. The α-diversity was measured using the ACE, Chao1, Shannon and Simpson indices, and the β-diversity by PERMANOVA analysis using the Bray method. The groups (with and without cachexia) were compared using the Wilcoxon rank-sum test.
Results: Of the total sample, 17.8% were cachectic. The microbiota composition at the phylum level did not show a significant difference between cachectic and non-cachectic patients at hospital admission (R^2= 0.023, F= 2.035, P= 0.088). Cachectic patients showed a non-significant lower richness compared to the noncachectic group and similar evenness (Table 1). Of the phylum identified in the samples (Figure 1), *Verrucomicrobia* was significantly increased in cachectic individuals (P= 0. 015), while *Acidobacteria* and *Chloroflexi* were present in cachectic patients but not in the noncachectic ones (P= 0.034).
Conclusions: Acutely ill older adults diagnosed with cachexia revealed a possible less diverse gut microbiota and divergent composition at the phylum level with a high abundance of *Verrucomicrobia* compared to non-cachectic. More studies are needed to elucidate these findings.

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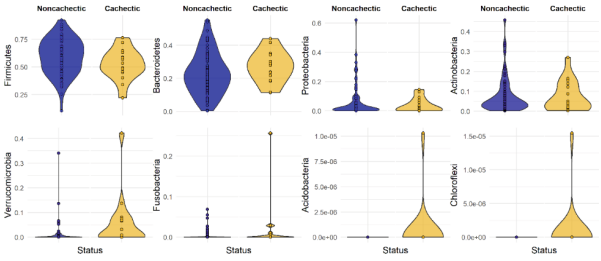
Table 1. Alpha-diversity index at hospital admission

	Noncachexia	Cachexia	P-value
N (%)	74 (82.2)	16 (17.8)	
ACE	228.48 ± 11797.64	173.46 ± 8305.97	0.1497
Chao1	227 ± 11798.08	174.113 ± 8411.6	0.15
InvSimpson	14.5 ± 145.084	14.128 ± 114.22	0.5163
Shannon	3.585 ± 0.428	3.281 ± 0.42	0.2035
Simpson	0.931 ± 0.004	0.929 ± 0.004	0.516

Figure 1. The main phylum identified in the gut microbiota of cachectic vs noncachectic acutely ill older adults.



3-03

Iron supplementation is sufficient to rescue skeletal muscle mass and function in cancer cachexia and glucocorticoid induced-atrophy

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Introduction: Cachexia is a wasting syndrome characterized by devastating skeletal muscle atrophy that dramatically increases mortality in various diseases. Knowledge regarding the mechanism of cancer-induced cachexia remains very scarce, making cachexia an unmet medical need. Iron deficiency anemia is frequently diagnosed in cancer patients especially in tumor types commonly associated with cachexia. Iron being an essential nutrient for mitochondrial metabolism and more generally for several essential metabolic processes, it plays a critical role in the optimal function of skeletal muscle. Therefore, we speculated that iron metabolism dysregulation could be involved in the atrophic process.
Methods: *In vitro,* we modulated iron levels in C2C12 and human myotubes by using iron supplementation, selective iron chelators, or by silencing iron metabolism genes with siRNA in order to analyze myotube diameter, and mitochondrial metabolism. *In vivo*, we investigated for iron metabolism in atrophic skeletal muscle induced by the C26 model or by a chronical dexamethasone treatment. We then evaluated the effect of iron supplementation (tail-vein injection of ferric carboxymaltose) on skeletal muscle atrophy in both models.
Results: In this study, we discovered strong alterations of iron metabolism in the skeletal muscle of tumor-bearing mice, and in particular a low iron availability in the mitochondria impeding a proper function of iron-dependent enzymes and therefore energy production. We found that modulation of iron levels directly influences myotube size *in vitro* and muscle mass in otherwise healthy mice. Furthermore, iron supplementation was able to restore mitochondrial function as reflected by increase aconitase or succinate dehydrogenase activity, ATP production increase and AMPK dephosphorylation ultimately resulting in protection of muscle function and mass in both cancer and glucocorticoid-induced atrophy.
Conclusions: Overall, our findings provide new mechanistic insights in both cancer-induced and glucocorticoid-induced skeletal muscle wasting and support targeting iron metabolism as a potential therapeutic option for muscle wasting diseases.

3-04

Prostaglandins mediate Toll-like receptor-induced hypothalamic inflammation via prostaglandin receptor EP4 in cancer cachexia

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Introduction: Cachexia is a multi-organ syndrome that is accompanied by systemic inflammation and central inflammation. During cancer-induced cachexia, both intestinal permeability and hypothalamic inflammation have been reported to be increased. Our preliminary data indicates intestinal permeability might amplify hypothalamic inflammation via Toll-like Receptors (TLR) interaction with tumour-derived prostaglandins. This abstract describes possible mechanisms behind the crosstalk between tumour, gut and hypothalamus.
Methods: To simulate the tumour-gut-brain crosstalk, hypothalamic (HypoE-N46) cells were incubated with Lipopolysaccharide (LPS) or Pam3CSK4 (Pam3) to imitate decreased intestinal integrity and combined with different tumour secretomes or prostaglandins. Selective inhibitors and agonists were investigated to confirm involvement of prostaglandin receptors (EP) and TLR metabolism. TLR inhibitors and EP antagonists were combined to explore the synergistic effect.
Results: Prostaglandin E2 (PGE2) was screened from various cachexia-inducing tumour secretomes and is a predominant player in amplifying TLR-induced IL6 secretion. EP4 antagonist L-161982 reduced IL6 release at 0.1 μM (P<0.001) while EP4 agonist TCS2510 amplified IL6 secretion to an equivalent level as PGE2 (264.9% vs. 333.9 % in PGE2+LPS compared to LPS), suggesting PGE2 amplified hypothalamic inflammation via EP4. IL6 secretion was inhibited by TLR4 inhibitor TAK242 at 20 ng/ml (55.3 nM, P<0.001) and decreased by the IκB kinase inhibitor BMS345541 at 7 uM (P<0.001), indicating that the TLR-NFκB signalling was involved in this inflammatory response. Finally, a combination of BMS and L-161982 eliminated the amplification (9.3% vs. 303.6 % in PGE2+LPS compared to LPS, P<0.0001; 41.4% vs. 555.5% in PGE2+Pam3 compared to Pam3, P<0.0001).
Conclusions: Tumour-derived PGE2 was confirmed to amplify TLR-induced hypothalamic inflammation in a model for cancer-related cachexia-anorexia syndrome. PGE2 binds to EP4 receptor and consequently mediates NFkB-induced IL6 secretion. This synergistic effect can be significantly attenuated by the combined inhibition of TLR and EP4 receptor.

3-05

Ketogenic diet slows down tumor growth but induces primary adrenal insufficiency that accelerates onset of cachexia in C26 and KPC murine models

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Introduction: Ketogenic diets (KD) containing high levels of fats are explored in medical research as adjuvant therapies in end-stages of cancer that are associated with cachexia. Metabolism of fats through non-enzymatic lipid peroxidation is a recognized source of highly reactive and mutagenic molecules, but the effect of lipid peroxidation products (LPPs) on established cancers remains unclear. Moreover, the biosynthetic pathway of corticosterone, the main regulator of metabolic stress, and the pathway for detoxification of LPPs require the same cofactors but their biochemical interdependency has not been explored.
Methods: Two murine models of cancer-associated cachexia were used: the subcutaneous C26 model of colorectal cancer and the genetically engineered autochthonous KPC model of pancreatic cancer. Weight-stable, tumor-bearing male were allocated into two experimental matched groups and fed with ketogenic or standard chow diet. Overall and progression-free survival were monitored, and 15% body weight loss was defined as cachectic endpoint. Glucose and ketone levels were measured longitudinally and comprehensive metabolic data were obtained by housing the mice in metabolic cages.
Results: Ketogenic diet slows down tumor growth but accelerates onset of cancer cachexia in tumor-bearing mice. Reduced tumor size results from accumulation of LPPs, saturation of the GSH detoxifying pathway and ferroptotic death of cancer cells. Moreover, systemic redox state imbalance in KD-fed tumor-bearing mice causes NADPH depletion and impaired biosynthesis of corticosterone in the adrenals (Addison's disease/primary hypoadrenalism). Dexamethasone treatment delays onset of cancer cachexia and extends survival of tumor-bearing mice fed with KD compared to untreated tumor-bearing mice on either KD or standard feeding by improving metabolic homeostasis and utilization of nutritional substrates.
Conclusions: Lack of an appropriate corticosterone release during cachexia leads to metabolic maladaptation and inability to use energy sources in mice fed KD. Dexamethasone administration improves tissue preservation, energy

expenditure and survival while preserving reduced tumor growth.

3-06

Overexpression of skeletal muscle PGC1α protects against cisplatin-induced cachexia

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Introduction: Chemotherapy promotes a cachexia-like phenotype, including skeletal muscle and mitochondrial dysfunction. The regulator of mitochondrial biogenesis, peroxisome proliferator-activated receptor-gamma coactivator-1 alpha (PGC1α), is often reduced in cachectic skeletal muscle. Here, we investigated if overexpression of PGC1α in skeletal muscle could protect against cisplatin-induced cachexia in young and old animals.
Methods: Young (2-month) and old (18-month) wild-type (WT) and PGC1α-transgenic (Tg) male and female mice were intraperitoneally injected with cisplatin (C; 2.5mg/kg) for 2 weeks, while control animals received saline (n=5-9/group).
Results: Young WT+C demonstrated losses in gastrocnemius mass (males: -16%; females: -11%), muscle force (-6%, both sexes), and motor unit number estimation (MUNE; males: -53%; females: -51%). Old WT+C exhibited greater gastrocnemius wasting (males: -22%; females: -27%), muscle weakness (males: -20%; females: -17%), and losses of MUNE (males: -82%; females: -62%), suggesting exacerbated cachexia compared to younger animals. In young animals, PGC1α overexpression exhibited mixed results against cisplatin-induced muscle wasting. However, muscle force and MUNE were unchanged in both male and female Tg+C, suggesting preservation of neuromuscular function. Protective effects with PGC1α overexpression were heighted in aged mice, with old male Tg+C demonstrating preserved muscle mass (gastrocnemius: +34%), muscle force (+13%), and MUNE (+3-fold). Similarly, old female Tg+C did not exhibit muscle wasting or reductions in MUNE and had preserved muscle force (+11%) compared to female WT+C. Molecular analysis revealed that cisplatin promoted greater loss of mitochondrial proteins in aged WT animals, including PGC1α, OPA1, CytochromeC, and Cox IV.
Conclusions: Our present studies demonstrate that cisplatin-induced cachexia is heighted with age. In contrast, overexpression of PGC1α combats the neuromuscular dysfunction caused by cisplatin, especially in older animals. Hence, our observations indicate that aged animals may be more susceptible to develop chemotherapy side toxicities and that mitochondria-targeted strategies may serve as a tool to prevent chemotherapy-induced muscle wasting and weakness.

3-07

Understanding BMP signaling in cancer cachexia

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Introduction: Cancer cachexia is a multi-factorial metabolic syndrome characterized by excessive body weight loss due to progressive fat and lean mass catabolism occurring in more than half of cancer patients. The loss of skeletal muscle mass and strength are considered as the most relevant features of cancer cachexia and predictors of poor outcomes.
Bone Morphogenetic Protein (BMP)/Smad1/5/8 pathway is a positive regulator of muscle mass homeostasis. We have demonstrated that diminished Smad1/5/8 signalling in muscles plays a critical role for the onset of cancer cachexia and pharmacological reactivation of the BMP pathway in the muscles of tumor-bearing mice prevents muscle wasting. The transcriptional activity of Smad1/5/8 is specifically required to mediate a beneficial effect on muscle mass. Moreover, several components of the BMP pathway are transcriptionally modulated in cachectic muscles.
Methods: We decided to use an unbiased genome-wide approach to investigate the chromatin remodeling that may occur in cancer cachexia, and we performed ChIP-seq experiments in muscles to characterize histone modifications in cachexia.
Results: We focused on H3K27Ac, a histone mark of active regulatory elements. An increase of acetylated histones was detected in muscles of C26- tumor bearing mice, compared to the ones of the control group. Process enrichment analysis reported the BMP pathway among the top 20 pathways with hyperacetylated histones. We searched for potential transcription factors binding sites in the hyperacetylated promoters of different BMP pathway components that are transcriptionally modulated in the context of cancer cachexia.
Conclusions: We aim to understand how the cancer stimulates transcriptional changes leading to BMP-Smad1/5/8 inhibition in skeletal muscles to favor cachexia onset in order to identify new potential therapeutic targets.

3-08

Colon cancer treatment with FOLFIRI exacerbates muscle fiber atrophy and induces a catabolic transcriptional program in skeletal muscle

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Introduction: Cancer is associated with muscle fibre atrophy. Clinically, this tumor effect is overlaid with systemic cancer therapies. Several cancer therapies induce muscle fibre atrophy when given to healthy animals. Possible interactions between cancer and treatment in the development of muscle wasting remain uncharacterized.
Methods: Female Fischer 344 rats with colon adenocarcinoma are treated with FOLFIRI (irinotecan/5-fluorouracil) at a dose/schedule that recapitulate treatment response and toxicity that align with clinical values (PMID10919639). HEALTHY controls were compared with TUMOR rats and TUMOR+FOLFIRI rats given 2 weekly cycles of FOLFIRI treatment (n=8/group). *Gastrocnemius* muscle fibre cross-sectional area (CSA) and mRNA sequencing was performed. Differential gene expression (DE) was assessed (fold-change≥1.5; p-value<0.05) and Ingenuity Pathway Analysis (IPA) was used for functional annotation of the DE mRNAs.
Results: Compared with HEALTHY, TUMOR growth (0.57±0.1% of body weight) resulted in a -22.2% ($p<0.05$) reduction in *gastrocnemius* mean fiber CSA. FOLFIRI shrank the tumor (-89%) and induced further -22% reduction in muscle fibre CSA. Muscles of TUMOR vs HEALTHY showed 1283 DE transcripts and 43 canonical pathways($p<0.05$). TUMOR+FOLFIRI expanded the DE to 2095 transcripts and 72 canonical pathways($p<0.05$). Expression of extracellular matrix proteins including structural fibrillar collagens, major structural components of basement membranes and connective tissue

microfibrils as well as subunits of integral membrane proteins including integrin are downregulated($p<0.05$) after FOLFIRI treatment. The top pathway (by p-value) revealed from TUMOR+FOLFIRI vs HEALTHY was *Protein Ubiquitination*($p=5.37E-05$). Expression of multiple heat shock proteins (HSPs), ubiquitin conjugating enzymes as well as ubiquitin-specific peptidases (USPs) were upregulated($p<0.05$) following FOLFIRI treatment. In addition, regulatory molecules of autophagy responses, ubiquitin-like-conjugating enzymes involved in cell-death related autophagy and autophagosome formation are upregulated($p<0.05$) by FOLFIRI treatment.
Conclusions: Tumor and FOLFIRI resulted progressive atrophy and changes in skeletal muscle transcriptome. FOLFIRI specifically exacerbates a catabolic transcriptional program, in spite of robust tumor response.

3-09

Modulating the Sympathetic Nervous System: Role in tissue wasting and inflammation in a novel mouse model for Cancer-Associated-Cachexia

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Introduction: Cancer-associated cachexia (CAC) is a wasting syndrome where the tumour rewires the body's neural, immune, and metabolic systems. Elevated β-adrenergic signalling is responsible for fat browning and atrophy in murine transplantation models and genetically engineered mouse models (GEMMs). Catecholamines provide anabolic effects in skeletal muscle, and β-agonists are beneficial in muscle wasting in both patients and mice. Furthermore, β-antagonists can ameliorate cachexia, pointing out that the adrenergic system mechanisms contributing to CAC development remain unclear. Using GEMMs, we investigate the role of the β-adrenergic system in CAC and its implication in modulating the cross-talk between tumour, cell metabolism, immune cells and the neuroendocrine system.
Methods: We characterized the progression of CAC in novel GEMM with Mx-Cre mediated deletion of *dopamine-β-hydroxylase* (Dbh) in a genetic model for skin cancer (K5-hSOSF). All experiments were conducted using mice of 5-week-old (pre-cachexia) and 7-week-old (endpoint, cachexia). The main features of adipose tissue atrophy, browning, and skeletal muscle atrophy were explored using standard immunohistochemical and immunofluorescence methods. Catecholamines were measured by LC-MS/MS, and cytokines by ELISA.
Results: Upon Dbh-inactivation, a drastic reduction in circulating and tissue levels of catecholamine was detected. Dbh-deficient mice displayed ameliorated body weight loss, reduced adipose tissue wasting and minimal to no skeletal muscle atrophy at endpoint and circulating IL-6, TNFα and IL-1β, remained similar to those of tumour-free control littermates. Reduced fat loss was observed at precachexia and cachexia timepoints alongside diminished WAT browning with decreased uncoupling protein 1. Decreased expression of molecules associated with the E3 ubiquitin-ligase, improved cross-sectional area, and reduced numbers of centro-nucleated muscle fibres were apparent. Granulocyte/lymphocyte ratio, albumin and cholesterol levels were comparable to controls.
Conclusions: β-adrenergic system inactivation rescues cachexia in a genetic model for skin cancer. Further experiments are underway to clarify the contribution of β-adrenergic signalling to the development of CAC.

3-10

Interleukin-6 initiates wasting in a novel C57BL/6 model of cancer-associated cachexia

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Introduction: To cover diverse etiologies of cancer-associated cachexia (CAC), models with varying degrees of cachexia symptoms are needed. So far, there is no tumor model syngeneic to C57BL/6-mice, that would allow a direct comparison of cachexigenic and non-cachexigenic tumors. Here, we present the novel CAC model CHX207, which evolved from the non-cachexigenic cell line MCA207.
Methods: C57BL/6-mice were injected with MCA207- or CHX207-fibrosarcoma cells and analyzed for tumor growth and alterations in body composition. Furthermore, food/water intake, activity, energy expenditure, circulating metabolites, and tumorkines were investigated. Adipose and muscle tissue wasting in cachectic mice was examined using NMR, histological analyses, mechanistic measurements *in vitro* and *ex vivo*, and mRNA/protein expression analyses. Interleukin-6 (IL-6) was deleted from cancer cells using CRISPR/Cas9-gene editing and cachexia was analyzed in $CHX207^{IL6KO}$-tumor bearing mice as described above.
Results: CHX207-, but not MCA207-tumor bearing mice, exhibit all major clinical features of CAC, including highly increased plasma IL-6, anorexia ($p\leq0.01$) and catabolic reprogramming, which in turn leads to adipose tissue loss ($p\leq0.001$) and muscle wasting ($p\leq0.01$) 13 days after cancer cell inoculation. Adipose tissue wasting results from reduced adipolipogenesis combined with increased lipolysis, but is not associated with browning of white adipose tissue. Ablation of adipose triglyceride lipase (ATGL) prevents adipose tissue wasting in ATGL-ko mice bearing CHX207-tumors. Specific deletion of IL-6 from CHX207-cancer cells completely protects $CHX207^{IL6KO}$-tumor bearing mice from adipose tissue and skeletal muscle wasting.
Conclusions: In this study, we present a novel cachexia-inducing tumor based on CHX207-fibrosarcoma cells in C57BL/6-mice. CHX207-induced cachexia is IL-6 dependent and represents an important tool to investigate mediators and metabolic consequences of CAC in direct comparison to the non-cachexigenic counterpart MCA207.

3-11

The effect of chemotherapy and fish oil supplementation on myosteatosis in a preclinical model of colorectal cancer: Does skeletal muscle fiber type composition matter?

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Introduction: Fat accumulation in skeletal muscle, known as myosteatosis, is a risk factor for poor outcomes in the tumor-bearing state and is exacerbated following chemotherapy. Recently, dietary Eicosapentaenoic acid (EPA) and Docosahexaenoic acid (DHA) in the form of fish oil have been shown to attenuate myosteatosis in Gastrocnemius muscle, a muscle of mixed fiber types. This study aimed to determine whether myosteatosis preferentially occurs in slow- or fast-twitch muscles and whether EPA+DHA mitigates chemotherapy-associated myosteatosis in other muscle types.
Methods: Chemotherapy was initiated two weeks after Ward colorectal carcinoma implantation in Female rats. Rats fed a semi-purified control diet were compared with experimental

groups provided EPA+DHA (2.0 g /100 g of diet) initiated on the first day of chemotherapy. They received chemotherapy on day 14 (Cycle 1) and 21 (cycle 2) after tumor implantation. Reference animals without any treatment were maintained on a control diet. Fatty acids in triglyceride (TG) and phospholipids (PL) were quantified by gas chromatography from Soleus (SOL; slow-twitch) and Extensor Digitorum Longus (EDL; fast-twitch) muscles.
Results: The tumor did not affect TG content of SOL nor EDL. After Cycle 1 chemotherapy (~3.5-fold, P=0.02), the increase in SOL TG content was not observed in EPA+DHA fed rats ($p = 0.007$). A significant reduction in the proportion of EPA was observed in SOL-PL after one ($p < 0.001$) and two ($p = 0.015$) cycles of chemotherapy that were increased in the rats fed EPA+DHA ($p < 0.05$). In contrast, EDL did not exhibit significant changes in TG nor PL content following chemotherapy nor with diet.
Conclusions: For the first time, we demonstrated muscle-specificity in myosteatosis, which may preferentially occur in slow-switch muscle, in a preclinical model of chemotherapy-associated myosteatosis. Understanding underlying mechanisms remain to be investigated.

3-12

Leucine-rich diet enhanced the PI3K-AKT-mTOR pathway expression profile during cancer cachexia but not in cancer cachexia-associated sarcopenia

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Introduction: Muscle loss occurs due to several chronic diseases (cachexia) and normal ageing (sarcopenia). Current evidence has shown that leucine can preserve muscle mass in pre-clinical cancer cachexia. However, the role of leucine in the process of cancer cachexia-associated sarcopenia is not totally known. Therefore, we evaluated this relationship in adult and aged Walker 256 tumour-bearing rats under the leucine-rich diet effects.
Methods: Adult (A) and aged (S) male Wistar rats distributed into four groups received viable Walker 256 tumour cells (W) and normoproteic or 3% leucine-rich (L) diet. After 21 days or a pre-agonic state, all animals were euthanised to analyse the morphometric and strength parameters, protein metabolism and gene expression in gastrocnemius muscle. The statistical analyses were performed by two-way ANOVA, followed by a post-hoc Tukey's test.
Results: The cachexia index decreased in both aged groups (SW*vs*AW: <19%; SWL*vs*AWL: <27%). All morphometric parameters were normalised by tibia length, which was lengthier in aged groups (SW*vs*AW and SWL*vs*AWL: both >12%). In aged groups (SW and SWL), the perigonadal fat was increased (~77% higher) and also the gastrocnemius muscle mass (~22% increased) than in adult groups, independently of diet supplementation. However, the grip strength was lower in aged groups (SW*vs*AW: <63%; SWL*vs*AWL: <66%). Aged groups had decreased protein synthesis (~80% reduction) and degradation (~60% reduction) than adult groups. The leucine-rich diet modulated the muscle *AKT1* and *mTOR* gene expressions positively only in the adult group compared to normoproteic (AWL*vs*AW: 114 and 88% higher, respectively) and also compared to aged tumour-bearing groups (AWL*vs*SWL: >69 and 62%, respectively).
Conclusions: Our preliminary results suggest that the leucine-rich diet modified the PI3K-AKT-mTOR pathway expression profile, minimising the degradation process, especially in adult rats, as the associated sarcopenia potentiated the deleterious effects of tumour growth.

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3-14

A mutation in desmin causes cardiac remodeling, altered proteome-wide protein fluxes, fibrosis and arrhythmia

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Background: Desmin mutations are a widely underdiagnosed cause of cardiomyopathies and commonly associated with life-threatening complications like sustained arrhythmias, conduction disorders and sudden death. The pathomechanism of this clinically heterogeneous disease is not well understood, and there is no specific treatment available.
Methods: We created a rat model with a mutation in R349P DES via CRISPR-Cas9, analog to the most frequent R350P DES mutation in humans. To characterize the extent of cardiac involvement, we performed echocardiography, electrocardiography, histology, and immunoblotting experiments on hearts of R349P DES mutants (DES) and wildtype littermates (WT). We also examined changes in proteome-wide protein turnover rates of heart tissue after treadmill exercise using LC-MS.
Results: There were no differences in gross anatomy and function between the genotypes, but we found ventricular arrhythmias in DES rats that were absent in WT animals. Cardiac tissue architecture was disorganized, with a pathological staining pattern for desmin and desmin-positive aggregates, as well as increased collagen levels and fibrosis in R349P rat hearts. Markers for membrane damage and oxidative phosphorylation were increased in DES compared to WT. Global protein fluxes were similar under sedentary conditions, but exercise had a significantly greater effect on DES than WT protein turnover.
Conclusions: The R349P DES rat model reflects the cardiac phenotype seen in human desminopathy including key hallmarks like fibrosis and arrhythmias. Future studies will be required to explore therapeutic strategies to prevent and treat myocardial involvement in desminopathy.

3-15

L-Leucine supplementation modulated muscle strength but unchanged the cachexia parameters in tumour-bearing mice

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Introduction: L-leucine supplementation has shown positive effects in muscle negative protein balance in Walker-256

tumour-bearing rats. Skeletal muscle function loss is intrinsically related to cancer cachexia poor prognosis. Therefore, we evaluated L-leucine supplementation effects on cachexia parameters and muscle strength in another preclinical cachexia model.
Methods: Male mice distributed into four groups (C, control; TB, tumour-bearing; Leu; leucine-rich diet and TBLeu, tumour-bearing plus leucine-rich diet) received or not $1x10^8$ viable Lewis lung carcinoma cells and fed control or 3% L-leucine-rich diets, during 28 days. Before euthanasia, grip strength evaluation was performed. After euthanasia, tumour, gastrocnemius, quadriceps and tibial muscles, spleen and perigonadal and perirenal fats were weighed.
Results: Both tumour-bearing groups had a reduced weight variation (TB < C, ~11% reduction; TBLeu < Leu, ~22% reduction) and decreased gastrocnemius muscle mass (TB < C, ~19 % reduction; TBLeu < Leu, ~20% reduction). Tumour weight was not affected by leucine supplementation (TBLeu = TB). Spleen weight increased in both tumour-bearing groups (TB > C; TBLeu > Leu and C). Perirenal fat increased in Leu group (Leu > C) and decreased in TBLeu (TBLeu < Leu and C). Additionally, gonadal fat reduced in both tumour-bearing groups (TB < C; TBLeu < Leu and C). Despite showing reduction in tibial and quadriceps muscles weights (TBLeu < Leu and C), the leucine-rich diet ameliorated the muscular grip strength in TBLeu group (TBLeu=Leu=C). This parameter decreased more in TB group (TB < C; ~23% reduction *vs* 13% reduction in TBLeu).
Conclusions: L-leucine supplementation increased perirenal fat. Although the tibial, quadriceps and gastrocnemius muscle weights reduced, we found that leucine supplementation ameliorated the muscle strength in the TBLeu group. We are currently analysing how the leucine-rich diet acts on muscle protein synthesis and degradation processes to correlate with muscle strength maintenance.

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3-16

C26 tumors induce body wasting independently of insulin resistance in Balb/c mice

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Introduction: Development of insulin resistance (IR) has been proposed as one of the mechanisms responsible for the loss of fat and muscle mass in cancer cachexia (CCx). IR may be the consequence of enhanced hepatic glucose production and chronic hyperinsulinemia during CCx. The aim of our study was to perform an in-depth analysis of the insulin sensitivity status during CCx pathogenesis in C26-tumor bearing (TB) mice, as well as in cachectic cancer patients.
Methods: We performed glucose or insulin tolerance tests at different stages of the disease (early non-cachectic, pre-cachectic and cachectic stages). In addition, non-cachectic PBS-injected or NC26-TB mice as well as cachectic C26-TB were injected either with a saline solution or a bolus of insulin to analyze the activation of the insulin signaling pathway. Finally, we calculated measures of insulin sensitivity (QUICKI and/or HOMA-IR index) in different cohorts of non-cachectic, pre-cachectic and cachectic mice as well as in a cohort of cachectic and weight stable cancer patients who underwent presurgical fasting.
Results: C26-TB Balb/c mice did not develop glucose or insulin intolerance at any stage of CCx pathogenesis. At a late stage, cachectic C26-TB mice had even a lower basal glycemia than control mice. Accordingly, C26-TB had very low basal levels of activating AKT phosphorylation in metabolic tissues and exhibited a stronger response to insulin than control mice. Finally, the insulin sensitivity index (QUICKI) gradually rose during CCx development. In cancer patients, CCx was associated with increased QUICKI and decreased HOMA-IR index.
Conclusions: All together, these data do not support any involvement of insulin resistance in the development of tissue loss in C26-TB Balb/c mice. Alteration of insulin sensitivity and resistance index in cachectic cancer patients support the reappraisal of this aspect in clinical studies.

3-17

Characterization of IL-6 and GDF15 expression during the transition from pre-anorexia to anorexia in the C26 tumor-bearing mouse model

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Introduction: Anorexia is a major symptom of cachexia for a large number of cancer patients, disrupting the physiological regulation of food intake and contributing to the deterioration of health status. Data from literature suggest that mechanisms underlying cancer-associated anorexia may involve both central and peripheral mediators, such as IL-6 and GDF15 cytokines, but they are poorly understood. Our objective was to study the mechanisms associated to the transition from pre-anorexia to anorexia.
Methods: We chose the C26 tumor-bearing mouse model characterized by a decreased food intake and loss of body weight (Bindels et al., Oncotarget 2018). The food intake of C26- and Sham male mice was measured daily. We performed biological analyses on two groups of C26-mice, on pre-anorexia stage and early stage of anorexia.
Results: The onset of anorexia was associated with a significant increase in the weight of tumor, spleen and liver. In the hypothalamus, a key site of food intake regulation, the mRNA expression level of IL-6, IL-1β and TNFα cytokines were not affected. The expression level of the orexigenic neuropeptide NPY was significantly increased. At the peripheral level, food intake was inversely correlated with plasma levels of IL-6 and GDF15 cytokines (R^2=0.82 and 0.70, respectively). Plasma GDF15 concentrations correlated with tumor mass (R^2=0.57), but the expression level of GDF15 mRNA did not change over time in the tumor, whereas it was increased in liver and intestine. Conversely, the expression level of IL-6 mRNA was high and increased over time within the tumor whereas it was not detectable in liver and intestine.
Conclusions: The magnitude of anorexia is correlated with circulating levels of IL-6 and GDF15, underlying the potential involvement of these cytokines. However, IL-6 and GDF15 expressions are regulated in different ways among the different tissues.

3-18

Reduced homeostatic and enhanced hedonic feeding behavior in mice with Pancreatic ductal adenocarcinoma (PDAC)

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Background: Anorexia, abnormal meal patterns and sensory alterations are prevalent symptoms contributing to reduced voluntary food intake. Hedonic feeding i.e. consuming highly palatable food when satiated, depends on a food's sensory attributes rather than energy balance state, and is mediated by mesolimbic reward circuitry, not homeostatic feeding circuitry. Hedonic feeding responses in cancer are uncharacterized.
Methods: 7-week-old C57BL6J mice (JAX; n=7) were acclimated and monitored in comprehensive lab animal monitoring system (Columbus Instruments); after baseline assessments, intraperitoneal PDAC injections were administered and mice monitored until baseline chow intake declined by 50% (predetermined endpoint). To assess hedonic feeding, mice (n=16) were habituated to consume a 200mg palatable treat, in the early part of the light cycle, and subsequent ingestive behaviour recorded.
Results: Baseline feeding behaviour and response to the treat was compared within PDAC animals to their endpoint(*Table*).

	Baseline	Endpoint	P, *Fishers exact, *ttest
Chow intake(kcal/d) PicoLab® 5L0D			
Total	11.1(0.8)	5.8(1.1)	
Light	3.4(.7)	1.9(0.5)	*<.001
Dark	7.5(0.9)	3.8(1.0)	
% of hourly feeding intervals			
No intake	4.5	13.8	
0.01-200 mg	31.8	31.7	*<0.007
>200 mg	13.6	5.0	
Hedonic treat intake, seconds(SD)			
BioServ Transgenic Dough Diet™	62.7(51.9)	20(15.4)	*<.001
Latency	194.8(134.4)	72(53)	
Total ingestion time			

Daily chow intake was reduced by 50% in PDAC-treated animals, both in light and dark. Hourly intervals containing zero food intake increased, and intervals with intake >0.2g were reduced. At baseline, chow feeding was prominent at the beginning of the dark cycle (lights-off cue); but this spike was attenuated in PDAC mice. By contrast, PDAC associated with sharply decreased latency to consume and time to ingest the palatable treat.
Conclusions: PDAC treatment suppressed food intake in mice, although they increasingly sought, seized and voraciously ingested a palatable treat. Despite the marked loss of appetite for chow in tumour-bearing animals, their drive to consume palatable food is paradoxically enhanced.

4-02

Medium-chain triglycerides as a nutritional supplementation against Cancer Cachexia

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Introduction: Cancer cachexia is characterized by a progressive and involuntary body weight loss and muscle wasting associated with anorexia and a general state of inflammation. One of the main features of cancer cachexia is a defective energy metabolism.
Ketosis is a metabolic state in which the body adapts to starvation burning fat rather than carbohydrates as primary fuel. Subsequently, an alternative energetic source known as ketone bodies, mainly β-hydroxybutyrate (β-HB), is produced. Medium chain triglycerides (MCT) are lipids with a high production rate of ketone bodies in the liver. The present study aimed to reprogram the energy metabolism from glycolytic to oxidative in the skeletal muscle of tumor-bearing mice through supplementation with MCT.
Methods: Tumor-bearing mice were inoculated with $5x10^5$ C26 cells into the intrascapular subcutis. Mice were randomly divided into four groups: Controls (n=6) and C26 tumor-bearing mice (n=10), untreated or treated with MCT. These latter received MCT daily by gavage (5g/kg body weight), for 17 consecutive days. Animal weight and food intake were recorded daily. Forelimb muscle strength was measured the day before C26 cell implantation and the day of sacrifice. Proteins involved in oxidative metabolism and autophagy were assessed by western blotting in the tibialis anterior muscle.
Results: Body and skeletal muscle weight were reduced in C26 tumor-bearing mice, irrespective of MCT administration. Loss of muscle strength in the C26 hosts was comparable in MCT treated and untreated mice. Moreover, markers of oxidative metabolism did not show a clear protective effect on skeletal muscle in treated mice. By contrast, p62, a protein accepted as marker of autophagy, was reduced in tumor-bearing mice receiving MCT.
Conclusions: The treatment with MCT does not rescue body weight loss and skeletal muscle wasting in cachectic mice. A new strategy of administration is needed to promote a long-term physiological state of ketosis.

4-03

The impact of cachexia on anorexia, dietary intakes, and quality of life in patients with advanced cancer

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Background: The relationships between cachexia stages and the FAACT ACS 12-item, 5-item anorexia symptoms, and 4-item anorexia concerns have not been investigated in Asian patients with cancer.
Methods: This is a multicenter questionnaire survey conducted in Japan. Consecutive patients with cancer referred to palliative care services were enrolled. Patient characteristics and anthropometric measurements were obtained. Patients evaluated their QOL using FAACT ACS. Subjects were divided into 2 groups, i.e., pre-cachexia (non-cachexia) and cachexia and refractory cachexia (cachexia), based on the international consensus. Comparisons were performed using the Mann-Whitney U test or chi-squared test. To evaluate the relationship between cachexia stages and FAACT ACS 12-item, 5-item anorexia symptoms, and 4-item anorexia concerns, adjusted ORs and 95% CIs were calculated in the logistic models.
Results: Among 495 patients, 378 (76.4%) responded. Due to missing data, 344 patients were classified into the non-cachexia group (n = 174) and cachexia group (n = 170), and 318 remained in the analysis of FAACT ACS. Advancing stages were associated with impaired performance status, a lower body mass index, lack of appetite, and reduced dietary intakes

(p = 0.021, <0.001, <0.001, and <0.001, respectively). QOL scores were significantly worse in the cachexia group in FAACT ACS 12-item, 5-item anorexia symptoms, and 4-item anorexia concerns (p <0.001, p = 0.001, and p <0.001, respectively). In the models of FAACT ACS 12-item, 5-item anorexia symptoms, and 4-item anorexia concerns, significantly higher adjusted ORs than in the non-cachexia group were observed in the cachexia group (2.24 [95% CI 1.34-3.77], p = 0.002; 1.77 [95% CI 1.08-2.92], p = 0.024; and 2.18 [95% CI 1.29-3.70], p = 0.004, respectively).
Conclusions: FAACT ACS 12-item, 5-item anorexia symptoms, and 4-item anorexia concerns are useful for identifying patients at risk of QOL in this population.
(291 words)

4-04

The relationship between cachexia and inflammatory biomarkers in patients with cancer; initial findings from the REVOLUTION cachexia characterisation study

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Introduction: The systemic inflammatory response has a role in the development of cancer cachexia; however, the role of inflammatory biomarkers and their relationship to the clinical phenotype of cachexia needs further elucidation. The REVOLUTION trial[1] is a prospective characterisation of cancer cachexia assessing clinical parameters, patient-reported outcomes, body composition and the biological components of cachexia. Herein we present initial findings relating inflammatory biomarkers to cancer cachexia parameters.
Methods: Using data from the REVOLUTION trial, we assessed C-reactive protein (CRP) in isolation and as part of the modified Glasgow Prognostic Score (mGPS), Body Mass Index (BMI), weight loss (>5% or >2% and BMI<20kg/m^2) and their relationships to specific inflammatory biomarkers[2,3]. We examined the following: IFNγ, IL-1α, IL-1β, IL-2, IL-4, IL-10, IL-12, MIP-1, MCP-1, visaftin, adiponectin, GDF-15, IL-1RA, IL-6, IL-8, intelectin-1 (ITLN1), leptin, resistin, TNF-α and VEGF. The relationship between these and cancer cachexia parameters was assessed using correlation coefficients and analysis of variance.
Results: Data were available for 38 patients. CRP was associated with IL-6 (r=0.44, p=0.02), VEGF (r=0.42, p=0.02), IL-8 (r=0.39, p<0.01), resistin (r=0.37, p=0.04) and ITLN1 (r=-0.34, p=0.04). In cachectic individuals, resistin (r=0.65, p<0.01), IL-1RA (r=0.45, p=0.05), VEGF (r=0.48, p=0.05) and IL-8 (r=0.45, p=0.05) were correlated with CRP. Decreasing BMI was associated with GDF-15 (r=0.51, p<0.01) and IL-1RA (r=0.49, p<0.01). Increasing inflammation (based on the mGPS) was associated with the ITLN1 (p=0.05). Moreover, the levels of ITLN1 were higher at baseline (p<0.01) compared to the 6-week follow-up measurement. Weight loss was not associated with any of the inflammatory biomarkers.
Conclusions: The findings provide further insight into the potential inflammatory drivers of cancer cachexia and how these relate to the clinical phenotype. It is of interest that weight loss, often regarded as a central tenet of cachexia, was not associated with any inflammatory biomarkers.

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4-07

The predictive role of sarcopenic obesity on the overall survival and its association with nutritional parameters in patients with renal cell carcinoma

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Introduction: Renal cell carcinoma (RCC) is a cancer for which the relationship between the skeletal muscle and visceral fat mass and the prognosis is still unclear. We therefore investigated the relationship between pre-operative sarcopenic obesity and the post-operative prognosis in RCC patients.
Methods: A retrospective observational study was conducted for 158 RCC patients who underwent open renal surgery between January 2008 and December 2020. We measured the total psoas muscle index (TPI; left and right psoas muscle area [cm^2]/height squared [m^2]) at the level of the third lumbar vertebra and the visceral fat area (VFA [cm^2]) at the level of the umbilicus using preoperative computed tomography (CT). Sarcopenia was defined by the previously reported TPI cut-off value for Asians, and a VFA ≥100 cm^2 was considered to indicate obesity. Patients were categorized as having non-sarcopenic non-obesity (NS-NO group, n=55), non-sarcopenic obesity (NS-O group, n=83), sarcopenic non-obesity (S-NO group, n=13), and sarcopenic obesity (S-O group, n=7).
Results: Of the 158 patients with RCC (median age 68), 103 (65.2%) were complicated with sarcopenia or obesity, of whom 7 (4.4%) had sarcopenic obesity. The CRP and mGPS tended to be higher in the S-O group than in the non-sarcopenia group (NS-NO and NS-O groups). The S-O and S-NO groups had a significantly shorter OS than the NS-NO and NS-O groups (log-rank, p<0.0001). According to a Cox proportional analysis, a higher mGPS was associated with a shorter OS (hazard ratio [HR]: 1.47, 95% confidence interval [CI]: 1.21-1.71, p<0.0001), and the S-O group was significantly associated with a shorter OS compared with the NS-NO group (HR: 11.24, 95% CI: 3.48–36.29, p<0.0001).
Conclusions: The preoperative combined presence of sarcopenia and obesity based on the skeletal muscle mass, visceral fat mass, and nutritional immune status may play a prognostic role in patients with RCC.

4-08

Identifying cancer patients with cachexia at scale by leveraging self-supervised natural language processing and predictive models on unstructured data in patients' electronic health records

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Introduction: International Classification of Diseases (ICD) codes often cannot accurately characterise patients with diseases like Cachexia accurately due to high probability of miscoding, while manual inspection of patient records is costly and slow. An AI driven workflow is presented which leverages structured, discrete values and unstructured textual data from Electronic Health Records, to automatically identify cancer patients who have Cachexia, especially those who might be miscoded or undiagnosed.
Methods: The proposed workflow is trained and tested on 29,637 and 29,339 discharge summaries respectively from the MIMIC-III dataset, consisting of unstructured data (care notes, discharge summaries, imaging reports) and structured data (vital signs, demographics, laboratory test results) of 46,520 ICU patients from the Beth Israel Deaconess Medical Centre (Boston, USA). First, the workflow builds patient profiles using state-of-the-art self-supervised Natural Language Processing to extract phenotypic features from discharge summaries. Second, the workflow classifies which cancer patients have Cachexia, based on their profiles using an Automated Machine Learning (AutoML) predictive model. The performance is evaluated on the test set, from which 100 discharge summaries are manually labelled by consensus between 3 clinicians based on the patients' phenotypic features, including cachectic/thin appearance, muscle wasting, weakness, loss of appetite, and evidence of malignancy.
Results: On the 100 clinician-labelled test set, the workflow achieves 0.878 AUCROC with precision 100% and sensitivity 75.7% whereas ICD codes have precision 78.0% and sensitivity 55.7%. On the entire test set with 29339 patients, the workflow identifies 316 Cancer patients with Cachexia while ICD codes find only 51, which lead to 520% more suitable patients identified.
Conclusions: This study demonstrates the AI driven workflow on textual clinical notes can help find more cachectic patients with high accuracy especially those who are miscoded and undiagnosed. This approach also finds new intelligence to characterise conditions such as Cachexia in Cancer and improve patient outcomes through screening and early diagnosis.

4-09

Examining the negative impact of weight loss and cachexia in Chimeric Antigen Receptor (CAR) T-cell therapy

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Introduction: CAR T-cell therapy is an immunotherapy that is revolutionising the treatment of haematological cancers. Whilst malnutrition and cachexia are associated with poorer outcomes in standard therapies (Arends,2017), the presence and impact of muscle wasting in CAR T-cell therapy is currently unknown (Cucchiaro,2021). The aim of this research was to identify the prevalence and impact of malnutrition and cachexia in CAR T-cell therapy.
Methods: Patients ≥18 years receiving CD-19 CAR T-cell therapy at University College London Hospital were evaluated (April 2019-September 2021) for body weight (BW), C-reactive protein (CRP), albumin, and patient outcomes (ICU admissions, length of hospital stay (LoS), 6-month survival).
Results: We reviewed 114 patients (55.6±15.1 years;49 females, 65 males). Average LoS for treatment was 35.7±13.8 days. Patients lost a significant amount of BW during their admissions (Z=-7.720, P<0.001), with 42.1% of patients losing 5-9.9% BW (n=48), and 18.4% losing ≥10% BW (n=21). ICU support was necessary in 22 patients (19.3%), with a significant relationship identified between weight loss 1-3 months prior to treatment and ICU admission (X^2=7.161,df=1, P 0.014). Using the modified Glasgow Prognostic Score (mGPS), 42 patients (41.6%) were identified with pre-cachexia and 2.0% (n=2) with refractory cachexia prior to admission. These patients with pre-cachexia or refractory cachexia prior to treatment had a significantly longer LoS (U=1558, P 0.037), lost more weight pre-admission (U=776.5,p=0.018) and had reduced survival at 6 months (X^2=3.716,df=1, P 0.049). We also found that 61.4% of patients (n=70) developed cachexia (Fearon,2011) during the 4–6-month treatment process.
Conclusions: Patients who received CAR T-cell therapy experienced significant weight loss, with preadmission weight loss and cachexia significantly impacting patient outcomes including ICU admission, LoS and 6-month survival. Interventions focusing on identifying at-risk patients and optimising nutritional status prior to treatment are essential, with the aim of maintaining functional muscle mass to improve patient outcomes.

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4-11

Evaluation of weight gain and overall survival of patients with advanced non-small-cell lung cancer (NSCLC) treated with first-line platinum-based chemotherapy

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Introduction: This post-hoc, pooled analysis examined the relationship between different weight gain categories and overall survival in patients with NSCLC treated with first-line platinum-based regimens.
Methods: Data were pooled from three phase 3 clinical trials (NCT00254891, NCT00254904, and NCT00596830), with maximum weight gain in the first 4.5 months since treatment initiation categorized as >0%, >2.5%, and >5%. Cox proportional hazards modeling of overall survival, including time to weight gain and time to confirmed objective response (RECIST v1.0) and baseline covariates, was used to estimate hazard ratios (HR) for each category.
Results: Of 1,030 patients with advanced NSCLC (stage IIIB 11.5% or stage IV 88.5%), 486 (47.2%), 299 (29.0%), and 164 (15.9%) experienced weight gain from baseline of >0%, >2.5%,

and >5%, respectively. The median time to weight gain was 24 (>0%), 43 (>2.5%), and 64 (>5.0%) days. After adjusting for time-dependent confirmed objective response, the risk of death was significantly reduced for patients with any weight gain: >0% vs. ≤0% (HR 0.70; 95% CI 0.61, 0.82), >2.5% vs. ≤2.5% (HR 0.70; 95% CI 0.59, 0.83), and >5% vs. ≤5% (HR 0.76; 95% CI 0.61, 0.94). The median overall survival was 13.6 vs. 8.3 months (weight gain >0% vs. ≤0%), 15.3 vs. 9.1 months (>2.5% vs. ≤2.5%), and 14.4 vs. 9.8 months (>5% vs. ≤5%).
Conclusions: In this pooled analysis, weight gain during treatment with first-line platinum-based chemotherapy was associated with a significantly reduced risk of death in patients with advanced NSCLC, independent of tumor response defined by RECIST criteria. The survival benefit was comparable for >2.5% vs. >5% weight gain. Weight gain of 2.5% occurred in 29% of patients and appears to be an early predictor of survival, with implications for cachexia treatment and the design of cancer cachexia trials.

4-12

A comparison of body composition changes between the FLOT and MAGIC regimes in patients with locally advanced oesophageal cancer

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Introduction: Recently, peri-operative FLOT (fluorouracil plus leucovorin, oxaliplatin, and docetaxel) chemotherapy has superseded the 'MAGIC' regimen (epirubicin, cisplatin plus fluorouracil or capecitabine) as standard of care for locally advanced oesophago-gastric adenocarcinoma. However, concerns have been raised regarding the toxicity profile of FLOT. This study aims to compare the changes in body composition between both regimens.
Methods: 115 patients treated with FLOT (n = 61) or MAGIC (n = 54) who underwent an oesophagectomy for oesophageal or gastro-oesophageal junction (GOJ) adenocarcinoma between 2014 and 2020 at Queen Elizabeth Hospital, Birmingham, UK were analysed. Changes in body composition between pre- and post-neo-adjuvant chemotherapy were determined by analysis of computed tomography imaging.
Results: In both regimes, a large proportion of patients were sarcopenic prior to starting chemotherapy (FLOT 44.2%, MAGIC 44.4%; p=0.984). The percentage of patients who were sarcopenic increased post chemotherapy (FLOT 63.9%, MAGIC 57.4%; p=0.474). There was no significant pre vs post chemotherapy change in L3 skeletal muscle index in both regimes (FLOT 2.96 ± 4.03 vs MAGIC 2.76 ± 4.21; p=0.792). There was also no significant pre vs post chemotherapy change in L3 fat index in both regimes (FLOT 2.49 ± 22.6 vs MAGIC 5.78 ± 24.2; p = 0.453). Myosteatosis was observed in 44.3% of patients pre-FLOT and 42.6% of patients pre-MAGIC (p=0.857). This increased to 62.2% post-FLOT and 46.3% post-MAGIC (p=0.085). FLOT chemotherapy was associated with better tumour regression grade compared to MAGIC (p<0.001).
Conclusions: A large proportion of patients with locally advanced oesophageal/GOJ adenocarcinoma were sarcopenic and had myosteatosis prior to starting chemotherapy. A further loss of muscle and fat occurs during chemotherapy but there was no significant difference in loss of fat or muscle across both FLOT and MAGIC regimes. However, patients treated with the FLOT regime had better pathological response as compared with MAGIC.

4-14

Presence of Sarcopenia, Cachexia or Low Muscle Attenuation is Associated with Poor Survival in Ambulatory Cancer Patients Receiving Systemic Therapy in Ireland (SARCONC Study)

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Introduction: International studies have shown a high prevalence of malnutrition & muscle wasting in oncology patients, which increase risk of poor tolerance to chemotherapy, decreased quality of life & poorer survival. Currently their prevalence and impact in Irish patients has not been described.
Methods: A study of adult cancer patients was conducted over 5 years in 2 chemotherapy daywards in Cork, Ireland. Baseline anthropometry & body composition (BC) using computed tomography (CT) were recorded. Sarcopenia & low muscle attenuation (MA) were defined using published cut-offs. Overall survival (OS) was evaluated using Kaplan-Meier Curves & Cox Proportional Hazards Models, adjusting for known prognostic variables.
Results: Overall, 940 patients had evaluable CT scans (56% male, mean age 62 years) and 58% had stage IV disease. At baseline, 9% had BMI <20 kg/m2 & 56% had BMI ≥25 kg/m2. However, 73% had at least one CT-evaluable abnormal BC phenotype. Specifically, 42%, 39% and 45% had cachexia, sarcopenia and low muscle attenuation, respectively. OS was poorer in those with abnormal BC phenotypes, (mean OS in non-metastatic 70.1 vs. 55.8 months (median not reached), Log rank p<0.001 and median OS in metastatic 25.6 months (95% CI: 20.2 – 30.9) vs. 14.2 months (95% CI: 12.3 – 16.1), Log rank p<0.001). This remained significant after adjustment for site, stage, age, sex, performance status and inflammatory status (HR: 1.416 95% CI: 1.069 - 1.875, p=0.015).
Conclusions: Patients across all cancer groups experience significant losses in weight and muscle mass both before and during chemotherapy. As these conditions are associated with poor clinical outcomes, more research is urgently needed to identify an acceptable screening tool which can be widely used to identify those cancer patients with the greatest needs for nutrition support. Furthermore, effective strategies to manage and treat cancer associated wasting are required.

4-15

Tumor metabolic activity is associated with myosteatosis and reduced survival in patients with non-small cell lung cancer

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Introduction: Cancer cachexia and tumor metabolic activity are both associated with poor survival, but it is unclear how tumors promote development of cachexia. We hypothesized that tumors with higher metabolic activity instigate peripheral metabolic alterations that lead to cachexia, and investigated whether tumor metabolic activity is associated with cachexia-

related body composition changes and survival in non-small cell lung cancer (NSCLC).
Methods: A retrospective analysis was performed on a cohort of 121 patients with NSCLC. 18F-fluorodeoxyglucose PET/CT-scans obtained before treatment were used to analyze tumor metabolic activity (standardized uptake value (SUV) and SUV normalized by lean body mass (SUL)) and body composition (skeletal muscle index (SMI), visceral/subcutaneous adipose tissue index (VATI/SATI), myosteatosis) at the L3 level. Subjects were divided into groups with or without myosteatosis based on age- and sex-specific thresholds of the mean Hounsfield units (HU) of muscle area. Mann-Whitney tests, Kaplan-Meier, Cox-regression, and Receiver Operator Characteristics (ROC) curves were used to analyze associations between tumor metabolic activity, myosteatosis, and survival.
Results: The overall prevalence of myosteatosis was 43.0% (52/121). Patients with myosteatosis had shorter survival compared with patients without myosteatosis (median: 25.8 vs. 42.7 months, p=0.03). Myosteatosis was independently associated with shorter overall survival (univariate Cox regression HR=0.482, 95% CI: 0.249-0.933, p=0.03). Muscle radiation attenuation correlated with tumor metabolic activity (SULpeak r_s=0.444, p=0.02; SUVpeak r_s=0.362, p=0.05), and patients in the myosteatosis group had higher tumor metabolic activity (SULpeak median 8.0, IQR 4.5-12.9, SUVpeak 11.4, 5.0-16.8) than those in the non-myosteatosis group (SULpeak 5.0, 2.0-7.6, p=0.03, SUVpeak 5.8 2.7-9.1, p=0.03, respectively). Tumor metabolic activity parameters predicted the occurrence of myosteatosis in ROC analysis (SULpeak: AUC=0.763, p=0.034, sensitivity/specificity:80%/75%; SUVpeak: AUC=0.744, p=0.038, sensitivity/specificity:85%67%). SMI and VATI were not associated with tumor metabolic activity or survival.
Conclusions: Higher tumor metabolic activity is associated with myosteatosis and shorter survival in NSCLC.

4-16

Assessment of muscle and lean mass in colon cancer patients on chemotherapy: correlations of d3-creatine, dual energy x-ray absorptiometry and computed tomography

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Introduction: Low skeletal muscle mass increases morbidity and mortality in cancer patients. D3-creatine (D3Cr) dilution to measure total body muscle mass has not been used in cancer patients on chemotherapy. We compared three methods to approximate muscle mass: D3Cr muscle mass; cross-sectional muscle area at the third lumbar vertebra on computed tomography (CT-CSA); and appendicular lean mass from dual energy x-ray absorptiometry (DXA-ALM); and examined associations with physical function.
Methods: At the start of adjuvant chemotherapy, colon cancer patients who completed curative-intent surgery (N=50 men, N=50 women) underwent measurements of total body muscle mass (D3Cr); L3 muscle area (CT-CSA); lean mass (DXA); and physical function (grip strength and 4-meter gait speed). We calculated Pearson correlations (R) for each measure.
Results: Mean (SD) age was 57 (14) years; BMI was 27 (5) kg/m^2. Men had higher mean (SD) D3Cr muscle mass (31 [6] vs. 21 [4] kg), CT-CSA (172 [32] vs. 116 [19] cm^2) and DXA-ALM (25 [4] vs. 16 [3] kg) than women. Correlations of D3Cr muscle mass with CT-CSA and DXA-ALM were high in men (R=0.73 and 0.75) and moderate in women (0.55 and 0.47, p<.001 for all). D3Cr/body weight was correlated with grip strength and gait speed (R=0.35 and 0.28, P<0.05), which were similar in strength to CT and DXA (R=0.35 and 0.22 and R=0.41 and 0.26, respectively, all P<0.05 except for DXA-ALM and gait speed p=0.06) in men, but no significant associations with any approximation of muscle mass and function in women.
Conclusions: D3Cr is correlated with CT and DXA in colon cancer patients on active chemotherapy, but these mass measures were correlated with grip strength and gait speed only in men. Next steps include examining whether changes in muscle and/or lean mass are associated with functional decline or clinical outcomes such as toxicity.

4-17

Making cachexia reversible: What is the priority strategy for aggressive intervention? A systematic review

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Introduction: The aim of this systematic review is to clarify which nutritional intervention is effective in ameliorating or reversing cancer cachexia.
Methods: PubMed, CINAHL and Scopus were searched from 2001 to 2020 for controlled trials that included nutritional intervention vs. placebo/conventional care in cancer patients with malnutrition/sarcopenia/cachexia. Weight, BMI, fat mass, lean body mass were the sought outcomes. Pediatric and terminal-phase patients were excluded.
Results: Preliminary results using PubMed yielded 213 hits. Twenty-four studies with patients with high risk of malnutrition or cachexia were included. A second group with fourteen studies was included with a variable proportion of patients at medium risk of malnutrition or cachexia. Finally, seven studies were included with the majority of patients being at low risk of malnutrition or having pre-cachexia.
Conclusion: The evidence from dietary counseling/nutritional therapy alone is inconsistent for the first (n=2) and second (n=6) groups. In the third group (n=2), results show improvements in the intervention group. Oral nutritional supplements (ONS) with dietary advice seem to show better results mitigating or ameliorating weight loss and sarcopenia in the first 2 groups (n=3). Supplementation with whey-protein-isolate, soy-whey-blended-protein, L-carnitine and ONS rich in leucine/isoleucine effectively improve body composition (n=5). Evidence from methylbutyrate/arginine/glutamine is also inconsistent (n=2). The effect of ONS enriched with n-3 fatty acids seems to be dose-dependent in all groups (n=8) and an amount of less than 2g doesn't produce any variation in weight, BMI or lean body mass (LBM) (n=7). Enteral nutrition seems to assist in weight maintenance for malnourished patients (n=1) or to increase weight, BMI and LBM with immunonutrients (n=1) but prophylactic supplementary tube feeding (n=1) or arginine supplemented pre/postoperative (n=1) didn't improve nutritional status or weight loss. Parenteral nutrition may have

a positive benefit in stabilizing body-composition and even in the increase of FFM in advanced/palliative cancer (n=2).

Disclosure of Interest: None Declared

4-18

Genetic susceptibility to cancer cachexia – A literature review

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Introduction: Cachexia leads to a major reduction in life quality of cancer patients, causing severe fatigue and reducing the response to anticancer therapy, consequently increasing morbidity and mortality. Although it is clear that some malignancies are more associated with cachexia than others, predicting which patients will develop this condition is still challenging. Besides, cachexia degree can vary within the same type of cancer. Conversely, single nucleotide polymorphisms (SNPs) seem to explain the interindividual variation in cachexia susceptibility. Thus, we summarized the current knowledge on the role of SNPs in cancer cachexia to clarify a possible underlying genetic predisposition.
Methods: The research was performed using the PubMed/Medline database, using the keywords "SNP", "polymorphism", "cancer" and "cachexia" and the Boolean operator "AND". Inclusion criteria included studies with human samples, published in the last 10 years (2012-2022). The exclusion criteria consisted of studies using only cell lines/other animals, in another language besides English or not reporting results related to nutritional status or cachectic status. Seven studies were selected.

Results: The results are summarized in the following table:

Reference	Gene	Polymorphism	Population characteristics	Type of cancer	Participants		Main results
Yehia *et al.*, 2021	*TNF*	308 G/A (rs1800629) and -1031T/C (rs1799964)	Egyptian	Non-Small Cell Lung Cancer	Cachectic (n = 69) and non-cachectic (n = 76)		The A allele of rs1800629 increases the risk of cachexia in both cancers; The rs1799964 C allele is protective for cachexia in non-small cell lung cancer patients
				Pancreatic cancer	Cachectic (n = 40) and non-cachectic (n = 18)		
Mazurek *et al.*, 2020	*ITGAM*	-323G>A (rs7193943)	Not specified	Head and neck cancer	Good nutritional status SGA-A (n = 15); moderate SGA-B (n = 32); malnutrition SGA-C (n = 22)		G allele is associated with higher risk of severe malnutrition; The A allele reduces the risk of severe disturbances in nutritional status
Powróze *et al.*, 2019	*SELP*	-2028 C/T (rs3753306)	Not specified	Head and neck cancer	Well-nourished SGA-A (n = 10); moderately malnourished SGA-B (n = 30); severely malnourished SGA-C (n = 26)		CC genotype is linked to a higher risk of severely malnourishment; TT genotype is associated with a decreased risk of severe weight loss >10%
Powróze *et al.*, 2018	*TNF*	−1031T/C (rs1799964)	Not specified	Head and neck cancer	Well-nourished SGA-A or non-cachectic (n = 9); moderately malnourished SGA-B or pre-cachectic (n = 29); severely malnourished SGA-C or cachectic (n = 24)		CC genotype is associated with a higher risk of being classified as cachectic , had significantly lower body mass and highest TNF-α plasma level
Johns *et al.*, 2017	*TNF* and *ACE*	−1031T/C (rs1799964) and A240T (rs4291) respectively	European descendent	Oesophageal Cancer	n=405		The rs1799964 C allele or rs4291 T allele are associated with a combination of weight loss and low skeletal muscle index
				Pancreatic Cancer	n=158		
				Non-Small Cell Lung Cancer	n=550		
				Other	n=163		
Ruzzo *et al.*, 2014	*IL6* and *IL6R*	-174G/C (rs1800795) and 48892 A/C (rs8192284)	Not specified	Advanced Gastric Cancer	n=161		The rs1800795 G allele and rs8192284 C allele are associated with poor survival
Tan *et al.*, 2012	*SELP*	T715P (rs6136)	European descendent	Oesophageal or gastric Cancer	n=389 (discovery study)	n=18 (validation study)	The C allele is associated with a reduced risk of developing cachexia (weight loss >10%)
				Pancreatic Cancer	n=114 (discovery study)	n=6 (validation study)	
				Non-Small Cell Lung Cancer	n=232 (discovery study)	n=19 (validation study)	
				Other	n=40 (discovery study)	n=58 (validation study)	

Conclusions: Overall, the studies indicate that SNPs may confer susceptibility to the development of cachexia and malnutrition in cancer patients. Genes involved in inflammatory pathways were most frequently studied. Among the eight SNPs reported, the TNF-α rs1799964 polymorphism is the one with more evidence. However, the results were controversial since one study states that C allele has a protective effect, while others demonstrate that the same allele is associated with weight loss, low skeletal muscle, with CC genotype increasing the risk of a patient being classified as cachectic. These inconsistent findings can be explained by differences in the study population in terms of ancestry, type of cancer and/or evaluated parameters. Additional studies are therefore warranted, especially on genes involved in pathways known to promote cancer cachexia.

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4-19

NAD+ repletion with niacin counteracts cancer cachexia

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Introduction: cancer cachexia and anti-cancer treatments have a devastating impact on skeletal muscle metabolism. Previously we demonstrated that NAD+ levels are depleted in the muscle of C26-bearing mice, in parallel to a strong downregulation of the muscle-specific *Nrk2* gene. In this work, we tested if the supplementation with niacin (NA), an NAD+ precursor that bypasses NRK2, prevented muscle NAD+ depletion in cancer cachexia.
Methods: NA was orally administered to C26-bearing mice undergoing FOLFOX chemotherapy (C26-F) and to one-year-old Villin-Cre/Msh2$^{loxP/loxP}$ (VCM) mice, the latter resembling the spontaneous progression of human gastrointestinal cancer. Quantification of NAD metabolites was performed using a validated colorimetric assay and mitochondrial respiration was assessed with the O2k-FluoRespirometer (Oroboros). Metabolomic profiling of muscle and serum samples was conducted at the Metabolomics Expertise Center (KU Leuven).
Results: consistent downregulation of *Nrk2/NRK2* was observed in the skeletal muscle of C26-F mice, VCM mice, KPC-bearing mice, and colorectal or pancreatic cancer patients. Although *Nrk2* repression was not always correlated to NAD depletion, "low *NRK2*" cancer patients displayed a distinctive metabolome profile compared to "high *NRK2*" and healthy subjects independently from cachexia classification. In animals, NA treatment mitigated muscle wasting in C26-F and VCM mice. In particular, NA prevented NAD+ depletion and improved protein synthesis in C26-F animals. Additionally, NA preserved mtDNA and OXPHOS protein content in C26-F and VCM mice, although not rescuing mitochondrial respiration in the C26-F group. Notably, both C26-F and VCM mice presented with a pronounced depletion of hepatic NAD metabolites that was completely reverted by NA. Moreover, NA-treated animals showed improved markers of mitochondrial mass and partial rescue of the respiratory capacity in the liver compared to untreated tumor-bearing ones.
Conclusions: the present study unveils a potential therapeutic use of NA as an anti-cachexia drug to support whole-body energy metabolism, foreseeing its prospective use in cachectic patients.

4-20

The p97-Nploc4 ATPase complex plays a role in muscle atrophy during cancer and amyotrophic lateral sclerosis

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The p97 complex participates in the degradation of muscle proteins during atrophy upon fasting or denervation interacting with different protein adaptors. We investigated whether and how it might also be involved in muscle wasting in cancer or amyotrophic lateral sclerosis (ALS).
As cancer cachexia models we used mice bearing colon adenocarcinoma C26, human renal carcinoma RXF393 or Lewis Lung Carcinoma (LLC), with breast cancer 4T1-injected mice as controls. As ALS models we employed mice carrying the mutation G93A in human SOD1. We electroporated plasmids into muscles or treated mice with disulfiram (DSF) to test the effects of inhibiting p97 and nuclear protein localization protein 4 (Nploc4), one of its adaptors, on atrophy.
The mRNA levels of p97 were induced by 1.5 to 2-fold in tibialis anterior (TA) of all the cachectic models but not in the non-cachectic 4T1. Similarly, p97 was high both in mRNA and protein in muscles from SOD1G93A mice. Electroporation of a shRNA for murine p97 into mouse muscle reduced the fiber atrophy caused by C26 or ALS. By qPCR, we found Nploc4 inductions in TA of cachectic and ALS models and also induced protein content by 1.5-fold. Electroporation of a CRISPR/Cas9 vector against Nploc4 into muscle reduced the fiber atrophy caused by C26 or ALS. Since DSF uncouples p97 from Nploc4, we treated myotubes with DSF, and found accumulated mono and polyubiquitinated proteins and reduced degradation of long-lived proteins, including actin. DSF halves Nploc4 in the soluble muscle fraction and given to C26-carriers limited the body and muscle weight loss, unchanging tumor growth.
Cancer cachexia and ALS seem to display similar mechanisms of muscle wasting at least at the catabolic level. The p97-Nploc4 complex appears to have a crucial role in muscle atrophy during these disorders and disrupting this complex might serve as a novel drug strategy.

4-21

Colorectal Cancer-induced Cachexia Reduces *DNMT3a* and Differentially Alters the Skeletal Muscle Transcriptome by Biological Sex

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Introduction: Cancer-cachexia (CC) is clinically defined by involuntary weight loss of >5% in less than six months without effective therapies to prevent or treat it. CC largely affects skeletal muscle, reducing cancer patients' quality of life and survival rates. Moreover, evidence suggests biological sex differences in CC. DNA methylation is important to regulate energy homeostasis and respond to environmental cues. Here, we investigated CC transcriptomics with specific consideration on DNA-methyltransferases (DNMT).
Methods: Eight-week-old BALB/c mice received C26 colorectal cancer cell injections. Tibialis Anterior was collected at 10-, 20-

, and 25-day following injection, using PBS administration as a control. Global gene expression analysis and differently expressed (DE) genes were determined in a subset of samples (31 males, 29 females; n=6-8/group) of control and tumor-bearing groups (TBG). mRNA content of *DNMT3a* was measured at each timepoint by RT-PCR, and one way-ANOVA across timepoints within each sex was performed (α=0.05).
Results: DE genes after 20 days of tumor implantation were 385 in females and 215 in males. Subsequently, after 25 days, they increased to 925 and 4,323 genes, with 618 and 2,214 upregulated genes and 307 and 2,109 downregulated genes within each sex, respectively (FDR<0.05). In 25-day TBG-males, *DNMT1* expression was 1.30-fold, and *DNMT3a* was 2.27-fold downregulated (FDR<0.05). In 25-day TBG-females *DNMT3a* was 1.55-fold (FDR=0.07) downregulated compared to control. RT-PCR confirmation of *DNMT3a* mRNA content was similarly 34% and 39% (p<0.05) lower in 20- and 25-day TBG-males, respectively, and 36% lower (p<0.05) in 25-day TBG-females when compared against control.
Conclusions: The global gene expression analysis shows TBG-females present fewer DE alterations than TBG-males, making evident biological sex differences in the transcriptomics of CC. Downregulation of *DNMT*s might be associated with hypomethylation of the genome, increasing the number of upregulated genes. However, further studies investigating other alterations on CC-methylomics are required.

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4-22

OPA1 overexpression may protect against cancer-induced muscle wasting

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Introduction: Cancer cachexia (CC) is a multifactorial syndrome characterised by unintentional loss of body weight and muscle mass in patients with cancer. Cachexia affects up to 80% of all cancer patients and is responsible for as much as 40% of cancer-related deaths. So far there is no cure or effective treatment for CC. One of the major hallmarks associated with CC development is mitochondrial dysfunction, including increased mitochondrial fission and decreased fusion. The protein content of Optic atrophy 1 (OPA1), a mitochondrial fusion marker, is ~50% lower during the early development of CC and this suppression is maintained throughout development of marked atrophy. The aim of this study was to determine if overexpression of OPA1 can attenuate cancer-induced skeletal muscle atrophy through regulating mitochondrial function.
Methods: To test the function of OPA1 in CC we utilised OPA1 transgenic mice. Transgenic male mice (C57BL/6J) overexpressing OPA1 and wild type (WT) littermates were injected with $1x10^6$ Lewis lung carcinoma (LLC) cells bilaterally to the hind flanks, while equal volume of PBS was injected in PBS controls. Grip strength test was performed weekly. At the end-point (~4 weeks after LLC/PBS injections) body weight and tissue wet weights (hind limb muscles/heart/liver/spleen) were measured. Also, mitochondrial respiratory function via respiratory control ratio and mitochondrial degeneration via MitoTimer fluorescent reporter were assessed at end-point.
Results: Mice overexpressing OPA1 present higher muscle mass of EDL (26.9%; p=0.010), gastrocnemius (10.5%; p=0.008) and soleus (14%, p=0.015) compared to WT regardless of the tumour-bearing state (PBS/LLC). Body weight, grip strength, mitochondrial respiratory function and mitochondrial degeneration were not affected by OPA1 overexpression.
Conclusions: Overexpressing OPA1 protects cancer-induced muscle wasting without necessarily alleviating mitochondrial dysfunction suggesting OPA1 may be an effective therapeutic target in CC. Data analysis is ongoing to clarify the effects of OPA1 overexpression on the cachectic phenotype.

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Activation of Akt-mTORC1 signaling reverts cancer-dependent muscle wasting

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Background: Cancer-related muscle wasting occurs in most cancer patients. An important regulator of adult muscle mass and function is the Akt-mTORC1 pathway. While Akt-mTORC1 signaling is important for adult muscle homeostasis, it is also a major target of numerous cancer treatments. Which role Akt-mTORC1 signaling plays during cancer cachexia in muscle is currently not known. Here we aimed to determine how activation or inactivation of the pathway affects skeletal muscle during cancer cachexia.
Methods: We used inducible, muscle-specific Raptor ko (mTORC1) mice to determine the effect of reduced mTOR signaling during cancer cachexia. On the contrary, in order to understand if skeletal muscles maintain their anabolic capacity and if activation of Akt-mTORC1 signaling can reverse cancer cachexia, we generated mice in which we can inducibly activate Akt specifically in skeletal muscles.
Results: We found that mTORC1 signaling is impaired during cancer cachexia, using the Lewis-Lung Carcinoma (LLC) and C26 colon cancer model, and is accompanied by a reduction in protein synthesis rates of 57% (P<0.01). Further reduction of mTOR signaling, as seen in Raptor ko animals, leads to a 1.5-fold increase in autophagic flux (P>0.001), but does not further increase muscle wasting. On the other hand, activation of Akt-mTORC1 signaling in already cachectic animals completely reverses the 15-20% loss in muscle mass and force (P<0.001). Interestingly, Akt activation only in skeletal muscle completely normalizes the transcriptional deregulation observed in cachectic muscle, despite having no effect on tumor size or spleen mass. In addition to stimulating muscle growth, it is also sufficient to prevent the increase in protein degradation normally observed in muscles from tumor-bearing animals.
Conclusions: Here we show that activation of Akt-mTORC1 signaling is sufficient to completely revert cancer-dependent muscle wasting. Intriguingly, these results show that skeletal muscle maintains its anabolic capacities also during cancer cachexia, possibly giving a rationale behind some of the beneficial effects observed in exercise in cancer patients.

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Low HMG-CoA Reductase Gene Expression in the Liver of Patients with Cancer Cachexia

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Disruption of circulating lipid content is correlated with weight loss, cachexia (CC), and increased mortality in cancer patients. We observed in a cohort of cancer patients a decrease in cholesterol levels in the patients with CC, as compared with weight stable cancer (WSC) patients and hypothesized that liver cholesterol synthesis and/or cholesterol secretion could be impaired in cachexia. Objective: to evaluate hepatic gene expression of proteins related to cholesterol synthesis, uptake, and secretion in patients with CC. Methods: Patients with cancer (cachectic and weight stable) selected for tumor resection surgery as initial treatment and subjects undergoing cholecystectomy or herniorrhaphy were recruited after the signature of the informed consent form. Blood was collected before the surgery, during which liver biopsies were obtained. Volunteers were separated into three groups: Control (subjects without cancer, n=63-68 for serum lipoproteins and n=4-5 for gene expression), WSC (subjects with cancer but not cachexia, n=66-68 for serum lipoproteins and n=4-5 for gene expression) and patients with CC (n=112-115 for serum lipoproteins and n=7/8 for gene expression). Liver gene expression was performed using specific primers for peroxisome proliferator-activated receptor-gamma, sterol regulatory element-binding protein 2, HMG-CoA reductase, cytochrome P450 family 7 subfamily A member 1, LDL receptor, scavenger receptor class B member 1 and 18S (housekeeping gene). Results: CC showed lower serum total cholesterol content as compared to Control group (p=0.0155) and lower LDL cholesterol, when compared with WSC (p=0.0373). Regarding gene expression, CC presented lower HMG-CoA reductase expression, as compared with WSC (p=0.0363) and a tendency (p=0.065) for lower expression, compared with the Control group. Conclusions: Diminished liver cholesterol synthesis in patients with CC is potentially associated with decreased levels of total circulating cholesterol in cachexia. Previous animal model results of our group suggest that these changes may be a consequence of local and systemic inflammatory input.

4-25

Muscle Wasting in Early-stage Cancer is Associated with Disorganized Extracellular Matrix Distinct from Fibrosis

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Introduction: In addition to catabolic mechanisms in skeletal muscle that characterize cachexia, a growing literature supports that muscle wasting in cancer also derives from impaired muscle regeneration. Muscle progenitor cells (MPCs) are activated in response to myofiber damage. However, these MPCs are unable to fuse and repair damaged muscle fibers, leading to muscle atrophy. This impaired muscle regeneration appears to be caused by cell-extrinsic factors, as MPCs can differentiate when removed from a cachectic environment. Therefore, we hypothesized that an altered microenvironment surrounding MPCs contributes to their inability to differentiate and counter muscle catabolism.
Methods: Electron microcopy and super resolution images of muscles from mouse models of cancer cachexia and resected cachectic patients with pancreatic ductal adenocarcinoma (PDAC) were observed for collagen structure. Muscle sections from mouse models and PDAC patients were immunostained for collagen I as a marker of the extracellular matrix (ECM). Additional sections were stained with picrosirius red to assess total ECM, and collagen gene abundance was measured by RT-PCR.
Results: Microscopy images from both mice and patients indicated that collagen structure in cachectic muscle is altered and abnormally occupies a greater area of the interstitium. However, collagen 1 staining did not appear to indicate a significant expansion of the ECM in cachectic muscle, although an increase in staining intensity was apparent. This suggests that muscle wasting in cancer, unlike muscle wasting in muscular dystrophy, is not associated with fibrosis. Consistent with this notion, picrosirius red staining was comparable between cachectic and control muscles and Col1a1 and Col1a2 gene expression was reduced, not increased, in muscles from cachectic mice and PDAC patients.
Conclusions: We propose that during early tumor-induced cachexia, the ECM within skeletal muscle becomes disorganized, and this disorganization creates an environment that is unsuitable for MPCs to properly differentiate, leading to a cachectic state.

4-26

Elevated systemic lipocalin 2 levels in cachectic patients are associated with neutrophil activation

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Background: Cancer cachexia is a multifactorial syndrome characterized by body weight loss and systemic inflammation, resulting in reduced quality of life and poor survival. Lipocalin 2 has recently been implicated in the development of appetite suppression in pancreatic cancer cachexia. However, the source of the elevated lipocalin 2 levels in cachectic patients is unknown. We hypothesized that elevated lipocalin 2 in cancer cachexia is associated with neutrophil activation, and investigated a set of neutrophil activation markers in pancreatic cancer patients with or without cachexia.
Methods: Plasma samples from non-cachectic pancreatic ductal adenocarcinoma (PDAC) patients (n=14) were compared with samples from cachectic PDAC patients with high (≥26.85 ng/mL, n=33) versus low (<26.85 ng/mL, n=34) circulating lipocalin 2 levels. Neutrophil activation markers calprotectin, myeloperoxidase, and elastase were analyzed using ELISA and related to the severity of cachexia.
Results: Cachectic patients with high systemic lipocalin 2 levels had higher concentrations of calprotectin, myeloperoxidase, and elastase than non-cachectic patients or cachectic patients with low lipocalin 2 levels (calprotectin: 529.3 ng/mL (IQR 361.3-722.1) vs. 471.5 ng/mL (244.9-623.8), p=0.8003 vs. 366.4 ng/mL (294.8-470.7), p=0.0129;

myeloperoxidase: 30.0 ng/mL (23.0-36.0) vs. 18.0 ng/mL (12.6-29.7), p=0.0822 vs. 20.2 ng/mL (15.9-28.7), p=0.0175; elastase: 132.5 ng/mL (90.9-227.2) vs. 100.3 ng/mL (67.2-218.2) p=0.8619 vs. 94.9 ng/mL (73.1-109.6), p=0.0097; respectively). Similarly, CRP/albumin ratio (inflammation marker) was higher in cachectic patients with high lipocalin 2 levels (3.2,1.4-6.7) as compared to non-cachectic patients (1.2, 0.6-1.7) or cachectic patients with low lipocalin 2 levels (2.3, 0.7-6.9). Although markers of neutrophil activation did not correlate with severity of cachexia, strong positive correlations between lipocalin 2 and calprotectin (r_s=0.36, p=0.0009), myeloperoxidase (r_s=0.48, p<0.0001), and elastase (r_s=0.50, p<0.0001) were observed.
Conclusions: These data suggest that elevated lipocalin 2 levels in pancreatic cancer cachexia are caused by neutrophil activation, and warrant investigations into the role of neutrophils in cachexia development.

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Masseter thickness index as an anthropometric prognostic biomarker in head & neck cancer cachexia: A retrospective pilot study

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Introduction: Cancer cachexia (CA-CX) is characterized by progressive loss of skeletal muscle, with or without loss of fat, that cannot be reversed by nutritional support. Criteria for CA-CX include either one or a combination of: weight loss >5% (last six months; no starvation), Body Mass Index (BMI) <20 + weight loss >2% and Appendicular Skeletal Muscle index (ASMI) indicating sarcopenia + weight loss >2%. ASMI is generally obtained from computerized tomography (CT). Unfortunately, full body CT is rarely available in head & neck cancer (HNC) patients. Here we analyze the masseter muscle thickness as an alternative method to discriminate between patients with HNC-cachexia and non-cachexia (NCX).
Methods: HNC CT datasets (DICOM) from sex-, race-, height- and age-matched white males were retrospectively analyzed. For three-group comparison, patients fulfilling all three criteria for CA-CX (CA-CX; n=6) and patients with cancer but no CX (CA-NCX; n=5) were analyzed relative to no cancer, non-cachectic, healthy control patients (CTRL; n=5). For two-group comparison we included: CA-CX and NCX (CA-NCX + CTRL) groups. Left masseter muscle was segmented with a 3D-imaging software. 3D distribution of masseter thickness, body weight, BMI, and MTI (average masseter thickness/height2) were retrieved. Area Under the Curve (AUC) of the Receiver Operating Characteristics (ROC) analysis was calculated. All statistical analyses were blinded.
Results: CA-CX subjects exhibited reduced body weight and BMI in both comparisons. CA-CX MTI was significantly reduced (CI95%: 2.33-3.38) relative to both CTRL (CI95%: 3.19-4.42) and NCX (CI95%: 3.33-4.06). When CA-CX relative to NCX, AUC-ROC (0.875; CI95%: 0.70-1.0) was significant (p<0.05) with sensitivity (66.7%; CI95%: 30.0-94.1), specificity (90.0%; CI95%: 59.6-99.5) and likelihood ratio (6.67), at an MTI cut-off<3.05.
Conclusions: MTI represents a promising tool to discriminate between CA-CX and NCX in HNC patients that will need validation in larger cohort studies including other ethnicities, both sexes and different age groups.

4-29

Cardiomyoblasts mitochondrial activity is altered in an *in vitro* model of cardiac cachexia induced by Walker-256 tumour

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Introduction: Cancer cachexia is a multifactorial syndrome affecting many tissues and organs, including the heart, with an unfavourable diagnosis. The mechanism of these cardiac alterations is not yet fully known, and thus experimental assays are essential for a better understanding of these mechanisms. Since studies have shown mitochondrial activities altered in many diseases, being one important target to find new therapies strategies, in this study, we used an *in vitro* cardiac cachexia model induced by Walker-256 tumour to evaluate mitochondrial activity.
Methods: H9c2 cells were exposed to 5% ascitic fluid (A) or thermally inactivated (IA), obtained from cachectic Walker-256 tumour-bearing rats. Cell viability was analysed by the MTT assay, cellular respiration by the oxygen consumption rate (OCR), and reactive oxygen species (ROS) detection by the DHE assay.
Results: Ascitic fluid decreased cell viability (Fig 1A) and showed a trend decrease in all cellular respiration parameters compared to the control group (Fig 1B). However, inactivated ascitic fluid partially restored cell viability (Fig 1A) and recovered cellular respiration at basal and maximal levels (Fig 1 B), also improving reserve capacity and mitochondrial ATP production in relation to ascitic fluid (A). Ascitic fluid with and without inactivation did not alter ROS production (Fig 1C).

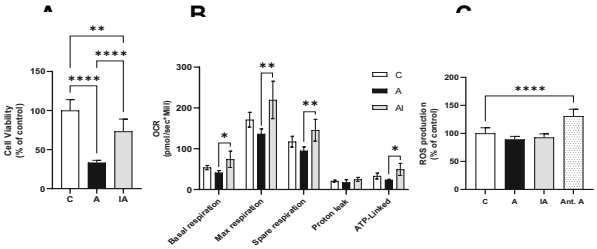

Figure1. H9c2 cell viability assay (A), oxygen consumption rate (OCR) (B), and ROS production (C). Data are mean ± SEM. *P < 0.05, **P < 0.01, ****P < 0.0001.

Conclusions: Ascitic fluid, simulating cardiac cachexia due to deleterious factors content, altered mitochondrial metabolism of cardiomyoblasts, but when the ascitic fluid was inactivated, there was a partial restoration to the normal pattern of myocardial cell activity in these cells. These changes may not be related to ROS production. More studies are undergoing to better understand the possible cellular mechanisms. Financial support: FAPESP (2017/02739-4; 2018/20581-1; 2019/14803-4; 2020/13222-5).

4-30

Increase of TIMP-1 expression and volume loss in subcutaneous fat predict poorer survival of patients with pancreatic ductal adenocarcinoma

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Introduction: Patients with pancreatic ductal adenocarcinomas (PDAC) often develop cachexia, an inflammatory syndrome associated with loss of fat and muscle tissue, as well as with elevated plasma levels of Tissue inhibitor of metalloproteinases-1 (TIMP-1). Here we investigated the prognostic value of loss of visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT), and, additionally, in a preliminary approach, a possible link to TIMP-1 expression in these tissues.
Methods: Patients with PDAC at various stages of disease were included in the study. Staging CT scans were used for the measurement of body composition parameters at the third lumbar vertebra in respect to VAT and SAT at the time point of inclusion in this study (n=186), and at 6 months (n=90) and 12 months (n=70) follow-up visits by employing the Slice-O-Matic Software V4.3 using pre-established Hounsfield unit thresholds. TIMP-1 expression in SAT and VAT biopsies, taken from 16 representative patients shortly after inclusion in this study, was analyzed by qRT-PCR.
Results: PDAC patients showed a significant decrease of SAT and VAT volume at 6 and 12 months follow-up visits, while there was no change in skeletal muscle volume. Loss of SAT, but not of VAT, at 6 months correlated with lower survival. Local TIMP-1 expression levels in SAT positively correlated with SAT content. High local expression of TIMP-1 in SAT was associated with poorer survival.
Discussion/Conclusions: Loss in SAT, and not in VAT, correlated with poorer survival in PDAC patients. A link between increased TIMP-1 expression in SAT and poor survival in PDAC, and a positive correlation between TIMP-1 expression in SAT and SAT content, are novel findings of this study and suggest a possible role of TIMP-1 as a "bad" adipokine in SAT in PDAC patients.

4-31

Respiratory Muscle Pathology in Esophageal Adenocarcinoma Patients

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Introduction: Esophageal adenocarcinoma (EGA) is increasing in incidence and mortality rate. Treatment is difficult, multidisciplinary and complicated by the presence of cancer cachexia, largely characterized by skeletal muscle atrophy and dysfunction. These factors contribute to the poor prognosis experienced by EGA patients. We hypothesized that respiratory muscles from EGA patients would display histological signs of pathology that associate with weight loss and cachexia status.
Methods: Individuals with biopsy-proven EGA were recruited to donate diaphragmatic crus and intercostal muscle during surgery (n=26). Tissue was stained with hematoxylin-and-eosin and Masson's trichrome to characterize morphology and collagen content. Fibrosis was quantified as collagen percent using ImageJ software. Clinical data, including pulmonary function testing and tumor variables, were compared to measurements.
Results: Most patients (78.3%) lost more than 5% body weight in the six months preceding surgery. Collagen content in diaphragm samples significantly correlated with weight loss (R=0.4857, p=0.0188), while collagen content in intercostal muscle samples tended to associate with weight loss (R=0.3880, p=0.0910). Both respiratory muscles displayed similar collagen content (9.91% v. 7.66%, p=0.2859). Fibrosis did not associate with age. Diaphragm collagen content significantly correlated with peak expiratory flow (R=-0.6273, p=0.0163) and tended to associate with forced expiratory volume in one second (R=-0.4571, p=0.1003). After neoadjuvant therapy, subjects with residual tumor (21.4% v. 9.86%, p=0.0145), lymph node metastases (22.4% v. 9.71%, p=0.0069), lymphovascular invasion (21.8% v. 11.4%, p=0.0464) and perineural invasion (26.6% v. 9.95%, p=0.0005) lost significantly more weight. Furthermore, diaphragm collagen content was increased in subjects with perineural invasion (14.6% v. 8.06%, p=0.0338).
Conclusions: Respiratory muscle fibrosis is a key phenotype of cachexia in EGA patients. We demonstrate herein that collagen deposition in diaphragm samples correlates to weight loss, cachexia status and pulmonary function. These findings highlight the need to study mechanisms that lead to respiratory muscle pathology in tumor bearing hosts.

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Study of the histological and inflammatory rearrangements of the subcutaneous adipose tissue among gastrointestinal cancer patients with cachexia

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Introduction: Different changes in peripheral tissues including the adipose tissue may occur during cancer cachexia.
By the present study, we verified the presence of histologic rearrangement, including the grade of fibrosis, adipocyte morphology and infiltration of inflammatory cells in the subcutaneous adipose tissue of patients with cancer according to the presence of cachexia.
Methods: We considered gastrointestinal cancer patients with and without cachexia (presence/absence of unvoluntary body weight loss > 5%), and controls with non-malignant diseases, undergoing surgery. We collected subcutaneous adipose tissue samples and we performed histomorphological analyses (cross-sectional area – CSA and grade of fibrosis) and immunohistochemistry to characterize the inflammatory cells of the adipose tissue.
Results: We enrolled 31 gastrointestinal (7 gastric, 8 pancreatic and 16 colorectal) cancer patients and 20 controls. In cancer patients (age 71 ± 12 y, BMI 26.1 ± 3.8 kg/m^2), cachexia was present in 13/31 (42%). The CSA of the adipocytes was reduced in cancer patients when compared to controls ($p<0.001$), in particular in cachectic vs non-cachectic patients ($p<0.05$) and in cachectic vs controls ($p<0.001$), as well as in non-cachectic vs controls ($p<0.05$). The degree of fibrosis was higher in cancer patients vs controls ($p<0.001$), in particular in cachectic vs non-cachectic patients ($p<0.05$). We observed a higher number of macrophages (CD68) ($p=0.0001$) and T-lymphocytes (CD3) ($p=0.002$) in cancer patients vs controls, whereas no differences were present between cachectic and non-cachectic patients.

Conclusions: Our study showed histological alterations of subcutaneous adipose tissue of cancer patients and in particular changes in CSA and grade of fibrosis when cachexia was present.

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Gene expression analysis in lung cancer patients with anorexia

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Rationale: The pathophysiology of cancer anorexia is multifactorial and we focused on the role of changes in gene expression of PBMCs in a cohort of lung cancer patients with and without anorexia.
Methods: Gene expression was assessed by genome-wide transcriptomic profiling analyses in patients with a new diagnosis of lung cancer naïve to any treatments. Anorexia was assessed by FAACT questionnaire in cancer patients and in a control group (non-cancer, non-anorexic). We confirmed the differentially expressed genes (DEGs) by quantitative Real-Time PCR; specifically, *Adam8*, *Smad4*, *Clu* and *Ccr4* mRNA levels were measured.
Results: We performed RNA-seq analysis on PBMC of 20 lung cancer patients (10 anorexic and 10 non-anorexic) and in 10 healthy controls. We identified a total of 983 DEGs (843 up-regulated; 140 down-regulated) in anorexic cancer compared to controls. The DEGs were mainly represented within the immune regulatory pathways, such as inflammation signaling, chemokine- and cytokine-mediated inflammation signaling, TGF-beta signaling and interleukin signaling pathways. The *Adam8*, *Smad4*, *Clu* and *Ccr4* expression levels were found to be in line with the trend of RNA-seq analysis. *Adam8* mRNA levels were decreased in cancer vs controls ($p<0.001$) and in anorexic vs controls ($p=0.001$). *Smad4* mRNA levels were lower in cancer vs controls ($p=0.003$), as well as in those with anorexia vs controls ($p=0.009$). Also, we observed increased *Ccr4* expression in cancer patients with anorexia vs non-anorexia ($p=0.011$) and a similar trend for *CLU* ($p=0.057$).
Conclusions: After validation by RT-qPCR, the major pathways involved in anorexia where those mediating inflammation, TGF-beta, chemokine and cytokine pathways. We found changes of several genes associated with anorexia in cancer that may play a major role for the development of this condition.

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Intramuscular lipid alterations in human pancreatic cancer cachexia

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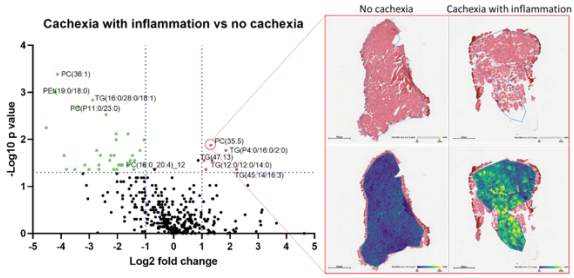
Background: Cancer cachexia is a multifactorial metabolic syndrome characterized by ongoing skeletal muscle loss resulting in weakness, poor quality of life, and decreased survival. Lipid accumulation in skeletal muscle is increasingly recognized as a defining cachexia feature that is promoted by inflammation and independently associated with muscle function and long-term survival. However, surprisingly little is known about the nature of the lipids that accumulate in skeletal muscle during cancer cachexia. We aimed to identify the types and distribution of intramuscular lipids in patients with cancer cachexia.
Methods: Rectus abdominis muscle biopsies were collected during surgery from pancreatic ductal adenocarcinoma patients (12 weight-stable, 24 with cachexia but without inflammation (CRP<10 mg/L), 12 with cachexia with inflammation (CRP≥10mg/mL). L3-CT scans were analyzed to assess body composition. Muscle sections were stained with Oil-RedO and H&E. Untargeted lipidomic analyses were performed on laser-microdissected lipid-rich muscle tissue areas using LC-MS/MS. Intramuscular lipid distribution was visualized by MALDI-MSImaging. Genes coding for enzymes involved in *de novo* ceramides synthesis were studied by qPCR.
Results: Muscle radiation attenuation was lower in cachectic patients with inflammation (median 24.3 HU, IQR 18.6-30.8) as compared to those without inflammation (34.2 HU, 29.3-38.7, $p=0.033$) or weight loss (37.4 HU, 33.9-42.9, $p=0.012$). Accordingly, intramuscular lipid content was lower in weight-stable patients (1.8%, 1.5-2.0) as compared to those with cachexia with inflammation (5.5%, 4.5-7.3, $p=0.005$) or without inflammation (4.8%, 2.6-6.1, $p=0.046$). Compared to weight-stable patients, cachectic patients with inflammation displayed increases in several intramuscular sphingolipids (Cer(m10:0/16:0), Cer(d18:0/17:3), Cer(m10:0/18:0)), glycerolipids (TG(47:13), triglycerides (12:0/12:0/14:0, 45:14/16:3), and glycerophospholipids (PC(35:5)) that could be visualized by MS-imaging (see figure). Genes related to ceramides synthesis such as SPT1/2, KDSR, Cers1-6, and DEGS1 showed higher expression in cachectic patients with inflammation.
Conclusions: Patients with cachexia exhibit intramuscular accumulation of specific lipid species that may be partly related to elevated ceramide synthesis.



Volcano plot of changes in intramuscular lipids from PDAC patients (left), PC(35:5) visualization with SCiLS™ Lab (right)

4-36

Superior effects of the novel long-acting ghrelin agonist PEP-064 vs. Anamorelin in the LLC model of cancer cachexia

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Introduction: Ghrelin is an endogenous peptide hormone that stimulates growth hormone release and food intake. The receptor (growth hormone secretagogue receptor, GHSR) is a well-established target in cachexia. Today, Anamorelin, a small molecule ghrelin mimetic, is approved in Japan for treatment of cancer cachexia and is being tested in ongoing Phase 3 trials. Here we present a novel long-acting and potent ghrelin

analogue, PEP-064, demonstrating superior effects in a disease model of cancer cachexia as compared to Anamorelin.
Methods: Potency was assessed in HEK cells cloned to over-express either the human or murine GHSR1α. Pharmacokinetic profile was assessed in mice. In vivo efficacy (7 days) was tested in healthy C57Bl/6 mice and in the Lewis Lung Carcinoma (LLC) model of cancer cachexia (14 days) compared to sham, vehicle control, or Anamorelin treatment. Body composition was measured by MR.
Results: The potency of PEP-064 on the human receptor was 14-fold lower than native ghrelin (EC50, nM; 49.2, n=2 vs. 3.6, n=10). Similar results were seen on the murine receptor. Half-life of PEP-064 (SC administration) was 6.6 hours with a Tmax at 4 hours. In vivo PEP-064 showed a dose-dependent increase in food intake and body weight in healthy mice, that was sustained throughout 7d sub-chronic treatment. Finally, in the LLC mice, PEP-064 caused a marked increase in food intake (acc. food intake, 14d, grams, 52.2±1.9 vs. 55.9±4.4 vs. 61.6±4.8, vehicle vs. Anamorelin vs. PEP-064, n=11-12) leading to a strong increase in tumor-free body weight (max effect. grams, 1.2 vs. 1.9g, Anamorelin vs. PEP-064). The increase in body weight was mainly attributed to a gain of fat tissue.
Conclusions: Long-acting ghrelin analogue PEP-064 demonstrates stronger efficacy than the ghrelin mimetic Anamorelin in the LLC model demonstrating the feasibility for a half-life extended approach for treating cancer cachexia.

5-03

Leucine-rich diet improves cachexia index and alters tumour thermogenic capacity in Lewis Lung tumour-bearing aged mice

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Introduction: Cachexia is the involuntary loss of weight, mainly muscle and fat mass, associated with several types of cancer,leading to increased morbidities, reduced quality of life, poor response to treatment and death. Leucine supplementation has been shown to play an important role in preventiing and treating this process. However, most studies with animal models of cancer-associated cachexia have been conducted in young or adult animals, whereas in humans, cancer usually occurs at an advanced age. In this line, the aims of this study were to analyse the aging impacts in metabolism and muscles, and the role of a leucine-rich diet in aged tumour-bearing mice.
Methods: Male aged C57BL/6J mice (19 - 28 months old) were distributed in control and LLC tumour-bearing groups, fed with a 3% leucine-rich or control diet. Functional analysis (food intake and body weight measurements, thermographic and strength tests) were performed before and after tumour implant, and morphometric aspects after euthanasia.
Results: After 23 days, body weight and food efficiency reduced, and cachexia index increased in both LLC tumour-bearing groups compared to control groups. Leucine-fed tumour-bearing mice had an attenuated effect on cachexia, and better feed efficiency than the tumour-bearing group which fed a control diet (Figure 1A). Normalised tumour temperature was increased in the leucine-fed mice at day 16 and decreased at day 23 (Figure 1B). Spleen weight increased, and perirenal and perigonadal adipose tissue weight reduced in LLC tumour-bearing groups compared to control groups (Figure 1C). Positive and inverse correlations were observed between tumour weight and cachexia index and tumour weight, body weight and food efficiency, respectively (Figure 1D).
Conclusion: Leucine supplementation partially protected the tumour-bearing aged mice from damage effects of cancer-associated cachexia and influenced the tumoral thermogenic response. Future studies are needed to elucidate the molecular events involved.

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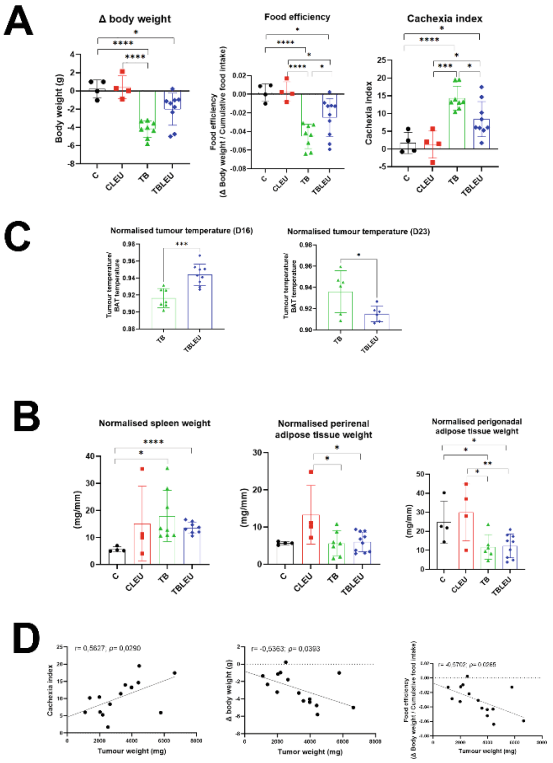

Figure 1: Functional and morphometric aspects of aged C57BL/6J mice in control and LLC tumour-bearing groups, fed with a 3% leucine-rich or control diet **(A).** Delta body weight, food efficiency and cachexia index **(B).** Spleen, perirenal and perigonadal adipose tissue weight in milligrams normalised by the mean of tibial bone measure in millimeters **(C).** Tumour temperature normalised by brown adipose tissue (BAT) temperature at days 16 and 23 **(D).** Scatter plots with fitted linear regression lines of cachexia index, body weight, food efficiency and tumour weight. (C) Control group fed with control diet; (CLEU) Control group fed with leucine-rich diet; (TB) LLC tumour-bearing group fed with control diet; (TBLEU) LLC tumour-bearing group fed with leucine-rich diet; (BAT) brown adipose tissue; *p≤0,05; **p ≤ 0,01; ***p ≤ 0,001; ****p ≤ 0,0001

5-04

Targeted nutritional intervention attenuates experimental lung cancer cachexia

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Introduction: Optimal nutritional care is pivotal in the treatment of cachexia and is recommended as a cornerstone of multimodal therapy. Here, we investigated the therapeutic effect of an intervention diet with a specific combination of high protein, leucine, fish oil, vitamin D, galacto-oligosaccharides and fructo-oligosaccharides on the development of cachexia in an orthotopic lung cancer mouse model.

Methods: Immune competent, 11 weeks old, male 129S2/Sv mice, were randomly allocated to either sham operated or tumor-bearing (TB) groups. Syngeneic lung epithelium-derived adenocarcinoma cells (K-ras^{G12D}; p53$^{R172H\Delta G}$) were inoculated intrapulmonary, and TB mice were allocated to either control diet (TB-CD) or isocaloric and isonitrogenous intervention diet (TB-ID) starting 7 days post tumor inoculation. Body weight and food intake were measured daily. At baseline and weekly after surgery, grip strength was measured and tumor growth and muscle mass were assessed using µCT imaging. Animals were euthanized and skeletal muscles of the lower hind limbs were collected at 5 days of consecutive body weight loss (cachexia) as predefined study endpoint.
Results: TB mice developed cachexia evidenced by significant loss of body weight and muscle strength, and reduced muscle and epididymal fat mass compared to sham control mice. Compared to the TB-CD group, the onset of cachexia was significantly delayed in the TB-ID group, resulting in prolonged time to reaching the cachexia-related study endpoint. Moreover, muscle function and muscle mass were better preserved in the TB-ID compared to TB-CD group. Additionally, alterations in molecular markers for proteolysis and protein synthesis, indicative for muscle atrophy signaling in TB-CD, were normalized in the skeletal muscle of the TB-ID group.
Conclusions: The targeted intervention diet delayed the onset and progression of cachexia in an orthotopic lung cancer mouse model resulting in prolonged maintenance of muscle function and average time to reaching cachexia-related study endpoint.

5-05

Digital food literacy for improved cancer care: a blended didactic and hands-on approach for healthcare professionals and medical students

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Rationale: Cancer patients are at high risk of malnutrition, negatively affecting Quality of Life, increasing treatment interruptions, unplanned hospital admissions, longer hospitalizations, and healthcare costs. Healthcare professionals (HCPs) are key in identifying patient's nutritional requirements but also their limitations in achieving adequate nutritional intake throughout the cancer care process. However, other than RDs, physicians have insufficient nutritional education and food literacy, as they lack knowledge, understanding and thus motivation in applying nutrition information to food choices.
Methods/Results: This study aims to develop a multidisciplinary evidence-based food literacy educational program, to be delivered online to all HCPs involved in cancer care, including medical students. The program includes asynchronous didactic content and synchronous hands-on confection workshops. The curriculum under construction will comprehend a 3-week program with 4hr didactic classes, 4hr hands-on sessions and 2hr group discussions. The latter will focus on motivational communication applied to clinical case studies, and preparation of materials for physicians to share with patients. Survey data will be collected before, during and after the completion of the program to better understand physicians' confidence and capacity to advise patients, or active integration of knowledge into clinical consultations.
Conclusions: By enabling physicians with the necessary skills to advise patients on food access, choices, storage and preparation, patients will be empowered to prevent and manage treatment-related symptoms. This way we intend to ameliorate patients' adherence to treatments, prognosis and Quality of Life, along with increased referral to dietitians in cancer care. In our current healthcare scenario, there is the need to incentivize further guidance and educational tools along the entire cancer care continuum, while triggering discussions for future best practices and policies. A digital food literacy educational program can reach innumerous professionals, thus contributing to improve patient-centered and outcome-driven cancer care, mandatory for healthy eating behaviors, vital for cancer survivorship.

5-06

Role of Ensure Protein Max on calorie and protein intake, appetite, and body weight in patients with advanced cancer receiving chemotherapy.

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Introduction: People with cancer experience a heightened risk of malnutrition, with anorexia-cachexia syndrome potentially occurring in up to 80% of patients with advanced cancer. β-Hydroxy β-Methylbutyrate (HMB), an integral ingredient in the Ensure Protein Max drink, has been shown to reduce skeletal muscle damage and increase muscle strength. Therefore, this study investigates the effects of Ensure Protein Max supplementation for patients with advanced cancer receiving chemotherapy.
Methods: This was a pilot, prospective, single-center, open-label feasibility study. Patients with a metastatic cancer, Karnofsky performance status of > 40%, and ability to drink Ensure orally were included. Patients with brain metastases or weight loss of > 10% in the preceding 3 months were excluded. Ensure was given in 235 mL portions twice daily for 90 days—appetite and symptoms were measured using the Patient Generated Subjective Global Assessment (PG-SGA) and Edmonton Symptom Assessment Scale (ESAS). Calorie and protein intake were measured using the 24-Hour Dietary Recall Assessment.
Results: Of the recruited patients (n=29), 20 were male and 9 were female, with a combined mean age of 64 years. The most common diagnosis was lung cancer (n=12), followed by colorectal (n=4), breast (n=4), and prostate cancer (n=3). 20 participants dropped out before the 90-day conclusion most commonly due to disease progression (n=9). Compared to baseline, patients after 90 days experienced reduced nutritional intervention needs and symptoms in tiredness, depression, anxiety, appetite, and well-being ($p < 0.01$). Patients also experienced an increase in daily protein intake from 51.14 g at baseline to 123.55 g ($p < 0.05$) and total body weight from 63.77 kg to 64.54 kg ($p < 0.05$).
Conclusions: Overall, patients with advanced cancer taking Ensure Protein Max over the 90-day trial experienced fewer symptoms related to cancer, improved physical functions, increased protein intake, and improved appetite and total body weight.

5-07

Leptin, Adiponectin, and Mortality Risk in a Prospective Hemodialysis Cohort

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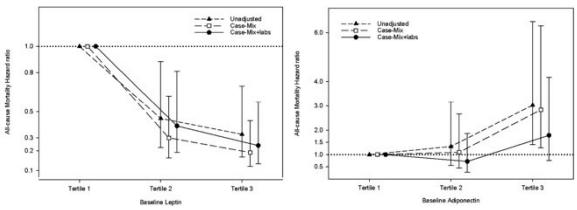
Introduction: Leptin and adiponectin are two major adipocytokines believed to play key roles in the regulation of metabolic status. While animal studies have shown that leptin and adiponectin have inverse effects on the cardiovascular system (i.e., leptin suppresses appetite and has a role in neuroendocrine regulation and inflammatory, whereas adiponectin has anti-inflammatory and insulin-sensitizing properties), the impact of these adipocytokines on the health and survival of hemodialysis (HD) patients remains unclear.
Methods: In a multi-center prospective cohort of 448 HD patients from the "Malnutrition, Diet, and Racial Disparities in Kidney Disease (MADRAD)" Study who underwent protocolized serum leptin and adiponectin measurements, we examined the relationship of each of these adipocytokines with all-cause mortality risk using unadjusted, case-mix, and case-mix+laboratory (i.e., adjusted for serum albumin, creatinine, nPCR, IL-6) adjusted Cox regression analyses. We additionally examined clinical characteristics associated with high leptin and adiponectin levels (defined as the highest tertile) using logistic regression.
Results: We observed that the lowest tertile of leptin values was associated with higher death risk across all Cox models (reference: highest tertile): adjusted HR 4.17 (1.74, 9.97) in case-mix+laboratory adjusted analyses (Figure). Conversely, we observed that the highest tertile of adiponectin values was associated with higher death risk in unadjusted and case-mix adjusted models; these associations narrowly missed statistical significance with incremental adjustment for laboratory covariates (Figure). In case-mix+laboratory logistic regression models, female sex, presence of diabetes, use of an AV access, and lower serum albumin were associated with higher leptin levels, whereas female sex, Black race, and longer dialysis vintage were associated with higher adiponectin levels.
Conclusions: In a prospective cohort of HD patients, lower leptin and higher adiponectin levels were associated with higher death risk. Further studies are needed to determine mechanistic pathways underlying circulating adipocytokine levels and survival in this population.

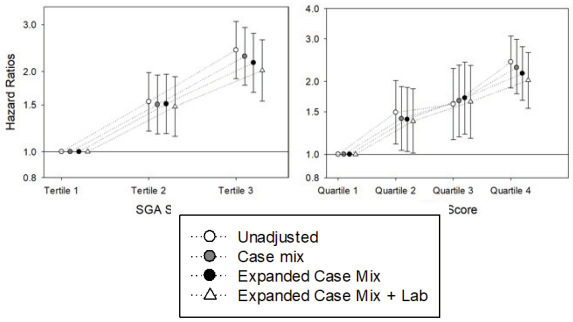


5-08

Subjective Global Assessment Scores and Mortality Risk in a Multi-Center Prospective Hemodialysis Cohort

JiHoon Yoon, Yoko Narasaki, Amy S.You, Andrea Daza, Silvina Torres, Lisa Le, Anyssa Dang, Danh V. Nguyen, Kamyar Kalantar-Zadeh, Connie M. Rhee
University of California Irvine School of Medicine, Orange, CA, USA

Introduction: Protein-energy wasting (PEW) is common in end-stage kidney disease (ESKD) patients receiving hemodialysis (HD), and it is one of the most potent predictors of mortality in this population. We sought to conduct Subjective Global Assessment (SGA) surveys, a simple yet validated nutritional assessment instrument, in a prospective cohort of HD patients in order to assess the relationship between PEW and survival in this population.
Methods: In a multi-center prospective cohort of 1018 HD patients from the "Malnutrition, Diet, and Racial Disparities in Kidney Disease (MADRAD)" Study who underwent protocolized SGA surveys, we examined the relationship between SGA scores with all-cause mortality risk using unadjusted, case-mix, expanded case-mix, and expanded case-mix+laboratory adjusted Cox regression models.
Results: In analyses of SGA scores categorized as tertiles, we observed that the middle and highest tertile of SGA scores were associated with increasingly higher death risk when compared with the lowest tertile across all Cox models (**Figure**): adjusted HRs (95%CIs) 2.02 (1.55, 2.63) and 1.48 (1.14, 1.91), respectively, in expanded case-mix+laboratory adjusted models. In analyses of SGA scores categorized as quartiles, we similarly observed that incrementally higher SGA quartiles were associated with increasingly higher mortality risk: adjusted HRs (95%CIs) 2.02 (1.55, 2.64), 1.65 (1.17, 2.33), and 1.37 (1.01, 1.86) for the second lowest, second highest, and highest quartiles of SGA scores, respectively, in expanded case-mix+laboratory adjusted models (**Figure**).



Conclusions: In a prospective cohort of HD patients, we found that increasing severity of PEW ascertained by SGA surveys were associated with higher mortality risk. These findings underscore the importance of using the SGA as a reliable nutritional assessment tool that can be conveniently applied at the chairside in order to identify HD patients with inadequate nutrition intake who may benefit from earlier implementation of nutrition interventions.

5-09

High nutritional risk in head and neck cancer radiotherapy: a retrospective analysis of predictors of malnutrition in patients undergoing IMRT

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Rationale: Radiotherapy (RT) has long played an integral role in the management of locally advanced head and neck cancer (HNC), both for organ preservation and to improve tumor control in the postoperative setting. Currently RT is evolving to

reduce treatment toxicity and increase quality of life without compromising locoregional tumor control. However, there is always weight loss associated with the cancer itself and due to radiotherapy-induced morbidity. Thus, this study aimed to analyze the prevalence of predictors of malnutrition in HNC patients undergoing RT.
Methods: A retrospective study based on data from hospital records on 28 HNC patients treated with IMRT between December 2017 and March 2018. Demographics, diagnosis, site, stage, therapeutic approach, side effects, clinical diary, weight and nutritional assessment throughout RT were evaluated. Data from transferred patients, unknown management process or deceased patients were excluded.
Results: Among 28 patients 96% had nutritional assessment while attending weekly appointments. The majority of patients were male (n=25). Median age was 58 years (range, 42-84). The factors significantly increasing the risk of malnutrition were concomitant chemoradiotherapy (71%), nodal irradiation (78%), tumor localization (35%) and advanced tumor stage III/IV (75%). There was an average weight loss of 7,2 kg during RT corresponding to an average weight loss of 9,7% during 46 days of treatment (25-35 fractions).
Conclusions: The combination of clinical factors and dosimetric aspects can result in an accurate prediction model that could help to identify the high-risk nutritional patients. This could enhance individualized nutritional assessment and improve nutritional intake by applying nutritional screening tools and identifying predictors of malnutrition among HNC patients even before they initiate RT. The present results might translate into an ineffective use of the timeline between diagnosis and start of RT.

6-01

Cachexia Trials Advisory Board and Trials Network: A route map for cachexia research progression

Barry J A Laird[1], Richard J E Skipworth[2], Denis C Guttridge[3], Jose Garcia[4,5,] Tora Solheim[6], Teresa A Zimmers[7,8], on behalf of the Cancer Cachexia Society
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The Cancer Cachexia Society Clinical Trials Advisory Board (CCS-CTAB) and the Cancer Cachexia Society-affiliated Clinical Trials Network (CCS-CTN) aim to provide a route for clinical trials and therapies for cachexia to progress. Launching in June 2022, our focus will be working with clinicians, scientists, pharmaceutical companies, and advocates to ensure that the most promising new therapies reach patients as quickly as possible. From pre-clinical development into the clinical arena, we seek to establish the best practice care for people with cancer cachexia worldwide.
Recent years have seen a number of developments in cancer cachexia from scientists and researchers, and a similar surge in interest from pharma. In addition, our increased understanding of the genesis of cancer cachexia has led to promising preclinical results, which may lead to new therapies in the near future. Yet translational research towards cachexia therapy development has faced a number of barriers. For people with cachexia, promising research has not translated to clinical treatments, and despite published guidelines, integrated cachexia care remains the exception in routine oncology treatment. For clinicians and researchers, there have been multiple barriers, including limited research funding, lack of consensus in clinical trial methodology and endpoints, differing cachexia definitions, and various guideline recommendations. Together, these have impaired investigator-led research and trials. For the pharmaceutical industry, additional challenges include identifying the investigators and sites with the relevant expertise and access to the appropriate patient cohorts for clinical trials in cancer cachexia has been and remains a significant challenge. Applying oncology or palliative medicine research models to cachexia has failed to yield success, and specific expertise and research design are needed.
The CCS-CTAB and CCS-CTN address all these issues, uniting the stakeholders in the community and providing an infrastructure to accelerate research and therapy development, increase collaboration, improve patient care, and help support 'clinical trial readiness' on an international scale. The CCS-CTAB and CCS-CTN aim to reshape the cancer cachexia research environment by reviewing and providing guidance on developmental therapeutic programs (CCS-CTAB) and developing and delivering cachexia research on an international scale (CCS-CTN).
Here we will present a detailed outline of the CCS-CTAB and CTN structure, leadership, and overall objectives. Membership of these will be established in due course with reviewers invited according to areas of expertise. The full remit of areas covered will be presented along with the process for engaging with these groups.

6-04

Long term dietary fish oil treatment is more effective than short term fish oil in reducing FOLFIRI induced inflammation in a preclinical model of colorectal cancer

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Introduction: Omega-3 fatty acids, particularly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), have lipid-lowering and anti-inflammatory properties. Both short and long-term fish oil (FO) treatment mitigates chemotherapy-induced myosteatosis in a preclinical model of colorectal cancer. However, the differential effects of both short (ST-FO) and long term (LT-FO) treatment in regulating inflammatory response in this model remain unexplored. To gain insight into the underlying mechanisms, we carried out transcriptomics analysis of gastrocnemius muscle using Next Generation RNA sequencing and Pathway analysis.
Methods: Female Fischer 344 rats were fed either a control diet for the entire study (control) or switched to a diet containing FO (2.0 g /100 g of diet) one week prior to tumor implantation (LT-FO) or at the start of chemotherapy (ST-FO). Chemotherapy (irinotecan + 5-fluorouracil; FOLFIRI) was initiated two weeks after tumor implantation (1-cycle) and one week thereafter (2-cycles).
Results: A total of 601 Differentially Expressed (DE) genes were identified (169 up-regulated and 405 down-regulated) with the Fold-change cut-off of ≥1.3 and P<0.05 between the ST-FO vs. Control (1 cycle). We identified 129 upstream regulators, including 35 molecules that were activated (Z-score >2) and 94 molecules that were inhibited (Z-score <-2). In the LT-FO vs. Control (1 cycle), 804 genes were DE, 27.2 % (222) were upregulated, and 72% (582) were downregulated. Out of the 258 upstream regulators, 68 molecules were activated, and 190 molecules were inhibited. Collectively, upstream regulators related to lipid metabolism (*PPARG, CEBPB*) and inflammation (*TNF-a, NFKB, IL-7, STAT3*) were inhibited in both ST-FO and LT-FO vs. Control (1-cycle). However, upstream regulators relating to inflammation were activated in the ST-FO vs. Control (2-cycle) and inhibited in the LT-FO vs. Control (2-cycles).
Conclusions: Provision of ST-FO and LT-FO inhibit myosteatosis; however, ST-FO appear to reduce inflammatory

response only after 1-cycle FOLFIRI treatment. LT-FO appears to be more efficacious than ST-FO in preventing inflammatory response after 2-cycles, which emphasizes the significance of the appropriate timing in the administration of FO to mitigate these deleterious effects in cancer patients receiving chemotherapy.

6-05

Comparison of low and medium frequency electromyostimulation on the lower extremities

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Introduction: Medium frequency electromyostimulation is known to be more effective for muscle activation than low frequency electromyostimulation. However, information on safety is still lacking, only medical devices that generate low-frequency electromyostimulation are used for personal use. Therefore, the purpose of this study is to compare the effects of low and medium-frequency electromyostimulation on lower extremity muscles through computational analysis.
Methods: The three-dimensional lower extremity models were reconstructed from CT images of men in their 20s without musculoskeletal disease. Conductivity and permittivity were applied to each tissue. Two 120mmx50mm size electrodes were attached, one on the upper hip and one on the lower hip, and two 80mmx120mm electrodes were attached, both on the front and the back of the thigh. A square wave electrical signal of 70 mA was applied to the electrode at three electrical stimulation frequencies (3Hz, 100Hz and 1000Hz) respectively, and computational analysis was performed.
Results: This study compared the distributions of currents over 250uA appearing in each muscle tissue. This is based on the previous clinical study that when 50mA current is applied to the human body through electrodes, muscle mass increases, and about 0.5% of the amount of current applied to the skin is measured on the muscle surface. Currents over 250uA were calculated to penetrate deeper at the midium-frequency (1000Hz) than at the low-frequency(3Hz). [upper hip:166.7%, lower hip:169.9%, front thigh:152.1%, back thigh:170.8%]
Conclusions: As a result of this study, it is expected that the penetration depth of electric current into the gluteus maximus, quadriceps and hamstring muscles increases as the frequency increases.

This work was supported by the 2020 National Innovation Cluster Demand Customized Project grant funded by the Korea government (#P0015271)

6-06

Testosterone levels dictating the maturation and antigen presentation of dendritic cells in a colorectal cancer cohort.

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Background: Testosterone might affect the immunosurveillance and immunotolerance against cancer. The aim of the study was to investigate the relationship between plasma testosterone levels and different dendritic cell (DC) properties, in colorectal cancer patients.
Methods: Early morning pre-operative blood samples were collected from 9 male patients, with advanced primary or recurrent rectal cancer. Plasma and peripheral blood mononuclear cells were isolated using Ficoll-Paque gradient. Mononuclear cells were antibody labelled to identify DC subpopulations using flow cytometry. DC were defined as lineage (CD3, CD14, CD16, CD19, CD34)$^-$, HLA-DR$^+$ cells either expressing CD11c (myeloid DC) or CD123 (plasmacytoid DC). Expression of activation markers CD40, CCR7 and gut homing marker CD103 were measured on the DC surface, while BODIPY (total lipid) and E06 (oxidised lipid) were measured intracellularly. Plasma testosterone was measured using the ELISA kit (Abcam; ab174569).
Results: The patients' median age was 57 years old and the median plasma testosterone was 1.16 ng/ml. We identified a significant negative correlation r_s -0.67 (p=0.05) between testosterone and CD40 on plasmacytoid DCs, a significant positive correlation between CD103 and testosterone r_s 0.7381 (p=0.046) on myeloid DC and a strong positive correlation between myeloid DC E06 and plasma testosterone levels r_s 0.714 (p=0.057). Weak associations between testosterone levels and CCR7 or BODIPY were not statistically significant.
Conclusions: Upon activation of CD40 by the ligand, DC mature and become activated resulting in increased anti-tumour cytokine production. In our cohort, the negative correlation between CD40 of DC and plasma testosterone supports the immunomodulatory effect of androgen. The positive correlation between testosterone and the expression of CD103 could potentially have a favourable prognostic impact on colorectal patients, as CD103 instructs DC homing to intestine and recruitment of CD8$^+$ T cells as part of the host anti-tumour immunity. However, a larger, more homogenous cohort needs to be investigated to strengthen the described correlations.

6-08

Metoprolol attenuates stimulated lipolysis in adipose tissue from cachectic patients with pancreatic cancer

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Introduction: Pancreatic ductal adenocarcinoma (PDAC) is associated with the development of cancer cachexia (CC), which is linked to excessive adipose tissue (AT) lipolysis. However, the impact of CC on different AT depots remains understudied. Despite no available treatment of PDAC-related CC, the administration of β-blockers mitigated cachexia in patients with severe chronic heart failure. Thus, we aimed to compare the lipolytic and endocrine activities of subcutaneous (SAT) and visceral (VAT) depot, and the ability of metoprolol to affect these activities in PDAC patients with/without CC and cancer-free subjects (controls).
Methods: 2-4 g of SAT and VAT were collected from 21 controls, 23 PDAC patient without CC and 8 PDAC patients with CC. AT explants were preincubated with 0.1 μM metoprolol and stimulated to lipolysis with 0.1 μm isoproterenol (ISO) in the presence/absence of 1nM insulin. In the conditioned media, levels of glycerol, FFA and several cytokines were assessed by colorimetric assay or ELISA.
Results: Relative capacity of insulin to suppress ISO-induced lipolysis was decreased in SAT of PDAC patients with CC. In contrast, VAT from PDAC patients (both with/without CC) was less sensitive to ISO treatment. Metoprolol suppressed ISO-induced lipolysis in both depots in all groups of patients. Secretion of adiponectin, leptin, ANGPTL4, IL6, serpin F1, and complement D factor by SAT was not different among the groups. IL6 was significantly more produced by VAT where its levels were higher in PDAC patients with CC compared to PDAC patients without CC.
Conclusions: We found differences in SAT and VAT lipolytic and endocrine properties related to PDAC and CC. Since metoprolol proved to be effective to decrease catecholamine-

stimulated lipolysis not only in AT from controls but also PDAC patients, it has the potential to lower or prevent the PDAC-induced AT wasting.

Funding: The study was supported by the Czech Health Research Council (NV19-01-00101), and by institutional support of Charles University (COOPERATIO Metabolic disease and 260531/SVV/2020)

6-09

Deletion of FNDC5/Irisin protects against cancer induced cachexia syndrome

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Cancer cachexia (CC) is characterized by severe skeletal muscle and metabolic abnormalities. As the browning of white adipose tissue is a feature of CC and as the hormone irisin has been shown to promote thermogenic energy conversion in adipocytes, we sought to determine if deletion of the precursor for irisin, Fibronectin type III domain-containing protein 5 (FNDC5), could improve CC. Irisin is a circulating hormone cleaved from FNDC5 in response to exercise.
FNDC5 KO animals were implanted with Lewis Lung Carcinoma (LLC) or metastatic MC38 colorectal cancer (mMC38). Our data show that male FNDC5 KO mice are protected against CC induced by both tumors. In contrast, no significant protective effects were observed in the female KO mice. Male FNDC5 KO tumor hosts maintained their normal body weight and skeletal muscle mass in spite of tumor growth in contrast to wildtype (WT) control mice carrying the same tumor mass. Moreover, the deletion of FNDC5/irisin protected against muscle weakness and increased total locomotor activity. Tumor secreted humoral factors have been shown to activate and elevate pro-atrophic pathways in cachectic skeletal muscle, such as STAT3 phosphorylation and *Atrogin1* and *Murf1* expression, all important regulators of protein catabolism. Surprisingly, these regulators were unchanged in the skeletal muscle of the LLC-bearing FNDC5 KO mice compared to non-tumor bearing mice. In addition, metabolic alterations such as increased levels of pyruvate dehydrogenase kinase 4 (PDK4) and succinate dehydrogenase (SDH) activity were unchanged in the skeletal muscle of tumor bearing KO mice compared to non-tumor bearers.
These observations suggest that counteraction of FNDC5/irisin protects against cancer-induced muscle wasting and weakness in a sex dependent manner. Our findings suggest that FNDC5/irisin could represent a novel target for the treatment and prevention of cancer cachexia.

6-10

Anti-RANKL treatment attenuates sarcopenia via suppressing inflammation and macrophage infiltration

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Introduction: Sarcopenia is an age-related geriatric syndrome which is associated with subsequent disability and morbidity. Currently there is no promising therapy approved for treatment. The receptor activator of nuclear factor NF-κB ligand (RANKL) is expressed in skeletal muscle and its activation mainly inhibits myogenic differentiation, which leads to skeletal muscle dysfunction. CD206 positive macrophage has been reported to be associated with progressive impairment of skeletal muscle function with aging. The study aims to investigate the effects of an anti-RANKL treatment on sarcopenic skeletal muscle and explore the related mechanisms in muscle inflammation and the polarization status of macrophages.
Methods: Sarcopenic senescence-accelerated mouse P8 (SAMP8) mice at month 8 were treated intraperitoneally with 5mg/kg anti-RANKL (Bio X Cell) every 4 weeks and harvested at month 10. Senescence accelerated mouse resistant-1 (SAMR1) were collected at month 10 as age-matched non-sarcopenic group. RNA-sequencing was performed in 6-month-old non-sarcopenic SAMP8 mice and 10-month-old sarcopenic mice. *Ex-vivo* functional assessment, grip strength and immunostaining of C/EBPa, CD206 and LYVE1 were performed. Data analysis was done with one-way ANOVA, and the significant level was set at p≤0.05.
Results: RNA sequencing results showed that pro-inflammatory markers TNFRSF19, TNFAIP2, M2 marker CD209d, Lymphocyte antigen 86 (LY86) and B-cell differentiation antigen CD72 expression were significantly higher in SAMP8 mice than in SAMR1 mice at month 10 (Fig. 1B), while CCL2 anti-inflammatory chemokine, PPRC1/PGC-1, MYF6 were significantly decreased. After anti-RANKL treatment, tetanic, twitch force and grip strength were significantly higher than CTL group (p<0.01 and p<0.001, Figure 1A). The SAMP8 mice at month 10 expressed significantly more C/EBPa, CD206 and LYVE1 positive area, while anti-RANKL treatment significantly decreased the expression of these factors (Figure 1C).
Conclusions: The anti-RANKL treatment protected against sarcopenic skeletal muscle through suppressing muscle inflammation and modulating M2 macrophages, which may represent a novel therapeutic approach for sarcopenia.
Acknowledgment: Collaborative Research Fund (CRF, Ref: C4032-21GF)

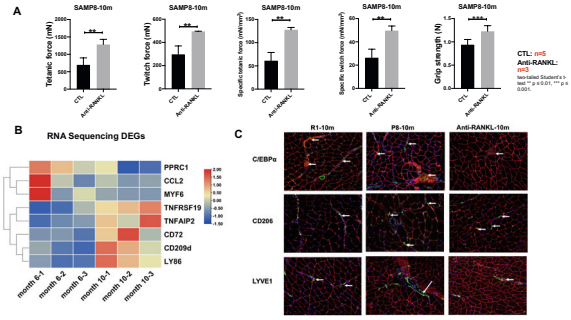

Figure 1. Ex-vivo muscle function test, RNA sequencing DEG heatmap and immunofluorescent staining of macrophage markers at month 10.

6-11

Inhibition of proteolysis through chloroquine but not bortezomib exacerbates fasting-induced tissue wasting

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Introduction: The breakdown and loss of tissue mass during conditions such as cachexia or starvation are associated with hospitalization, loss of independence and decreased life expectancy. Despite efforts by the scientific community, safe and efficient treatments for the preservation of healthy tissue during those conditions are still sparse. To develop such strategies, we need a thorough and systemic understanding of the mechanisms driving tissue breakdown. The autophagy-lysosome and the ubiquitin-proteasome are widely regarded as the dominant tools for protein degradation in cells.

Methods: To gain insights into the individual contribution of these processes during tissue breakdown, and their effects on local and systemic metabolism, we treated mice with the autophagy-lysosome inhibitor chloroquine (FAST+CLQ) and the ubiquitin-proteasome inhibitor bortezomib (FAST+BORT) during an 18h fast and compared them to fasted (FAST) and refed (FED) animals.
Results: Despite a 3h refeed, FED animals lost 6.7 ± 0.6 % body weight, and FAST mice lost 10.5 (± 1.3) % of body weight. FAST+CLQ significantly worsened body weight loss (13.5 ± 4.5 %) ($p<0.01$). FAST and FAST+CLQ both resulted in loss of liver mass ($p<0.05$ and $p<0.01$). However, FAST+BORT completely prevented the loss of body weight and liver mass. Muscle mass tended to decrease with FAST+CLQ but none of the other groups. Insulin levels trended to be increased in FAST+BORT compared to FAST and FAST+CLQ ($p=0.1$), leading to severe hypoglycemia, and higher abundance of beta oxidation substrates in the serum. The high serum insulin was further associated with increased phosphorylation of key insulin-PI3K pathway components in the liver and skeletal muscle. Autophagy-lysosome and ubiquitin-proteasome signaling was largely consistent with the previously reported effects of the drugs.
Conclusions: To conclude, inhibition of the autophagy-lysosome through chloroquine exacerbates fasting-induced tissue wasting, while inhibition of the ubiquitin-proteasome through bortezomib preserves tissue mass and body weight, likely via insulin.

6-12

Weight Change and Clinical Outcomes in Heart Failure with Reduced Ejection Fraction: Insights from the EMPEROR-Reduced trial

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Background: Baseline body mass index (BMI) and weight loss promoted by sodium-glucose co-transporter 2 inhibitors (SGLT2) may impact the clinical outcomes in patients with heart failure with reduced ejection fraction (HFrEF).
Objectives: To assess the relationship between baseline BMI, weight loss and clinical outcomes in patients with HFrEF treated with empagliflozin.
Methods and Results: In this post-hoc analysis of the EMPEROR-Reduced trial, we categorized patients according to their baseline BMI and investigated treatment effects of empagliflozin vs placebo on the primary outcome (time to first hospitalization for heart failure (HHF) or cardiovascular (CV) death), the key secondary outcomes total (first and recurrent) HHF and rate of decline in eGFR across BMI categories. Among the 3730 patients, 180 had a baseline BMI<20 kg/m^2, 1038 had BMI 20 to <25 kg/m^2, 1345 had BMI 25 to <30 kg/m^2, 774 had BMI 30 to <35 kg/m^2, and 393 had BMI ≥35 kg/m^2. The treatment effect of empagliflozin on the primary outcome was consistent across all BMI categories (HR: 0.85 [95%CI, 0.48–1.50] for BMI<20 kg/m^2; HR: 0.66 [95%CI,0.51–0.86] for BMI 20 to <25kg/m^2; HR: 0.69 [95%CI, 0.54–0.89] for BMI 25 to < 30kg/m^2; HR: 0.88 [95%CI, 0.65-1.18] for BMI 30 to <35 kg/m^2; and HR: 0.82 [95%CI, 0.55–1.23] for BMI ≥ 35 kg/m^2) (p-value for interaction trend= 0.32). The benefit of empagliflozin versus placebo on the rate of decline of eGFR and time to first renal composite outcome was consistent across the BMI categories (p for interaction trend 0.76 and 0.67, respectively). When the two treatment groups were analysed separately, weight loss within each group was similarly associated with increased risk of all-cause mortality. Overall, incidence rates of any or serious adverse events were comparable between the treatment groups across all BMI categories.
Conclusions: Weight loss was associated with higher risk of all-cause mortality, regardless of treatment group, in patients with heart failure and a reduced ejection fraction. However, the benefits of empagliflozin versus placebo were consistent across all BMI categories. No new safety signals were observed.

6-13

Pectoralis major flap to compensate for increased risk of pharyngocutaneous fistula in laryngectomy patients with low skeletal muscle mass: study protocol for a randomized controlled trial

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Introduction: Pharyngocutaneous fistula (PCF) is one of the most common severe postoperative complications after total laryngectomy (TL) and is often difficult to treat. Development of a PCF is associated with multiple problems including need for additional surgery and postponement of adjuvant therapy. The use of a prophylactic myofascial pectoralis major flap (PMMF) for reinforcement of the pharyngeal closure is recommended for patients with a high risk for PCF. Patients with low skeletal muscle mass (SMM) have an approximately three-fold increased risk compared to patients without low SMM. The aim is to investigate if the use of prophylactic PMMF in TL patients with low SMM, can reduce the risk of PCF to a level of TL patients without low SMM.
Methods: In a multicenter randomized clinical trial funded by the Dutch Cancer Society (KWF, projectnumber: R5159, NL8605) patients who are planned for TL in head and neck centers of the Dutch Head and Neck Society will be recruited. SMM will be measured on pre-treatment CT or MRI scans at the level of C3. One hundred and twenty eight patients with low SMM will be randomized between TL with or without prophylactic PMMF (1:1). The primary outcome is the development of PCF within 30 days after TL. Secondary outcomes are shoulder and neck function, swallowing function, voice quality, quality of life, length of hospital stay, patients' perspective on the given treatment, and cost-effectiveness.
Conclusions: This randomized controlled trial investigates whether the use of prophylactic PMMF will reduce the development of PCF in patients with low SMM who are planned for TL. In addition, the effect of PMMF on different physical functions and quality of life and its' cost-effectiveness will be evaluated.

6-14

Protocol for a phase II double-blind placebo controlled parallel arm fixed dose multi-site trial of anamorelin for anorexia in small cell lung cancer: The LUANA trial

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Introduction: Anorexia is prevalent in people with small cell lung cancer (SCLC) and associated with worsening of functional capacity, tolerance to treatment, quality of life and clinical outcomes. Despite the significant importance of cancer-related anorexia, current therapies are limited, have marginal benefits or unwarranted side effects.
Methods: In this multi-site, randomised, double blind, placebo controlled, fixed arm phase II trial, participants will be randomly assigned (1:1) to receive once daily oral dosing of 100mg of anamorelin HCl or matched placebo for 12 weeks. Participants can then opt into an extension phase (weeks 13-24) to receive blinded intervention medication for another 12 weeks at the same dose and frequency.
Adults (≥18 years) with SCLC newly diagnosed with planned systemic therapy OR with first recurrence of disease following successful treatment with a documented disease-free interval ≥ 6 months, AND with anorexia (i.e. ≤ 37 points on the 12-item Functional Assessment of Anorexia Cachexia Treatment (FAACT A/CS) scale) are eligible and will be invited.
The primary outcomes are safety, desirability (sufficient signal in the efficacy evaluation) and feasibility outcomes to inform the design of a robust Phase III effectiveness trial. The secondary outcomes are the effects of study interventions on body weight and composition, functional status, nutritional intake, biochemistry, fatigue, harms, survival and quality of life. Primary and secondary efficacy analysis will be conducted at 12 weeks. Additional exploratory efficacy and safety analyses will also be conducted at 24 weeks (for those who opt into the extension phase) to collect data over longer treatment duration.

Trial registration number: Australian New Zealand Clinical Trials Registry [ACTRN12622000129785]

6-15

Effects of bioarginine c supplementation on functional parameters in adults with long covid: a randomised clinical trial

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Introduction: Long Covid syndrome is associated with decline in physical function. Bioarginine C supplementation may be used to improve physical function through its action on immune system and endothelial function.
Methods: This open label, placebo-controlled randomised clinical trial was conducted in adults 20 to 60 years with persistent fatigue and attending the COVID-19 post-acute outpatient service at the Fondazione Policlinico Universitario Agostino Gemelli IRCCS (Rome, Italy). Participants were randomised 1:1 to receive twice daily oral supplementation with either 1 vial of BioArginine C (containing 1.66 g of L-arginine plus 500 mg of liposomal vitamin C) or placebo for 28 days. Six-minute walk test (6MWT) and handgrip strength were assessed at baseline and at the end of treatment.
Results: A total of 46 participants (mean age 46.7±11.7, 65% women) were enrolled. Relative to baseline values, Bioarginine C significantly increased the 6-min walk distance (median change [IQR]: +30 [40.5] m vs. +0 [75] m, p=0.001) and handgrip strength (median change [IQR]: +3.4 [7.5] kg vs. +1 [6.6] kg, p=0.03). At 28 days, fatigue was reported by only 2 participants in the Bioarginine C group and 21 in the placebo group (p<0.0001).
Conclusions: Bioarginine C supplementation improved walking performance, muscle strength and fatigue in adults with Long Covid. Therefore, Bioarginine C should be considered to restore physical performance and relieve symptom burden in people with Long Covid.

6-16

Weekly cisplatin versus triweekly cisplatin chemoradiotherapy in head and neck squamous cell carcinoma patients with low skeletal muscle mass: design of the CISLOW randomized clinical trial

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Introduction: Primary cisplatin chemoradiotherapy (CRT) is a standard curative therapy for head and neck cancer (HNC) patients with locally advanced disease. Triweekly high dose cisplatin of 100 mg/m^2 body surface area is effective for survival and local control. However, high rates of acute adverse events often lead to cisplatin dose limiting toxicity (CDLT), which can limit the cumulative dose. A cumulative dose of 200 mg/m^2 or more is advised to improve survival and locoregional control. HNC patients with a low skeletal muscle mass (SMM) have a three times higher risk at CDLT. Currently weekly 40 mg/m^2 cisplatin is proposed as an alternative schedule to decrease CDLT, which may lead to a higher cumulative dose.
Methods: In this multicenter study 70 HNC patients with low SMM (<43.2 cm^2/m^2) are randomized between triweekly 100 mg/m^2 and weekly 40 mg/m^2 cisplatin CRT. Patients with a normal SMM receive cisplatin CRT according to local standard and are an observational cohort. Follow-up will be 24 months. Primary outcome is compliance to chemotherapy of patients receiving weekly 40 mg/m^2 cisplatin compared to patients receiving three-weekly 100 mg/m^2 cisplatin. Compliance is defined as absence of CDLT causing >4 days treatment postponement, >50% dose-reduction or therapy termination before the third cycle. Secondary outcomes are toxicity, cumulative cisplatin dose, time to recurrence and survival, quality of life and cost-effectiveness.
Results: This multicenter trial is ongoing, therefore results cannot yet be presented.
Conclusions: A higher cumulative dose of cisplatin during CRT is associated with a better oncologic outcome. A low SMM is predictive for CDLT in HNC patients receiving triweekly 100 mg/m^2 cisplatin. The CISLOW study aims to identify whether compliance to the proposed cisplatin scheme of HNC patients with low SMM receiving weekly 40 mg/m^2 cisplatin CRT is superior compared to patients receiving triweekly 100 mg/m^2 cisplatin CRT.

6-17

Cancer appetite recovery study (CAReS): study protocol for a dose-ascending, multicenter, randomized controlled phase 1/2 trial of art27.13 in patients with cancer anorexia and weight loss

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Background: Cannabinoids have been proposed as a treatment for Cancer anorexia cachexia syndrome (CACS) by targeting the cannabinoid 1 (CB_1) receptor which regulates appetite and body weight. ART27.13 (Artelo Biosciences) is a development stage CB_1/CB_2 receptor agonist which increased body weight in healthy volunteers. An early phase trial programme is now underway examining this in patients with cancer anorexia using a mechanistic paradigm with endpoints chosen accordingly.
Methods/design: CAReS is a two-stage randomised, double-blind, placebo-controlled clinical trial to investigate the utility of ART27.13 in cancer anorexia and weight loss. CAReS will recruit adult patients of all cancers on no or stable anti-cancer therapy who have documented weight loss of >5% body weight in the prior 6 months from enrolment.
Stage 1 will determine the optimal dose of ART27.13 to be used in the second stage efficacy study. In stage 2, patients will be randomised and receive the recommended ART27.13 dose, or placebo, for 12 weeks. The primary endpoint of the phase 2 trial is to determine point estimates of activity of ART27.13 in terms of weight gain, lean body mass, KPS, and improvement of anorexia. Critically these studies will focus on mechanistically sensitive endpoints (e.g. patient reported outcome measures of anorexia) and measures of physical function that are meaningful to patients (physical activity measured using actigraphy).
Discussion: ART27.13 represents a novel therapeutic strategy to stimulate appetite and weight gain known to arise from CB_1 receptor activation that could significantly benefit patients with CACS. For the broader community, the data that will arise from this study will help elucidate the potential of modulating the peripheral cannabinoid system in the control of appetite and weight. These studies also explore endpoints, which are more meaningful for patients than have been traditionally examined in CACS.

Trial registration: EudraCT NUMBER:2020-000464-27
Research Ethics Committee reference: 20/NE/0198.

6-18

BIO101 in age-related sarcopenia: results of the SARA Program

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Introduction: Sarcopenia is a progressive muscle disorder increasing with age that may lead to mobility disability. SARA program strives to develop a viable option to treat community dwelling seniors suffering from sarcopenia.
Methods: SARA-INT is a randomized three-arm interventional study (BIO101 175 mg bid / BIO101 350 mg bid / placebo) with treatment duration of 6 months. Eligibility criteria for sarcopenia were meeting FNIH criteria and Short Physical Performance Battery (SPPB) score ≤ 8/12 in men and women aged ≥ 65 years; primary endpoint was the 400-meter walking test (400MWT).
Results: 233 participants were randomized, 232 and 156 participants were included in the Full Analysis Set (FAS) and Per-Protocol (PP) populations, respectively. Due to COVID-19 pandemic, most end-of-treatment efficacy assessments are missing for 55% of the participants, reducing the studies' power. Although primary analysis of the primary parameter (mix of 6/9-month) did not show a statistically significant improvement in 400MWT compared to placebo, BIO101 350 mg bid treatment after 6 months led to an improvement in the 400MWT of 0.07 m/s in the FAS population (not statistically significant) and of 0.09 m/s in the PP population (nominally statistically significant, p=0.008); this is close to the Minimal Clinically Important Difference (MCID) in sarcopenia (0.1 m/s). BIO101 350mg bid treatment effect on the 400MWT is confirmed in PP sub-populations at high risk of mobility disability. Trends were observed with other endpoints, correlation will be presented. BIO101 showed a very good safety profile at both doses.
Conclusions: After 6-month treatment, BIO101 at 350 mg bid showed promising results with a clinically meaningful improvement in the 400MWT gait speed, confirmed in sub-populations at higher risk of mobility disability. BIO101 showed a very good safety profile at the two doses. Biophytis is preparing to start a phase 3 program, targeting a similar patient population.

6-19

Neutralization of GDF15 ameliorates muscle weakness and exercise intolerance in $Polg^{D257A}$ mtDNA mutator mice

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Primary mitochondrial myopathies (PMM) are genetic disorders caused by pathogenic mutations in genes in the nuclear DNA (nDNA) and mtDNA that encode mitochondrial proteins or proteins involved in mitochondrial function. PMM affects predominantly, but not exclusively, skeletal muscle with most common symptoms of muscle weakness, exercise intolerance and progressive external ophthalmoplegia with no approved therapy. GDF15 is a cytokine reported to cause anorexia, aversion/emesis and weight loss in preclinical models and is associated with cancer cachexia and poor survival in patients. Neutralization of GDF15 was reported to mitigate anorexia, weight loss and improve muscle function and physical performance in preclinical cancer cachexia models. Interestingly, elevated circulating GDF15 was reported in patients with PMM but it is unclear whether GDF15 contributes to muscle weakness, fatigue and exercise intolerance. In this study, circulating GDF15 is elevated while muscle force generation and exercise capacity are reduced in the $Polg^{D257A}$ mtDNA mutator mice (Polg) resembling patients of PMM. Treatment with a selective and potent GDF15 antibody (mAB2) increases muscle force generation and exercise capacity assessed by voluntary wheel and treadmill running in Polg mice. In addition, mAB2-treated mice have increased body weight and lean mass compared with the IgG-treated group. These results suggest GDF15 inhibition could hold the potential for a new therapeutic approach for PMM.

7-02

The role of resistance exercise training for improving cardiorespiratory fitness in healthy older adults: a systematic review.

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Introduction: The Western World has an ageing population due to decades of improving life expectancy. This increase in lifespan has not been matched by an increase in healthy life expectancy, leading to an increasing number of people living in poor health in later life. Declines in cardiorespiratory fitness (CRF) and muscle mass are both associated with advancing age and are each associated with poor health outcomes. Resistance exercise training (RET) is a key intervention to mitigate sarcopenia. If RET is also able to improve the CRF of older adults, as it has been shown to in younger populations, then it has the potential to improve multiple frailty-associated health outcomes in an expanding section of society.
Methods: This systematic review aimed to identify the role of RET for improving CRF in healthy older adults. A search across CINAHL, MEDLINE, EMBASE, EMCARE, PubMed and Cochrane databases was conducted. Meta-analysis was carried out to identify improvements in established CRF parameters following RET. Eligibility criteria included older adults (>60y), healthy cohorts (i.e., disease specific cohorts were excluded), and a RET intervention.
Results: Thirty-seven eligible studies were identified. A significant improvement was found in VO_2 peak (mean difference (MD) 1.89 ml/kg/min; 95% confidence interval (CI) 1.21 ml/kg/min to 2.57 ml/kg/min), aerobic threshold (MD 1.27 ml/kg/min; 95% CI 0.44 ml/kg/min to 2.09 ml/kg/min), and 6-minute walking distance test (MD 30.89; 95% CI 26.7 to 35.08) in RET interventions <24 weeks. Curiously, there was no difference in VO_2 peak or 6MWT in longer interventions.
Conclusions: This systematic review adds to a growing body of evidence supporting the implementation of RET for improving multiple aspects of whole-body health in older adults. The improvements in CRF from RET with shorter intervention length may be relevant in time limited clinical pathways (i.e. prehabiliation for surgery).

7-03

The relationship between CT-derived sarcopenia, measures of pre-treatment fitness, and systemic inflammation in patients with OG cancer

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On behalf of The Caledonian Cachexia Collaborative

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Background: Sarcopenia is defined as a loss of muscle mass and function. Taken together, CT-derived skeletal muscle index (SMI) and density (SMD), may provide an objective measure of sarcopenia. However, the relationship with commonly utilised assessments of pre-treatment physical function in patients with cancer is unknown. Therefore, the aim of this study was to examine the relationship between the CT-derived sarcopenia score (CT-SS), ECOG-PS, cardio-pulmonary exercise testing (CPET) performance and systemic inflammation in patients with oesophago-gastric (OG) cancer who underwent neoadjuvant chemotherapy with a view to surgery.
Methods: The study included 247 patients with primary operable OG cancer. Tumour and patient characteristics including ECOG-PS and CPET variables (VO2 AT and peak) were recorded. Presence of low SMI and SMD were determined from pre-treatment staging CT scans using recognised threshold values and combined as follows to form the CT-SS: a normal/high SMI irrespective if SMD=0, low SMI and normal/high SMD =1 and low SMI and low SMD =2. Systemic inflammation was determined by mGPS and NLR. Categorical variables were analysed using χ^2 test for linear-by-linear association.
Results: Of the 247 patients included, 66% (n=164) of patients were CT-SS 0, 9 % (n=21) CT-SS 1 and 25% (n=62) CT-SS 2. 80 % (n=197) of patients had an ECOG-PS of 0, 37% (n=92) a low V02 AT and 60% (n=147) a low VO2 peak using established threshold values. On univariate analysis, the CT-SS was significantly associated with a low V02 AT ($p<0.05$) and peak ($p<0.05$), mGPS ($p<0.05$) and NLR ($p<0.05$). On univariate analysis, the CT-SS was significantly associated with V02 Peak ($p<0.05$) and mGPS ($p<0.05$) in patients who were ECOG-PS 0.
Conclusions: CT-SS was negatively associated with objective assessment of pre-operative fitness and inflammation in patients with OG cancer, even in those with optimal performance status

7-08

Functional Capacity evaluation in older adults affected by CoVid-19

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Introduction: Virus SARSCoV-2 is responsible for CoViD-19 disease which is mainly a respiratory disease but that is known to affect other organs and systems of human body specially muscle. Despite knowledge of respiratory sequalae, the knowledge on musculoskeletal system or other systems sequalae is yet not too profound, and more research is still needed, especially for sequelae in functional capacity, to preview future needs of health and social support.
Purpose_ Identify eventual limitations perceived by patients who were diagnosed with CoViD-19 more than 3 month ago, on muscle strength, functional aerobic capacity, and frailty levels
Methodology: Thirty subjects aged between 60 and 84 years (69,2±6,1 yr) with a BMI of 27,9±4,3 kg/m^2 and a dyspnea perception of 2,2±1,1 measured by MRC scale (12 males) and diagnosed with Covid-19 more than 3 months ago, were assessed. Participants were collected in the community (n=11) and in a pulmonology service (n=19) of a central hospital at Lisbon (8 have recovered in Intensive care units (ICU))
We compared 3 groups of participants (at home, nursery, and ICU) in several variables of functionality: frailty (clinical frailty scale); functional aerobic capacity (2 minutes step test with SPO2 monitorization), handgrip strength (JAMAR dynamometer) and maximal inspiratory (MIP) and expiratory (MEP) pressures using the Micro RPM manovacuometer. Statistical analyses were performed with IBM SPSS software with kruskall-wallis analysis for between group analysis in continuous variables.

Results: Groups were identical for age (p=0,429) and BMI (p=0,069). No differences were observed between 3 groups for analyzed variables.
Conclusions: For this sample no differences were observed between patients who were hospitalized in ICU or in nursery or at home with CoViD-19 disease in respiratory pressures (MIP and MEP), muscle strength (Handgrip left or wright) and functional aerobic capacity.

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