The International Society
of Exercise and Immunology (ISEI)
www.exerciseimmunology.com

The 15th ISEI Symposium

"Exercise Immunology Gets Personal"

Precision Prescriptions
for the
Prevention and Management of Chronic Diseases

24th – 27th October, 2022

The Westin La Paloma Resort & Spa
3800 East Sunrise Drive, Tucson, Arizona, USA, 85718

WELCOME
to the 15th Symposium
of the
International Society of Exercise and Immunology

The Executive Committee for the 15th International Society of Exercise and Immunology Symposium (ISEI 2022) welcomes you to the city of Tucson in the beautiful Sonoran Desert of Arizona.

The 15th ISEI symposium comes one year later than planned due to the COVID-19 pandemic and, for many of us, will be the first in-person meeting we have attended in several years. For this reason, we are especially excited to bring the ISEI community back together, allowing us to reconnect with colleagues, exchange ideas, foster new projects, and continue the ISEI tradition of making new connections and friendships.

The exercise immunology field continues to expand and cut across multiple disciplines related to disease (e.g. infection, cancer, diabetes, cognitive impairment), lifestyle (e.g. nutrition, sleep, stress, social interactions, occupational factors) and human performance (e.g. athletes, warfighters and explorers). It quickly became apparent during the pandemic that physical inactivity was a risk factor for severe COVID-19 disease, thus bringing the exercise immunology field back to the fore as we further our understanding on how exercise and nutrition can modulate immunity to prevent and manage illness and chronic disease, as well as optimizing performance. The theme of the 2022 ISEI symposium embraces the emerging practice of precision medicine, allowing us to move away from a 'one-size-fits-all' approach and start asking questions related to how variability in genetics and the environment can influence the effects of exercise and nutrition on immunity.

The 2022 ISEI symposium will include presentations by established international researchers as well as early career investigators on topics such as immunosenescence, inflammation, immunoregulatory tissue and organ crosstalk, microbiome and the brain, immunonutrition, infection, human performance, immunometabolism, metabolic disease and therapeutic adjuvants. Many of the abstracts submitted focused on the effects of exercise and/or nutrition in the context of cancer. To accommodate this expanding interest, we included two sessions in the 2022 Symposium devoted to cancer and introduced the inaugural Pernille Hojman memorial seminar in recognition of Dr. Hojman's outstanding work in exercise immuno-oncology, which was prematurely curtailed by her untimely passing in 2019.

The proceedings of this symposium will be published in *Frontiers of Sports and Active Living*. In addition, a special Frontiers research topic entitled "Current Advances in Exercise Immunology" has been released to coincide with the 2022 ISEI Symposium. We strongly encourage you to develop your 2022 ISEI symposium abstracts into full articles that can be considered for publication in this research topic. Manuscripts are due December 9th 2022, with *Frontiers in Physiology*, *Frontiers in Nutrition*, *Frontiers in Immunology* and *Frontiers in Sports and Active Living* the participating journals in this special topic.

If this is your first time in Tucson, AZ, you will experience the Southwest as it was meant to be. The city is home to a wide variety of museums, restaurants, historic sites, hiking trails, golf courses and some of the most unique flora and fauna in the world. Located in the heart of the Sonoran Desert, “Old Pueblo” provides a modern perspective of the old west.

We hope you enjoy the meeting and your time in *The Grand Canyon State*.

Richard Simpson
ISEI President-Elect
Conference Convenor
The University of Arizona (USA)

Ana Teixeira
ISEI President
University of Coimbra (Portugal)

Shlomit Radom-Aizik
University of California - Irvine (USA)

Forrest Baker
The University of Arizona (USA)

Erik Hanson
University of North Carolina – Chapel Hill (USA)

Brandt Pence
University of Memphis (USA)

Guillaume Spielmann
Louisiana State University (USA)

Sponsors and Exhibitors of the 15th ISEI Symposium

Program (All oral presentations will take place in the Grand Ballroom.)

Monday 24th October 2022

13:00 – 16:30	**Registration and Poster Mounting**
16:30 – 17:00	**Opening of the Symposium** **Ana Teixeira (ISEI President)** **Richard Simpson (Symposium Chair, ISEI President Elect)**
17:00 – 18:00	**Welcome Keynote Seminar—Jeff Woods (USA)** *"Exercise immunology in the age of pandemics"* **Chairs: Ana Teixeira (Portugal) and Richard Simpson (USA)**

18:00 – 20:00 Welcome Reception – Grand Ballroom Foyer

Tuesday 25th October 2022

07:30 – 08:30	**Continental Breakfast (Grand Ballroom Foyer)**
08:30 – 10:00	**Session 1: Honorary Lecture & Highlighted Topic** **Chairs: Katsuhiko Suzuki (Japan) and Brandt Pence (USA)**
08:30 – 09:00	**Jonathan Peake (Australia)** *"Look how far we've come! Where to next?"*
09:00 – 09:30	**Marian Kohut (USA)** "*Mechanisms underlying the benefits of exercise training in protection from respiratory viral infection and enhanced antibody response to single session exercise post-immunization*"
09:30 – 10:00	**Shlomit Radom-Aizik (USA)** *"Molecular Transducers of Physical Activity Consortium (MoTrPAC) - Multi-omics approach to understanding the health benefits of exercise in children and across the lifespan"* ***Sponsored by Kids of Steele***
10:00 – 10:30	**Tea/Coffee Break (Grand Ballroom Foyer)**
10:30 – 12:00	**Session 2: Inflammaging and Immunosenescence** **Chairs: Jeff Woods (USA) and Marian Kohut (USA)**
10:30 – 11:00	**Mladen Jergovic (USA)** *"The role of IL-6 in age-related frailty syndrome"*
11:00 – 11:30	**Karsten Krüger (Germany)** *"Immunomodulatory effects of exercise training on T-cells in the context of healthy aging and inflammation"*
11:30 – 11:45	**Ivan Bautmans (Belgium)**

	"Strength training alters LPS-induced immune responses in peripheral mononuclear blood cells of older persons"
11:45 – 12:00	**Ana Pedrosa (Portugal)**
	"The impact of 28-week muscle-strength and multicomponent exercises on salivary stress biomarkers and well-being in frail older women"
12:00 – 13:00	**Lunch (Grand Ballroom Foyer)**
13:00 – 14:30	**Session 3: Immunity, Gut and the Brain**
	Chairs: Emily LaVoy (USA) and Hiromi Yano (Japan)
13:00 – 13:30	**Monika Fleshner (USA)**
	"Exercise and prebiotics optimize gut microbial ecology and promote stress robustness"
13:30 – 14:00	**Suzi Hong (USA)**
	"Brain to Immune and Back: neuroendocrine regulatory pathways of inflammation underlying psychological and physical health interface from an exercise immunology perspective"
14:00 – 14:30	**Jacob Allen (USA)**
	"*The impact of exercise and nutrition on microbiome-immune interactions for health*"
14:30 – 15:00	**Break**
15:00 – 16:30	**Session 4: Immunoregulatory Tissue and Crosstalk**
	Chairs: Monika Fleshner (USA) and Ana Teixeira (Portugal)
15:00 – 15:30	**Barbara Wessner (Austria)**
	"Immune-muscle crosstalk during recovery from exercise – age matters"
15:30 – 16:00	**James Turner (UK)**
	"Immunological characteristics of adipose tissue with ageing and exercise"
16:00 - 16:15	**Phillip Zimmer (Germany)**
	"Exercise and the kynurenine pathway – from bench to bedside"
16:15 – 16:30	**James Vanhie (Canada)**
	"Bone marrow-derived extracellular vesicles from exercise trained mice promote mesenchymal stromal cell osteogenic differentiation in mice"
16:30 – 19:00	**Poster Session and Reception (Canyon II/IV)**
JUDGES: Lindy Castell (UK), José Cesar Rosa Neto (Brazil), Jonathan Peake (Australia), Shlomit Radom-Aizik (USA), James Turner (UK) & Barbara Wessner (Austria)	
	Poster viewing and judging for early career investigator awards

Wednesday 26th October 2022

07:30 – 08:30	**Continental Breakfast (Grand Ballroom Foyer)**
08:30 – 10:00	**Session 5: Immunonutrition**

	Chairs: Neil Walsh (UK) and Barbara Wessner (Austria)
08:30 – 09:00	**David Nieman (USA)**
	"Nutrition and Exercise Immunology: scientific discoveries using multiomics approaches"
09:00 – 09:30	**Jonathan Little (Canada)**
	"Immunomodulatory potential of exogenous ketone supplementation"
09:30 – 09:45	**Heather Caslin (USA)**
	"Weight cycling induces innate immune memory in adipose tissue macrophages"
09:45 – 10:00	**David Ostrov (USA)**
	"The potential for lactoferrin combined with diphenhydramine to influence immune responses to COVID-19 and other infectious diseases"
10:00 – 10:30	**Tea/Coffee Break (Grand Ballroom Foyer)**
10:30 – 12:00	**Session 6: Infection and Human Performance**
	Chairs: David Nieman (USA) and Karsten Krüger (Germany)
10:30 – 11:00	**Neil Walsh (UK)**
	"Sleep and immune health in the athlete and warfighter"
11:00 – 11:30	**Brian Crucian (USA)**
	"*Countermeasures-based improvements in stress, immune system dysregulation and latent herpesvirus reactivation onboard the International Space Station – relevance for deep space missions and terrestrial medicine*"
11:30 – 11:45	**Fabio Lira (Brazil)**
	"Physical activity level induces strong impact on systemic and cellular immunometabolic response in mild-to-moderate COVID-19"
11:45 – 12:00	**Forrest Baker (USA)**
	"T-cell and neutralizing antibody responses to acute exercise in humans with natural and synthetic immunity to SARS-CoV-2"
12:00 – 13:30	**Lunch (Grand Ballroom Foyer)**
	ISEI Board Meeting – South Rim Room
13:30 – 15:00	**Session 7: Immuno-Oncology 1**
	Chairs: Richard Simpson (USA) and Kathryn Schmitz (USA)
13:30 – 14:00	**Erik Hanson (USA)**
	"The immune response in cancer survivors: new cells, alternative approaches and standardized techniques"
14:00 – 14:30	**John Campbell (UK)**
	"Physical activity and exercise as therapeutic adjuvants for human blood cancers"
14:30 - 14:45	**Gitte Holmen Olofsson (Denmark)**

	"Aiming high in HI-AIM; A clinical testing of exercise in cancer"
14:45 – 15:00	**Dong-Woo Kang (USA)**
	"Changes in immune parameters after 12-week high-intensity interval training in men with prostate cancer undergoing active surveillance"
15:00 – 15:30	**Break**
15:30 – 17:00	**Session 8: Immuno-Oncology 2**
	Chairs: Michael Gustafson (USA) and David Bartlett (UK)
15:30 – 16:00	**Keri Schadler (USA)**
	"Differences in exercise-induced immune response to melanoma models in mice"
16:00 – 16:30	**Alejandro Lucia (Spain)**
	"Exercise in Pediatric Cancer"
16:30 - 16:45	**Helena Batatinha (USA)**
	"Human lymphocytes mobilized with exercise have an anti-tumor transcriptomic profile and exert enhanced graft-versus-leukemia effects in xenogeneic mice"
16:45 – 17:00	**Tobias Esser (Germany)**
	"Effect of a single bout of aerobic exercise on NK cell mobilization and infiltration in tumor tissue in prostate cancer patients"
17:30 – 18:30	**Pernille Hojman Memorial Seminar—Kathryn Schmitz (USA)**
	"Effects of exercise on factors influencing the tumor microenvironment; some evidence, more questions"
	Sponsored by The University of Arizona Cancer Center
	Chairs: Shlomit Radom-Aizik (USA) and Erik Hanson (USA)
19:00 – 21:30	**Symposium Dinner – Sonoran Room**

Thursday 27th October 2022

07:30 – 08:30	**Continental Breakfast (Grand Ballroom Foyer)**
08:30 – 10:00	**Session 9: Exercise Immunology - Open Presentations**
	Chairs: Jonathan Peake (Australia) and Suzi Hong (USA)
08:30 – 08:45	**Hiromi Yano (Japan)**
	"Gut microbiota and short-chain fatty acids in TLR5 gene-deficient mice"
08:45 – 09:00	**Kristina Gebhardt (Germany)**
	"Effect of training status and acute endurance exercise on metabolic signatures of CD4+ cells"
09:00- 09:15	**Jason Edwards (UK)**

	"Cutaneous in vivo immunity as a clinically relevant measure of respiratory infection burden in otherwise healthy young adults"
09:15-09:30	**Liliana Baptista (USA)**
	"Impact of genetically modified Lactobacillus Paracasei probiotic designed to express Angiotensin (1-7) combined with exercise training in an aging male rat model: evidence for altered neuro-remodeling and inflammation gene expression"
09:30-09:45	**Eunhan Cho (USA)**
	"Acute exercise increases NK cell mitochondrial respiration and effector functions under hypoxic conditions"
09:45-10:00	**Garett Jackson (Canada)**
	"Sex-based differences in leukocyte, endothelial, and platelet derived extracellular vesicles in healthy adults"
10:00 – 10:30	Tea/Coffee Break (Grand Ballroom Foyer)
10:30 – 12:00	**Session 10: Immunometabolism and Metabolic Disease**
	Chairs: Guillaume Spielmann (USA) and Jonathan Little (Canada)
10:30 – 11:00	**Brandt Pence (USA)**
	"Metabolic regulation of innate immunity by exercise-derived metabolites"
11:00 – 11:30	**José Cesar Rosa Neto (Brazil)**
	"Exercise and immunometabolism in inflammation and obesity: the role of metabolic sensors and physical fitness in immune cells"
11:30 – 12:00	**Hawley Kunz (USA)**
	"Immune and metabolic determinants of inflammation in obesity and insulin resistance"
12:00 – 13:00	**Closing of the Symposium and Early Career Research Awards**
	Announcement of the 16th ISEI Symposium and new President-Elect

We send our deepest thanks to the National Institute of Food and Agriculture (NIFA-USDA), The School of Nutritional Sciences and Wellness and the College of Agriculture and Life Sciences at the University of Arizona, Kids of Steele, The University of Arizona Cancer Center, Frontiers in Sports and Active Living, and the Bio5 Institute who kindly contributed to the costs of this meeting

Poster Presentations

1. Latent CMV reactivation and immune response during long-duration space flight.
   Authors: **Nadia Hayat Agha**, Guillaume Spielmann, Austin Bigley, Hawley Kunz, Satish K Mehta, Bridgette Rooney, Preteesh L Mylabathula, Duane L Pierson, Brian Crucian, Richard J Simpson

2. The combined effect of PHGG and exercise on obesity via changes in gut microbiota.
   Authors: **Takafumi Aoki**, Eri Oyanagi, Chihiro Watanabe, Hiroki Hamada, Masato Kawashima, Hiromi Kitamura, Michael Joseph Kremenik, Hiromi Yano

3. Lymphocyte and Dendritic Cell Response to a Period of Intensified Training in Young Healthy Humans and Rodents: A Systematic Review and Meta-Analysis.
   Authors: **Carla Leanne Baker**, John Hough, Jessica Piasecki, John Hunt

4. Systemic β2-Adrenergic Receptor Activation Enhances the Anti-Leukemia Activity of Expanded $\gamma\delta$ T-Cells via DNAM-1 Upregulation and PVR/Nectin-2 Recognition in Humans.
   Authors: **Forrest L Baker**, Kyle A Smith, Preteesh Mylabathula, Tiffany M Zúñiga, Douglass M Diak, Helena Batatinha, Grace M Niemiro, Charles R Pedlar, Daniel P O'Connor, Branden Lau, Jamie Colombo, Michael Seckeler, Emmanuel Katsanis, Richard J Simpson

5. Neuropsychiatric Diseases and Exercise Therapy.
   Authors: Richard Baskerville, Thomas McGrath, Marcelo Rogero, **Lindy Castell**

6. Voluntary wheel running slows human leukemia progression in immunodeficient NSG-IL15 mice independently of donor lymphocyte infusion
   Authors: **Helena Batatinha**, Douglass M Diak, Grace M Niemiro, Forrest L Baker, Kyle A Smith, Tiffany M Zúñiga, Branden Lau, Emmanuel Katsanis, Richard J Simpson

7. Testosterone suppression during prostate cancer decreases T-cell perforin and CD57 frequency but not cell counts
   Authors: **Lauren C Bates-Fraser**, Erik D Hanson, Samy Sakal, Shadney Que, Eunhan Cho, Guillaume Spielmann, Elif Kadife, John Violet, Claudio L Battaglini, Lee Stoner, David B Bartlett, Glenn K McConell, Alan Hayes

8. Is Hydrolysis of cAMP by Phosphodiesterase-4 Required for Lymphocytes to Rapidly Egress Peripheral Blood Upon Cessation of Exercise? – Preliminary Findings
   Authors: **Elizabeth Beattie**, Kyle A Smith, Forrest L Baker, Tiffany M Zúñiga, Helena Batatinha, Michael Seckeler, Emmanuel Katsanis, Richard J Simpson

9. Using Simulated Altitude and Exercise to Enhance Immune Cell Mobilization within the Peripheral Circulation
   Authors: **Travis M. Byrd**, Courtney M. Wheatley-Guy, Jordan K. Parks, Dara S. Missan, Gabrielle A. McCoy, Lester W. Myers, Michael P. Gustafson, Bruce D Johnson

10. Acute exercise enhances the in vitro efficacy of rituximab in humans with chronic lymphocytic leukaemia
    Authors: **Harrison David Collier-Bain**, Annabelle Emery, Adam John Causer, Frankie Fantom Brown, Rebecca Oliver, Rachel Eddy, Daniela Rothschild-Rodriguez, David Dutton, John Graby, Daniel Augustine, Sally Moore, James Murray, James Edward Turner, John P. Campbell

11. Relationship between T-lymphocytes and physical function in adults with chronic lymphocytic leukemia: results from the HEALTH4CLL pilot study
    Authors: **Justin C Crane**, Max J Gordon, Karen Basen-Engquist, Alessandra Ferrajoli, Melissa M Markofski, Che Young Lee, Sara Fares, Richard J Simpson, Emily C LaVoy

12. Effects of daily immunonutrient intake on inflammation and sarcopenia: role of physical activity
    Authors: **Andreas Delaere**, Ivan Bautmans, Rose Njemini, Sara Rasoulian

13. Influence of COVID-19 vaccine on the basal immune response and menstruation in female athletes
    Authors: **Shih-Hua Fang**, Ming-Ru Chiang, Li-Chun Shih

14. Immune ('biomarker') analysis in the FORTEe consortium: presentation of a project
    Authors: **Carmen Fiuza-Luces**

15. Protective Effect of Acute and Chronic Acetyl-L-carnitine Administration on Poly I:C- induced Fatigue-like behavior in Mice
    Authors: **Hiroki Hamada**, Eri Oyanagi, Chihiro Watanabe, Masato Kawashima, Takafumi Aoki, Michael J. Kremenik, Hiromi Yano

16. Immunological perturbations after exhaustive exercise are associated with subjective well-being in young healthy adults
    Authors: **Sophie Hill**, Philipp Zimmer, Alexander Schenk, Niklas Joisten, David Walzik, Tobias Esser, Sina Trebing, Lisa Heesen

17. Sex Influences Peripheral Blood Mononuclear Cell Survival and Interferon-Gamma Production following Culture in Low-Glucose or High-Lactic Acid Media
    Authors: **Charles Fee Hodgman**, Rebekah Mary Hunt, Justin Cier Crane, Emily C LaVoy

18. Characterization of the Mobilization of Transitional Memory CD4+ and CD8+ T-cells During and After an Acute Bout of Exercise
    Authors: **Rebekah Hunt**, Mahmoud Elzayat, Emily LaVoy

19. Blunted interleukin-10 function in type 2 diabetes ex vivo
    Authors: **Hashim Islam**, Garett Jackson, Alice Mui, Jonathan P Little

20. Additive benefits of exercise and dietary inulin supplementation on physical characteristics and glucose metabolism
    Authors: **Masato Kawashima**, Takafumi Aoki, Hiroki Hamada, Chihiro Watanabe, Eri Oyanagi, Takashi Yamagata, Michael Joseph Kremenik, Hiromi Yano

21. Effect of Polychlorinated Biphenyls and Exercise on Average Body Temperature Following LPS Stimulation
    Authors: **Todd K. Keylock**, Mahesh R. Pillai, Howard Casey Cromwell, Lee A Meserve

22. Effects of 9 months of Aerobic and Resistance Exercise on serum Free Light Chains in Type 2 Diabetics
    Authors: **Youyoung Kim**, John Campbell, Neil M Johannsen, Tim Church, Guillaume Spielmann

23. The Effects of an 8-Week Cannabidiol Intervention on Sleep, Immunophenotype, and Natural Killer Cell Function
    Authors: **Jacob Norbert Kisiolek**, James M Haughian, Victoria A Flores, Arjun H Ramani, Laura K Stewart

24. 30 Days of Probiotics Supplementation Reduces Endotoxemia and Gut Permeability in Marathon Runners After a Race
    Authors: **Geovana SF Leite**, Helena Batatinha, Edgar S Tavares, Ayane S Resende, José Cesar Rosa Neto, Ronaldo Thomatieli-Santos, Antonio H Lancha Junior, Cristina Stewart Bogsan

25. Microbial-derived aromatic amino acid metabolites modify inflammatory signaling and cellular energy status in a human monocyte cell line
    Authors: **Chia-Hao Lin**, Mikaela Webb, Jacob Allen

26. Monocyte response is not the same for duration- and intensity-matched bouts of treadmill walking or resistance exercise
Authors: **Melissa M Markofski**, Kristofer Jennings, Emily C LaVoy

27. Is physical activity associated with immunosenescence and inflammageing in community-dwelling octogenarians?
Authors: **Emelyn Mathot**, Veerle Knoop, Aziz Debain, Axelle Costenoble, Siddhartha Lieten, Rose Njemini, Ivan Bautmans

28. TIGIT Blockade Augments the Anti-Leukemic Activity of Exercise Expanded Gamma-Delta T-cells
Authors: **Grace M McKenzie**, Kyle A Smith, Emmanuel Katsanis, Richard J Simpson, Forrest L Baker

29. Energy systems contribution during an acute exercise bout are linked with systemic inflammation and exercise-induced NK cells mobilization in athletes
Authors: **Luciele G Minuzzi**, Gilson Dorneles, Caique Figueiredo, Karsten Krüger, José CR Neto, Fabio Lira

30. The relationship between synovial fluid biomarkers and characteristics of pain sensitization in patients with knee osteoarthritis: a preliminary analysis
Authors: **Rose Njemini,** Sofie Puts, Laurence Leysen, Thierry Scheerlinck, Jo Nijs, David Beckwée, Ivan Bautmans

31. Effect of partially hydrolyzed guar-gum intake on LPS-induced systemic inflammation via gut microbial fermentation in mice
Authors: **Eri Oyanagi**, Chihiro Watanabe, Takafumi Aoki, Hiroki Hamada, Masato Kawashima, Michael J. Kremenik, Hiromi Yano

32. Circus Physical Exercise Decreases Lymphocyte Differentiation to Th1 and Th17 Profile in Overweight/Obese Children
Authors: **José Paulo de Moraes Junior**, Heloisa Helena de Oliveira, Amanda Lins Alecrim, Maria Elizabeth Pereira Passos, Otávio Augusto Soares Machado, Cesar Miguel Momesso Santos, Patricia Fátima Oliveira Martins, Vinícius Leonardo Sousa Diniz, Laiane Cristina Santos de Oliveira, Adriana Cristina Levada-Pires, Maria Fernanda Cury-Boaventura, Tania Cristina Pithon-Curi, Renata Gorjão

33. Aerobic exercise reduces immunosuppression in the pancreatic adenocarcinoma microenvironment in intensity-dependent manner
Authors: **Sumedha Pareek**, Riccardo Ballaro, Hannah Savage, Jonghae Lee, Hetal Patel, Emily LaVoy, Florencia McAllister, Keri Schadler

34. The effect of lifelong sports training on mitochondrial function: the impact of acute exercise
Authors: **Ana Vieira Pedrosa**, Carlos M Soares, João Pedro Alves, Fátima Rosado, Vanessa Fonseca, Vilma A Sardao, Luis Manuel Rama, Ana Maria Teixeira

35. Twenty weeks of exercise intervention alter molecular pathways involved in immune processes in boys and girls with overweight/obesity – a pilot study
Authors: **Abel Plaza-Florido**, Signe Altmäe,Francisco J. Esteban,Augusto Anguita-Ruiz,Kaarel Krjutškov,Shintaro Katayama,Elisabet Einarsdottir,Juha Kere,Shlomit Radom-Aizik,Francisco B. Ortega

36. Effects of a cardiovascular rehabilitation program on the function of neutrophils from normoglycemic and type 2 diabetic myocardial infarcted patients
Authors: **Sarah Oliveira Poma**, Renato Lopes Pelaquim, Raquel Freitas Zambonatto, Eliane Borges Da Silva, Mariana Mendes De Almeida, Flavio Gomez Faria, Juliana de Freitas Germano, Mario Hiroyuki Hirata, Sonia Quarteli Doi, Rui Curi, Renata Gorjão, Angela Rubia Cavalcanti Neves Fuchs, Tania Cristina Pithon-Curi, Adriana Cristina Levada-Pires

37. Investigating changes in hematopoietic stem and progenitor cell concentrations during and after continuous vs. interval-based exercise bouts
Authors: Fendi Pradana, Tarondeep Nijjar, Paul T Morgan, Tim Podlogar, Samuel J.E. Lucas, Mark T Drayson, Francesca A.M. Kinsella, **Alex J Wadley**

38. Exercise-induced effects on inflammatory markers and BDNF in patients with knee osteoarthritis: A systematic review with meta-analysis
Authors: **Sofie Puts**, Keliane Liberman, Laurence Leysen, Louis Forti, Eveline Muyldermans, Peter Vaes, Jo Nijs, David Beckwée, Ivan Bautmans

39. Developing a New Take on An Old Assay: Exploring Natural Killer Cell Function in Humans
Authors: **Arjun H. Ramani**, Jacob N. Kisiolek, Laura K. Stewart, James M. Haughian

40. Serum cortisol, skeletal muscle strength, and relative body fat—but not CMV seropositivity—predict post-exercise circulating T cell response in healthy older adults
Authors: **Seth M Rinehart,** Kristofer Jennings, Melissa M Markofski

41. Regulation of Circulating Putative 'Angiogenic' T-Lymphocytes in Humans: Influence of G-CSF, β2 Adrenergic Signalling and Exercise
Authors: **Mark D Ross**, Grace M Niemiro, Kyle A Smith, Forrest L Baker, Tiffany M Zúñiga, Douglass M Diak, Michael Seckeler, Emmanuel Katsanis, Richard J Simpson

42. After 3 months of resistance training, the expression of inflammation related genes is changed in PBMCS with or without a LPS challenge
Authors: **Lene Salimans**, Keliane Liberman, Wilfried Cools, Rose Njemini, Florence Chainiaux, Louis Forti, Ron Kooijman, Ingo Beyer, Ivan Bautmans

43. The effects of resistance exercise investigated on the acute exercise response on the immune cell function: a systematic review
Authors: **Lene Salimans**, Keliane Liberman, Rose Njemini, Inge Kortekaas Krohn, Jan Gutermuth, Ivan Bautmans

44. Characterization of PPARγ knockout macrophages population in breast cancer model and the influence of moderate aerobic training
Authors: **Loreana Sanches Silveira**, Alexandre Abilio De Souza Teixeira, Luana Amorim Biondo, Edson Alves de Lima, Lindssen de Lima Torquato, Igor Santiago-Carvalho, Maria Regina D'Império Lima, José Cesar Rosa-Neto

45. Potential Diversion of Myeloid-Derived Suppressor Cells into Skeletal Muscle by Physical Activity: A Pilot Study
Authors: **Lea Haverbeck Simon**, Luke Krynski, Nicholas A. Pullen, Reid Hayward

46. Anti-Tumor Effects of Exercise in Murine Lymphoma are Dependent Upon Both NK-Cells and ß2-Adrenergic Receptor Signaling
Authors: **Kyle A Smith**, Helena Batatinha, Emmanuel Katsanis, Richard J Simpson

47. Manipulation of the Catecholamine-β2-Adrenergic Receptor Signaling Axis Alters the Mobilization of Effector Lymphocytes at Varying Intensities of Exercise
Authors: **Kyle A Smith**, Forrest L Baker, Tiffany M Zúñiga, Helena Batatinha, Grace Niemiro, Preteesh L Mylabathula, Michael Seckeler, Emmanuel Katsanis, Richard J Simpson

48. Effects of exercise-conditioned human serum from master athletes on in vitro growth characteristics and bioenergetic phenotype of human lung carcinoma cells.
Authors: **Carlos M Soares**, Ana Pedrosa, Fernanda M. Silva, Fátima Rosado, Luis Manuel Rama, Ana Urbano, Ana Maria Teixeira

49. Impact of Exercise Training on Peripheral Blood Mononuclear Cells Mitochondrial Function in Older Adults
Authors: **James E Stampley**, Eunhan Cho, Bailey Theall, Brett Davis, Heather Quiriarte, Neil Johannsen, Guillaume Spielmann, Brian A Irving

50. Exercise training controls skeletal muscle rhythmicity in tumor-bearing mice, through modulation of clock genes and myokine expression
Authors: **Alexandre Abilio De Souza Teixeira**, Luana Amorim Biondo, Loreana Sanches Silveira, Edson Lima, Tiego A Diniz, Fabio Lira, Marilia Seelaender, José Cesar Rosa Neto

51. Aerobic Training Reduces Chronic Airway Inflammation and Mediators of Remodeling in Asthma
Authors: **Rodolfo P Vieira**, Renilson Moraes Ferreira, Maysa Alves Rodrigues Brandao Rangel, Thiago Gonçalves Gibson-Alves, Anamei Silva-Reis, Victor Hugo Souza-Palmeira, Hélida Cristina Aquino-Santos, Claudio Ricardo Frison, Luis V F Oliveira, Regiane Albertini

52. A Nutritional Blend Suppresses the Inflammatory Response from Bronchial Epithelial Cells Induced by SARS-CoV-2
Authors: **Rodolfo P Vieira**, José Roberto Mateus-Silva, Carlos Rocha Oliveira, Maysa Alves Rodrigues Brandao-Rangel, Anamei Silva-Reis, Fabiana Olímpio, Flavio Aimbire, Lucas Dos Santos Zamarioli

53. A Phytotherapic Blend Immunity-6™ Inhibits Myeloid Leukemic Cells Activation Involving Purinergic Signaling
Authors: **Rodolfo P Vieira**, Carlos Rocha Oliveira, Maysa Alves Rodrigues Brandao Rangel, Anamei Silva-Reis, Lucas Dos Santos Zamarioli, Juliana M. B. Santos, Regiane Albertini, Rodrigo A. B. Lopes-Martins, Luis Vicente Franco Oliveira

54. Exercise Alters Gut Microbiota and Induces Prevention of Depression-Like Behavior in Mice
Authors: **Chihiro Watanabe**, Eri Oyanagi, Takafumi Aoki, Hiroki Hamada, Masato Kawashima, Michael J. Kremenik, Hiromi Yano

55. Exercise training modifies gut and serum xenometabolites with immunomodulatory potential
Authors: **Mikaela C Webb**, Brian D Piccolo, Jeffrey Woods, Sean H Adams, Jacob M Allen

56. Noradrenergic stimulation increases T cell-induced acetylcholine production
Authors: **Takashi Yamagata**, Eri Oyanagi, Chihiro Watanabe, Takafumi Aoki, Masato Kawashima, Hiroki Hamada, Michael J Kremenik, Hiromi Yano

57. Acute exercise mobilizes NKT-like cells with a cytotoxic transcriptomic profile but does not augment the potency of cytokine-induced killer (CIK) cells
Authors: **Tiffany M. Zúñiga**, Forrest L. Baker, Kyle A. Smith, Helena Batatinha, Branden Lau, Michael P. Gustafson, Emmanuel Katsanis, Richard J. Simpson

58. Acute exercise preferentially mobilizes the most dominant T-cell clones within the repertoire that display transcriptomic profiles associated with cytotoxicity, activation, and apoptosis
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ORAL PRESENTATION ABSTRACTS

15th Symposium

of the

International Society of Exercise and Immunology

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Exercise Immunology in the Age of Pandemics

The SARS-CoV-2 pandemic has been a wake-up call emphasizing the need for increased attention to and research on public health and personal health behaviors. The International Society for Exercise Immunology is well-positioned to contribute to such a need as our members have actively been doing exercise immunology research for over 30 years. This keynote address will highlight historical contributions of our members to exercise immunology research relevant to viral pandemics. Topics such as the effects of exercise on susceptibility to viral infections, the role for exercise in modulating anti-viral immune defense, the impact of exercise on vaccine responses, and the general role that a physically active lifestyle plays on risk factors associated with susceptibility to viral infections will be highlighted.

Jonathan M. Peake

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Look how far we've come! Where to next?

During its relatively short life, the field of exercise immunology has progressed significantly since it was first established 30 or so years ago. In the early days, exercise immunology brought together a small group of research scientists and clinicians from with wide and varied academic interests, including exercise physiology, sports medicine, immunology/inflammation, trauma, allergy, biochemistry and endocrinology. Early research in the field focused on documenting and explaining illness in athletes, while also characterizing fundamental changes in immune cell counts and function in response to different forms of exercise. As the field has matured, the research focus has expanded to include investigations into nutritional interventions to support athlete health, and the importance of the immune system in mediating the benefits of regular exercise in older individuals and those with chronic disease. Technological advances in the past two decades have enhanced understanding of the complex effects of exercise on the immune system. Looking to the future, the field will no doubt continue to grow by directing more attention to precision/personalized health, exploring new methods of non-invasive sampling of biofluids and accessing public repositories of '-omics' data. Exercise immunology is therefore no longer a curious sub-discipline of sports science and medicine. It has established itself as a discipline in its own right, with important application not only for athlete health, but also the wider community.

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Mechanisms underlying the benefits of exercise training in protection from respiratory viral infection and enhanced antibody response to single session exercise post-immunization.

Regular exercise training provides immune benefits with respect to host-pathogen interaction, including reduced severity of respiratory viral infection. The exercise benefit extends to aged populations which is important from a public health perspective as aged individuals experience disproportionately greater morbidity from Influenza or other respiratory viral pathogens. A single session of exercise also confers immune benefits in the context of vaccination. The mechanisms that underlie the immuno-enhancing benefits of exercise are multifactorial and challenging to define. Using viral challenge and vaccination models that include transcriptomic and metabolic approaches, we find that a more rapid upregulation of interferon pathways, coupled with reduced inflammation and altered immune cell profile within the respiratory tract, are mechanisms by which exercise protects against severe respiratory viral infection. These mechanisms of protection are also observed under conditions of aging or obesity. In addition, pathways linked to neutrophils and endosomal TLRs are upregulated with exercise, whereas viral load reduction is reflected by decreased aggrephagy. In vaccination models, a single long-term session of light to moderate intensity exercise increases antibody to Influenza or SARS-CoV-2 vaccination, a response linked to interferon signaling and altered metabolic profile. The findings show that exercise alters the immune-metabolic milieu post-immunization, linked to downstream effects on adaptive immunity. Given that serum antibody is considered a significant correlate of protection, it is possible that single session exercise may enhance vaccine-associated protection, but further studies are needed to confirm this possibility. In summary, exercise may improve host defense against pathogens in two ways, 1) by directly enhancing immune response or 2) by improving the protection conferred through immunization.

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Molecular Transducers of Physical Activity Consortium (MoTrPAC) - Multi-Omics Approach to Understanding the Health Benefits of Exercise in Children and Across the Lifespan

Rigorous descriptive and observational studies demonstrate that exercise and physical activity are essential for optimal health at all ages in the lifespan of humans. However, translating this scientific knowledge into actual clinical practice has proven to be one of the great challenges of public health in our days. Childhood obesity and physical inactivity remain at epidemic levels and have been exacerbated by the COVID-19 and its attendant social restrictions. Cardio-vascular, metabolic, and neoplastic diseases that could be prevented or mitigated by regular exercise remain among the most prevalent causes of morbidity and mortality in adults. The optimal level of physical activity for our increasingly aging population remains unknown.

It is this inconsistency that spurred that National Institutes of Health through the multidisciplinary Common Fund mechanism to instigate a transformative set of studies. The bold vision of the Molecular Transducer of Physical Activity Consortium (MoTrPAC) is to comprehensively address one of the major knowledge gaps in exercise medicine, namely, the molecular mechanisms and pathways that connect exercise to health. Like the Human Genome Project, MoTrPAC will build a library of physiological and biological mechanisms that will fuel the next generation of policies and therapies that optimize the role of physical activity in health. MoTrPAC is the largest targeted NIH investment of funds (~$200M) into the mechanisms of how physical activity improves health and prevents disease. The overall goals of this U.S. national project are to generate a map of molecular responses to physical activity and exercise using omics technologies and create a user-friendly public data resource that any qualify researcher can access. The University of California Irvine Pediatric Exercise and Genomics Research Center is the sole pediatric center out of six clinical centers (10 sites) across the U.S. The Center recruits children (10-17y/o) from diverse racial and ethnic groups with a goal to map the molecular mechanisms through which exercise benefits health. Low and highly active participants perform an acute bout of endurance exercise with blood collection before, 20- and 40-min during exercise and 10 min, 0.5 h and 3.5 h into recovery. A subgroup of low active participants repeats the assessment following 12 weeks of supervised endurance training program. Nine chemical analysis sites and a bioinformatic data center will perform integrative multi-omics (genomics, proteomics, and metabolomics) analysis to create an accessible database for future researcher.

MoTrPAC will set the stage for future discovery designed to enhance health across the lifespan by optimizing fitness at its earliest possible stages and developing strategies to maintain fitness throughout life that will embed emerging concepts of social determinants of health and the role of biological sex in health and disease.

Mladen Jergovic

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The role of Interleukin-6 in age-related frailty syndrome

Aging is accompanied by chronic low-grade inflammation – a term which relates to increase in serum levels of cytokines such as interleukin 6 (IL-6), TNF-α and acute phase proteins such as C-reactive protein. Multiple studies in humans have shown that IL-6 most reliably increases with aging. Frailty is a geriatric syndrome characterized by decrease in physical ability and increased vulnerability to stressors. One of the most consistent findings in frail subjects is an elevation of serum IL-6 but we lack research which delineates is this a causational relationship. We developed a mouse model with inducible IL-6 expression (IL-$6^{TET\text{-}ON/+}$ mice) that enables overexpression of IL-6 following stimulation with doxycycline (dox) administrated in food. IL-6 induction was dose dependent and led to increase in frailty as measured by 30-point murine clinical frailty index. Mice induced to express high levels of IL-6 quickly displayed an increase in frailty index, decrease in muscle grip strength and loss of fat. Mice induced to express 3-4 fold increase in IL-6 similar to frail humans displayed similar changes after months of induction. We measured IL-6 levels in serum and various tissues (gut, muscle, adipose, spleen) of aged (28-month-old) frail mice and adult controls as well as dox fed IL-$6^{TET\text{-}ON/+}$ mice. We observed that IL-6 levels were increased in serums and spleen homogenates of aged mice and IL-$6^{TET\text{-}ON/+}$ mice but not in other tissues. We determined that neutrophils were the main producers of IL-6 and their numbers were higher in spleens of aged and IL-$6^{TET\text{-}ON/+}$ mice compared to adult controls. We conclude that elevated IL-6 serum levels are directly associated with age-related frailty and that spleen neutrophils are likely the main producers of IL-6.

Karsten Krüger

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Immunomodulatory Effects of Exercise Training on T-cells in the Context of Healthy Aging and Inflammation

T cells are cellular components of the adaptive immune system, which are characterized by their antigen specificity and immunological memory. Acute exercise leads to an adrenergic-induced mobilization of predominantly more differentiated CD8+ cells, whereas CD4+ and naive cells enter the bloodstream to a lesser extent. This mobilization seems to favor mainly exercise-induced redistribution to other tissues. This appears to optimize the exercise-associated repair of damaged tissues and also promote immunological barrier function.

Regular exercise significantly affects the composition of T cell subpopulations, counteracting age- and disease-associated changes. With age, the CD4+/CD8+ cell ratio and naïve T cell numbers decrease, whereas abdominal obesity, in particular, appears to favor a proportional increase in CD8+EMRA cells. This progress in T cell aging appears to be associated with metabolic disorders, as a dysregulated glucose metabolism can be predicted by the proportion of CD8+EMRA cells. At the molecular level, age and disease induce mainly maladaptive processes. In particular, a condition of systemic low-grade inflammation leads to hyperactivation of some intracellular signaling pathways, such as PI3K/Akt/mTOR and MAPK signaling, and dysregulation of immunometabolic functions.

Physical activity counteracts many of these processes. Regular exercise increases the CD4+/CD8+ ratio and the number of naive T cells, whereas the proportion of highly differentiated T cells decreases. Altering the composition of T cell subpopulations through exercise has many functional implications, as it also improves key functions of overall T cell populations, such as proliferative capacity and cytotoxicity. Exercise improves intracellular Ca2+ signaling, balances NFκB signaling, and optimizes the metabolic function of T cells, such as mitochondrial metabolism. Indirect exercise effects may include increased availability of metabolic intermediates such as lactate, which increases STAT3 activity.

In conclusion, an active lifestyle and good cardiopulmonary fitness counteract T cell dysfunction in age and disease. This occurs both through changes in the local milieu, the composition of T cell subpopulations, and molecular adaptations within cells.

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Strength training alters LPS-induced immune responses in peripheral mononuclear blood cells of older persons

BACKGROUND: Recently, we showed that 3 months of strength training affect 18 canonical pathways related to chronic inflammation in peripheral mononuclear blood cells (PBMC) of older adults. It remains unclear whether these exercise-induced changes also alters the stress-induced immune response in PBMC. AIM: To investigate if resistance training improves the stress response of PBMC by mimicking in-vitro an acute infection by lipopolysaccharide (LPS)-challenge. METHODS: 14 women aged =65 years were randomized into 3 months of either 3×/week intensive strength training (IST: 3×10 rep at 80% 1RM), strength endurance training (SET: 2×30 reps at 40% 1RM) or control (CON: 3×30 sec stretching). Before and after 3 months training, PBMC were isolated and cultured with and without LPS. Prior culture and after 24 hours of culture, RNA was collected from pre-cultured, post-cultured and LPS challenged PBMC's, respectively. Targeted RNA sequencing including 407 inflammation-related genes was performed. Pathway analysis was performed with Ingenuity Pathway Analyses using all 407 genes, a Benjamini-Hochberg p-value <0.05 and a z-score of =-2 or =2 were considered as significant. RESULTS: Strength training altered 23 pathways in LPS-stimulated PBMC; (IST: 7 upregulated and 2 down-regulated, SET: 5 upregulated and 10 downregulated). None of the altered pathways overlapped between IST and SET. The Cytotoxic T Lymphocyte-mediated Apoptosis of Target Cells pathway was enriched oppositely in both training groups (downregulated in IST versus upregulated in SET). CONCLUSION: We conclude that three months IST and SET can induce changes in the inflammatory stress response of PBMC, but by affecting different genes and related pathways. A balanced exercise program altering both training regimes might therefore provide optimal immune adaptations in older persons.

Ana Pedrosa, Guilherme E. Furtado, Matheus U Chupel, Marcelo P. Barros, Andre L Lacerda Bachi, Eef Hogervorst, José P. Ferreira, Ana M. Teixeira

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The impact of 28-week muscle-strength and multicomponent exercises on salivary stress biomarkers and well-being in frail older women

BACKGROUND: In recent years, the role of several types of physical exercise programs in the improvement of functional fitness in older frail individuals has been recognized1. However, only a few numbers of studies have looked at the effects of exercise on stress biomarkers and psychometric status simultaneously. Goals: This study aimed to analyze the effects of 28 weeks of two different chair exercise interventions on salivary stress hormones and psychological well-being in frail older women. METHODS: A total of 59 participants (81±7.84 years) were allocated into three distinct groups: elastic band muscle-strength (ESE, n=18), multi-component (ME, n =24), and a control non-exercising group (CGne, n = 17). Data on salivary α-amylase, salivary cortisol (sCor), and mental well-being were collected pre- and post- 28 weeks. RESULTS: One-way Analysis of Variance showed statistic significant differences in time versus group effect were verified only in sCor, with a moderate increase for the ME and a slight decrease for the ESE. A large significant increase in sCor at the end of the study was observed in the CG. Salivary α-amylase scores revealed statistically significant variations throughout time and time vs. group. A slight decrease in both exercise programs parallels a moderate increase in the CG regarding the α-amylase/sCor ratio; only time versus group treatment showed statistical differences. A substantial improvement in general self-efficacy and attitudes towards aging and diminished subjective perception of stress and depression were observed ($p > 0.05$). CONCLUSION: Overall, the ME group presented more noticeable results than the ESE group. Present results evidence a positive effect of exercise in improving individual general psychological well-being in frail older women.

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Exercise and Prebiotics Optimizes Health Promoting Microbial Ecology and Increases Stress Tolerance

Commensal gut bacteria and their metabolites impact host physiology and brain function. Stressor exposure can destabilize healthy gut microbial ecology and produce negative impacts on host physiology and sleep. It is of interest, therefore, to discover ways to stabilize and optimize health-promoting microbial ecology. Previous preclinical and clinical work revealed that regular physical activity elevates gut probiotic species and alters the relative abundances of select genera which are associated with increased resistance to the negative effects of stressor exposure and modulation of stress-reactive neural circuitry. More recently, we and others have reported that diet enriched in prebiotics also produces stress-protective changes in the gut microbiome/metabolome. Galactooligosaccharide (GOS) and polydextrose (PDX) are non-absorbable complex carbohydrates that are selectively utilized by beneficial microorganisms that confer health benefits to the host. This presentation will 1) provide foundational evidence from preclinical research that ingestion of GOS+PDX may be a feasible intervention to promote a stress robust phenotype; 2) highlight relationships between health-promoting microbial species, microbial-dependent bile acids, and stress protective effects on sleep, diurnal rhythm realignment, anxiety-like behavior, and inappropriate inflammation; and 3) discuss emerging mechanisms and challenges in the field.

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Brain to Immune and Back: Neuroendocrine Regulatory Pathways of Inflammation Underlying Psychological and Physical Health Interface from an Exercise Immunology Perspective

BACKGROUND: Inflammation underlies both physical and psychological pathology. The link between brain and inflammation is central to the co-morbid mental and physical symptom manifestations. Meanwhile, the knowledge of the mechanistic pathways of immune regulation and psycho-biologic disease outcomes remains limited resulting in limited therapeutic as well as precision health options. In this Immunity and Stress session, the neuroendocrine regulatory and leukocyte migration pathways that cross-cut neuropsychiatric and chronic physical conditions such as cardiovascular disease and obesity will be discussed. METHODS: In a series of studies, neuroendocrine regulation of inflammatory responses were investigated in individuals of diverse age (19 – 90 years), BMI (22 – 40), BP (normo- to hypertension), subclinical depressive symptoms or cognitive impairment. The intracellular cytokine expression in lipopolysaccharide-stimulated monocytes was investigated via cellular stimulation using beta-adrenergic, glucocorticoid and nicotinic acetylcholine receptor agonists for sympathoadrenal, hypothalamic adrenal and cholinergic pathways of inflammation regulation (IR). Profiles of migration and cell adhesion molecules of immune cells in blood and CSF were investigated in relation to depressive mood and neurocognitive function. Lastly, behavioral therapeutics such as Tai Chi practice in their impact on the brain-immune interface were tested. RESULTS: Somatic depressive symptoms were associated with obesity and IR and mediated obesity-inflammation associations. Sex differences emerged such that BMI was more strongly associated with depressive symptomatology among women ($\beta = 0.34$, $p < 0.01$; vs $\beta = 0.18$, $p > 0.1$). Poorer IR predicted higher somatic symptoms in women ($\beta = -0.23$, $p< 0.05$), but not men. Higher cardiometabolic dysregulation predicted elevated somatic symptoms in men (ß= 0.26, p< 0.05), but not in women. Physical fitness is associated with better IR in those reporting depressive mood. CONCLUSION: Identification of cellular mechanisms of the brain-inflammation interface in chronic psychological and physical conditions can shed light on precision-health oriented and efficacious therapeutics.

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Exercise and nutrition to promote immune-modifying microbial metabolites

Exercise modifies the gut microbiota and contributes significantly to metabolic and immune health. However, to what extent exercise-induce changes in the microbiota influences human physiology has not yet been thoroughly characterized. The microbiota produces and modifies a range of bioactive metabolites that may underly some of the benefits of exercise. Our laboratory has recently uncovered coordinated shifts in microbial metabolites in both the gut and serum in response to an exercise training intervention in humans. We have specifically honed in on a shared class microbial-derived aromatic amino acid (ArAA) metabolites produced by the microbiota with potential immunomodulatory properties. Recently, we have begun to explore the potential that these metabolites impact the physiology of monocytes, vital innate immune cells that are critical mediators of early inflammatory responses to infection, wound repair, and exercise adaptation. Our preliminary analysis has revealed ArAA metabolites that tune both the metabolic and immune capacity of monocytes, highlighting the exciting possibility that exercise-induced shifts in monocyte function are supported by microbial metabolites. Our work has also uncovered a select group of fermented foods containing high levels of the same microbial-derived ArAA metabolites. These data led us to hypothesize that there is a common class of microbial products modifiable by exercise and nutrition with anti-inflammatory potential. However, how fermented food and exercise interact to modify microbial metabolites and immune health has never been explored. To fill this gap in knowledge our lab is 1) Further testing the immune modulating potential of microbial ArAA metabolites and 2) Identifying exercise prescriptions and fermented food diets that most effectively increase immune-modifying microbial metabolites.

Barbara Wessner

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Muscle-immune crosstalk during recovery from exercise – age matters

It is well known that physical exercise promotes health by neutralizing the risks related to (age-associated) degenerative diseases involving several cells, tissues and organs such as skeletal muscle and immune cells but also adipose tissue, liver and brain. One mechanism thought to mediate the systemic benefits of regular exercise is through the release of so-called exerkines, a very heterogeneous group of molecules. During the last years, the secretion of extracellular vesicles (exosomes, microvesicles, apoptotic bodies) has emerged as a promising candidate to enable cell-to-cell communication through the transfer of functional cargo from donor to recipient cells. Specific proteins, mRNA and microRNAs have been shown to be embedded in those transport packages and several studies have confirmed the role of miRNAs as mediators of signaling pathways involved in the adaptive response of muscle cells to exercise and regeneration. Thereby, the main function of miRNAs is to serve as post-transcriptional regulators of targeted mRNAs by repressing their translation or degrading them. When regarding long-term exercise-induced changes of miRNAs in various tissues and body fluids, some of the miRNAs have been described only in one compartment, but there is a decent overlap of microRNAs that are similarly down- or up-regulated in skeletal muscle and blood. Preliminary data from our lab reveal that young and older athletes differ with respect to their whole blood microRNA profile during recovery from eccentric resistance exercise. The gene ontology network of potential target genes of these microRNAs hint to a distinct response between the two age groups.

James E Turner

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Immunological characteristics of adipose tissue with ageing and exercise

Adipose tissue is a metabolically active endocrine organ that has an important role in sensing and managing energy status, responding to under- or over-nutrition and exercise or physical activity. Adipose tissue releases hormones, adipokines, cytokines and chemokines that affect the function of cells, tissues, and organs throughout the body, subsequently influencing overall health. Although many of the health consequences of increasing adiposity are often assumed to be attributable to adipocytes, adipose tissue comprises a variety of other cell types, including cells of the immune system, which contribute to overall tissue functioning. This presentation will summarise recent work that has investigated the immunological characteristics of adipose tissue with ageing and with experimental manipulation of exercise or physical activity/inactivity. For example, examining adipose tissue from 12 younger (27 ± 4 years) and 12 older (66 ± 5 years) physically active non-obese males showed that ageing is associated with approximately 2-fold more immune cells per gram of tissue, driven by an accumulation of effector memory T cells. Other work examining the immunological characteristics of adipose tissue before and after long-term (60-day) bed rest and a 10-week randomised controlled exercise trial will also be summarised. Finally, knowledge gaps will be highlighted and recommendations for future work will be made.

Philipp Zimmer

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Exercise and the Kynurenine Pathway – From Bench to Bedside

The majority of the essential amino acid Tryptophan is metabolized along the evolutionary highly conserved Kynurenine Pathway (KP). Research of the past decades has shown that metabolites of the KP have numerous tissue and cell regulating properties and are further dysregulated in chronic diseases, such as cancer and neurodegenerative disorders. Besides pharmacological treatments, targeted physical exercise has emerged as powerful tool in the prevention and rehabilitation of these diseases. Interestingly, physical exercise provokes distinct alterations of the KP which are related to immunological and neurological adaptions. This talk aims to highlight systemic and local consequences of physical exercise for the KP and further bridges the gap of from mechanistic research to clinical implications.

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Bone marrow-derived extracellular vesicles from exercise trained mice promote mesenchymal stromal cell osteogenic differentiation in mice

Mesenchymal stromal cells differentiate into adipocytes and osteoblasts that impact hematopoiesis. Obesity promotes adipogenesis while exercise promotes osteogenesis. The mechanisms responsible for MSC differentiation remain unknown; however, extracellular vesicles (EVs) may be responsible. Therefore, we investigated the effects of bone marrow-derived EVs from mice with high-fat diet (HFD)-induced obesity and exercise (EX) on MSC proliferation and differentiation.

Donor EVs were isolated from CBA mice via differential centrifugation for recipient injection and microRNA analysis. 650 million HFD- or EX-induced EVs were injected into recipient CBA mice 24 hours post-irradiation. Bone marrow MSC, adipocyte progenitor, and osteoprogenitor cell proportions were measured 4 weeks after irradiation. Additionally, C3H 10T1/2 MSCs were cultured with 5.1 million HFD- or EX-induced EVs and induced to proliferate or differentiate into adipocytes or osteoblasts in vitro.

HFD-EX-induced EVs had lower microRNA-193 and microRNA-331-5p content compared to sedentary (SED) HFD-induced EVs. Mice receiving HFD-induced EVs had higher MSC proportions ($p<0.05$) compared to control (CON) diet-induced EVs with no effect of EX. Mice receiving HFD-SED-induced EVs had higher adipocyte progenitor cell proportions that was attenuated with HFD-EX-induced EVs ($p<0.05$). Osteoprogenitor cell proportions were lower with HFD- ($p<0.05$) and EX-induced ($p<0.01$) EVs. In vitro MSC proliferation was lower with EX-induced EVs at 6 hours ($p<0.05$) with a trend to be lower at 24 hours ($p=0.09$). HFD-induced EVs had higher MSC adipogenesis in vitro ($p<0.01$) compared to CON-induced EVs with no effect of EX. EX-induced EVs had higher MSC osteogenic differentiation compared to SED-induced EVs ($P<0.05$) with no effect of diet.

The differential effects of EVs on adipocyte and osteoprogenitor cell proportions in vivo and MSC adipogenesis and osteogenesis in vitro suggest EVs are partially responsible for MSC differentiation fate, potentially due to downregulated microRNA-193. These results provide novel evidence that EX- or HFD-induced EVs regulate MSC fate.

David C. Nieman

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Nutrition and Exercise Immunology: Scientific Discoveries Using Multiomics Approaches

The influence of nutrition on the immune response to exercise is complex. Recent advances in mass spectrometry allow these relationships to be studied more effectively using genetics, transcriptomics, epigenetics, proteomics, lipidomics, metabolomics, and whole genome shotgun sequencing of the microbiome. Intervention effects on thousands of biochemicals can be analyzed at one time using these systems biology approaches and bioinformatics. One example of the usefulness of multiomics approaches in advancing scientific understanding in nutrition and exercise immunology is with interventions using polyphenols. Earlier studies reported few discernable benefits of increased polyphenol intake on inflammation and immunity for athletes, but research design deficiencies portrayed a misunderstanding of polyphenol bioavailability and metabolism, the appropriate outcome measures, and the most effective dosing protocols. More recent exercise-based studies are focused on increased intake of plant extracts and fruit during a 2- to 4-week period, with the complex physiological outcomes captured using multiomics approaches. For example, 2-weeks intake of blueberries has been shown to strongly increase blood levels of gut-derived phenolic metabolites with a related decrease in pro-inflammatory oxylipins in cyclists following a 75-km cycling bout. Traditional measures of inflammation such as changes in immune cell counts and plasma levels of cytokines did not capture this effect. A precision sports nutrition-exercise immunology approach based on multiomics data to individualize recommendations at the small group and individual athlete level is an emerging discipline. This approach is expensive and will require years of additional investigation before this approach becomes accurate and practical for athletes and coaches. Challenges in this area include unexplained metabolic and immune heterogeneity, cost, and the translation of data to provide acceptable, efficacious nutrition guidance.

Jonathan P Little

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Immunomodulatory potential of exogenous ketone supplementation

Fasting and dietary carbohydrate restriction lead to the endogenous production of the ketone body, beta-hydroxybutyrate (BHB). Emerging data indicate that BHB can act as a signaling molecule with anti-inflammatory and immune modulating effects, suggesting that BHB could play an important role linking metabolism to immune cell function. The recent development of exogenous oral ketone supplements, which can raise circulating BHB concentrations within minutes of consumption, allows researchers to test the direct immunomodulatory effects of BHB in vivo and raises the intriguing possibility of harnessing the therapeutic potential of BHB without the need for restrictive dietary practices. This talk will highlight the mechanistic studies describing how BHB impacts immune cell function, discuss how different types of exogenous ketone supplements impact physiology, and present data from human experimental trials examining how exogenous ketone supplements influence inflammatory outcomes. After attending this talk, you will be up-to-date on the emerging science of exogenous ketone supplementation and be able to evaluate how nutritional ketosis might impact immune function.

Heather L Caslin, Matthew A Cottam, Jacqueline M Pinon, Likem Y Boney, Alyssa Hasty

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Weight cycling induces innate immune memory in adipose tissue macrophages

Weight loss improves diabetes risk relative to obesity. However, weight loss is hard to accomplish and even harder to maintain and most individuals regain weight quickly. Weight loss and regain, or weight cycling, worsens the risk of developing diabetes and cardiovascular disease beyond obesity itself. Our lab has previously shown that obesity-associated immunological changes are retained in the adipose tissue after weight loss, suggesting that immune cells may remember obesity. Thus, we hypothesized that weight cycling can induce a specific type of memory, innate immune memory, in adipose tissue macrophages. In a culture model of innate immune memory, we primed bone marrow-derived macrophages with palmitic acid or adipose tissue conditioned media for 24 hours and then washed the stimuli out. One week later, cells treated with palmitic acid or adipose tissue conditioned media had increased maximal glycolysis, maximal oxidative phosphorylation, and increased LPS-induced TNFα and IL-6 production, consistent with the development of innate immune memory. In a mouse model of weight loss, systemic glucose tolerance was improved compared with obese animals, but adipose macrophages retained elevated LPS-induced cytokine production. Furthermore, in our mouse model of weight cycling, adipose tissue macrophages had high metabolic function and secreted higher levels of basal TNFα than adipose tissue macrophages from control animals. Together, these data suggest that weight gain and weight loss promote innate immune memory in adipose macrophages which drives enhanced inflammation upon weight regain and may contribute to worsened glucose tolerance associated with weight cycling.

David A. Ostrov, Glenn Knox

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The potential for Lactoferrin combined with Diphenhydramine to influence immune responses to COVID-19 and other infectious diseases

Although community transmission for COVID-19 continues to be high in many regions, there is a significant probability that far more individuals will be infected with the coronavirus in the fall and winter of 2022. Physicians have knowledge about tools to use against SARS-CoV-2, but are well aware of limitations in terms of risk and benefit. Since the majority of vaccinated individuals were exposed to the ancestral sequence of the SARS-CoV-2 spike protein, vaccine efficacy against currently circulating variants has declined (from 90-95 % to 75-80%) as the spike protein has changed due to new mutations. Bivalent vaccines updated with the sequence of omicron, and the antiviral drug Paxlovid, are tools that are currently limited in terms of availability. Moreover, Paxlovid is a new drug without a long history of safety. Side effects and Paxlovid-rebound are likely to influence physician recommendations for patients that have questions about how to prevent COVID, treat COVID and manage Long-COVID. Since physicians commonly prescribe drugs off-label (one in five prescriptions), COVID patients have been prescribed specific drugs (including hydroxychloroquine, ivermectin, fluvoxamine, metformin). Efforts to repurpose existing drugs for prevention and treatment of COVID led to the identification of Lactoferrin, a nutritional supplement generally recognized as safe by the FDA, as a direct inhibitor of SARS-CoV-2 replication and infection. Diphenhydramine, an over-the-counter allergy relief medication, was also demonstrated to exhibit direct antiviral activity. Moreover, usage of Diphenhydramine was associated with lower risk of COVID. We found that the combination of Lactoferrin with Diphenhydramine dramatically increased antiviral activity (from 30 % to 99% inhibition of SARS-CoV-2 replication). Since Lactoferrin and Diphenhydramine are inexpensive, widely availability without a prescription, and have long histories of safety, physicians may consider these potential tools for currently circulating variants. Anecdotal reports from physicians that have recommended Lactoferrin combined with Diphenhydramine, and self-medicating individuals, describe benefit for prevention and treatment of COVID, and alleviation of Long-COVID symptoms. Since viruses can acquire resistance to drugs that bind a single molecular target, this antiviral combination is more likely to prevent COVID rebound than Paxlovid because Lactoferrin and Diphenhydramine bind separate target proteins. Lactoferrin is pleiotropic and exhibits well-characterized immune stimulatory activity in addition to antiviral activity. Diphenhydramine is a sigma receptor binding ligand that likely inhibits SARS-CoV-2 by preventing cell stress involved in generation of the coronavirus replication site: a compartment budding from the endoplasmic reticulum of infected cells. These data suggest that Lactoferrin combined with Diphenhydramine will be effective against new SARS-CoV-2 variants and all coronaviruses.

Neil P. Walsh

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Sleep and Immune Health in the Athlete and Warfighter

The offline conditions during sleep are widely considered to foster beneficial adaptive and restorative immune processes. Dr Allan Rechtschaffen, a pioneer in the field of sleep research, probably put it best… "If sleep does not serve an absolutely vital function, then it is the biggest mistake the evolutionary process has ever made." Habitually falling short of the recommended 7–9 hours' sleep each night raises the risk of morbidity and mortality. For example, habitual short sleep (< 6 hours/night) is associated with a raised risk of respiratory infection and with diseases associated with inflammation, including cardiovascular disease and diabetes. Sleep disruption is an occupational hazard for the warfighter and a growing body of research evidence shows that athletes are also susceptible to sleep disturbances during periods of intensified training and when travelling for international competition, coinciding with a raised risk of infection. Sleep disruption (e.g., sleep restriction due to early morning training, circadian misalignment due to transmeridian travel etc.,) influences immunity by activating the hypothalamic–pituitary–adrenal axis and the sympathetic nervous system. Another possibility is that environmental interactions during wakefulness activate pattern recognition receptors on immune cells, in-turn triggering increases in inflammatory cytokines, e.g., circulating interleukin-6 is raised in long-term shift workers. This talk will place sleep and immune health under the spotlight for those working in exercise immunology, highlighting the effects of sleep disruption on immune health in athletes and warfighters and providing contemporary sleep hygiene recommendations. The talk will tackle key questions and ongoing controversies such as — does sleep chronotype matter ('larks versus owls')? Are afternoon naps and sleep extension ('banking sleep') useful countermeasures? Can we adapt to sleep restriction or is it harmful to long-term immune health? Is a one-size-fits-all recommendation of 7–9 hours' sleep each night necessary for all for optimal immune health?

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Countermeasures-based Improvements in Stress, Immune System Dysregulation and Latent Herpesvirus Reactivation onboard the International Space Station – Relevance for Deep Space Missions and Terrestrial Medicine

Spaceflight-associated immune dysregulation, including altered peripheral leukocyte distribution, reduced T-cell function, reduced NK cell function and altered plasma cytokine profiles, was recently shown to persist in astronauts for the duration of 6-month orbital space mission. Primary knowledge regarding immune alterations in astronauts has been obtained via the return of blood and saliva samples, collected onboard ISS, and returned to Earth for analysis. Concurrent with the observed immune dysregulation, ISS astronauts also manifest the persistent reactivation of latent herpesviruses (EBV, HSV, VZV). This reactivation is typically believed to be asymptomatic, however two recent case reports of ISS astronauts (atopic dermatitis, atypical allergy symptoms, and hypersensitivity) seem to link these outcomes to measurable immune alterations. It is logical to assume that for upcoming deep space missions beyond the Van Allen belt, where all stressors will be increased and the ability to care for crews may be reduced, crews may be at elevated risk of experiencing increased adverse health events related to immune dysregulation.

Countermeasures for deep space missions to restore immune competence and mitigate clinical risks would be beneficial. Looking at immunity in ISS crews over the 15 year lifespan of ISS, more recent crews have displayed both improved immune status, and reduced latent virus reactivation, during 6 month orbital missions. Major physiological improvements seem to have initiated approximately 2012, a period coinciding with operational changes onboard ISS including cargo delivery and resupply frequency, personal communication, improved exercise equipment and protocols, food quality and variety, nutritional supplementation, and schedule management. We conclude that spaceflight associated immune dysregulation has therefore been positively influenced by biomedical countermeasures already deployed ISS. Evidence suggests improved aerobic and resistive exercise (duration and load) played a major role in reducing the incidence of latent virus reactivation in crewmembers.

Regrettably, many of these countermeasures relied on the substantial up/down mass, habitable volume, and ample power, onboard ISS. Deep space missions to the lunar 'Gateway' Station, onboard the Orion Capsule, or descending in the lunar lander, will be far more operationally constrained. An international team recently developed a new countermeasure protocol specific for deep space missions. This protocol is currently being validated at Palmer Station, Antarctica. A follow up validation onboard ISS is baselined should the ground validation be successful.

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Physical activity level induces strong impact on systemic and cellular immunometabolic response in the mild-to-moderate COVID-19

Individuals with higher physical activity levels exhibit a better response to SARS-CoV-2 compared to sedentary counterparts, although the impact of mild-to-moderate COVID-19 on inflammatory (systemic and cellular) response and metabolic profile are lacking. To determine the potential associations between physical activity levels and SARS-CoV-2 infection responses, we analyzed systemic (serum and whole blood) and cellular (PBMC) immunometabolic responses, immune phenotypic profile, and metabolic parameters in young adults after mild-to-moderate COVID-19 infection. Patients infected with SARS-CoV-2 (the range between 30 until 180 days after infection; n=20) and healthy-controls (n=20) were evaluated before vaccination. Physical activity levels, metabolic parameters, immune phenotypic characterization, cytokine production from liposaccharide (LPS)-stimulated whole blood cultures and LPS and Phorbol 12-myristate 13-acetate (PMA)-stimulated PBMC cultures, and mitochondrial respiration in PBMCs were evaluated. The COVID-19 group exhibited lower levels of moderate to vigorous physical activity (MVPA) ($p=0.038$) and serum IL-6 concentration ($p<0.01$), while they had a higher serum IgG, ACE activity and PGE-2 levels ($p<0.01$ for all) compared to controls. After MVPA adjustment, the COVID-19 group demonstrated increased serum and LPS-stimulated whole blood IL-10 concentrations ($p=0.047$). The COVID-19 group had a lower percentage of Treg cells ($p<0.05$), while CD4+ and CD8+ T cells from the COVID-19 group had a higher expression of PD1 ($p<0.05$). CD28 expression on CD8+ T cells from COVID-19 group was also lower. When PBMCs were stimulated with LPS, the relative production of IL-6 was lower in the COVID-19 group ($p<0.01$) compared to control group, but this difference was not apparent after MVPA adjustment ($p=0.157$). Finally, when exploring mitochondrial respiration in PBMCs, we observed a higher LEAK state value and lower OXPHOS (Complex I) in the COVID-19 group compared to control ($p<0.05$). In conclusion, individuals with prior mild-to-moderate COVID-19 infection appears to have lower physical activity levels, which may impact immunometabolic responses in a complex manner.

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T-cell and Neutralizing Antibody Responses to Acute Exercise in Humans with Natural and Synthetic Immunity to SARS-CoV-2

Regular exercise is purported to enhance immunosurveillance against many common viruses through the mobilization and redistribution of effector lymphocytes that occurs with every exercise bout. Evidence suggests that physically active individuals have improved clinical outcomes and reduced symptoms following severe-acute-respiratory-syndrome-coronavirus 2 (SARS-CoV-2) infection, but the mechanisms by which exercise can ameliorate symptoms and enhance immunity against SARS-CoV-2 is still under investigation. Previously, we reported that acute exercise mobilized SARS-CoV-2 T-cells and increased circulating neutralizing antibodies in a single individual, but we have not confirmed this finding in a larger cohort. Moreover, it is unknown if exercise mobilizes SARS-CoV-2 T-cells and neutralizing antibodies (nAbs) after COVID-19 vaccination in uninfected individuals. PURPOSE: Compare the exercise-induced immune response to SARS-CoV-2 in humans with natural and/or synthetic (vaccinated) immunity. METHODS: Healthy participants were recruited with four different SARS-COV-2 immunity status: (I) natural immunity through previous infection (n=8); (II) synthetic immunity through COVID-19 vaccination (n=11); (III) hybrid immunity through previous infection and vaccination (n=7); and (IV) none-immune controls (n=11). Participants completed a 20-minute bout of graded exercise on a cycling ergometer and blood samples were collected at rest, during-exercise (60% and 80% VO2max stages), and 1-hour post-exercise. Whole blood SARS-CoV-2 peptide stimulation, anti-RBD-1 nABs ELISA, ELISPOTs, 8-color flow cytometry, and deep T-cell receptor (TCR)ß sequencing with immunoSEQ T-MAP COVID assays were performed on collected samples. RESULTS: Exercise mobilized MHC-I-specific SARS-CoV-2 T-cells ($p<0.001$) to the blood compartment in an intensity-dependent manner in all participants with SARS-CoV-2 immunity, while SARS-CoV-2 T-cells were undetectable in controls. Exercise mobilized SARS-CoV-2 T-cells recognized the three major structural proteins of the virus; surface ($p<0.005$), membrane ($p<0.005$), and nucleocapsid antigen ($p<0.005$), and maintained broad TCR-β diversity in participants with natural and hybrid immunity. SARS-CoV-2 T-cells from participants with synthetic immunity were exercise responsive ($p>0.05$) but only recognized the surface protein antigen and had a more restricted TCR-β repertoire. Exercise transiently elevated SARS-CoV-2 nAbs ($p<0.05$) in participants with natural and hybrid immunity but not in those with synthetic immunity. Moreover, participants with synthetic immunity had a blunted exercise-induced mobilization of naïve and CM CD4+ T-cells ($p<0.05$) and naïve CD8+ T-cells ($p<0.05$) compared to participants with natural and hybrid immunity. CONCLUSION: A single bout of exercise mobilizes SARS-CoV-2 T-cells regardless of immunity status, while exercise maintains a broad TCR-β diversity and transiently elevates nAbs against the virus only in individuals with natural or hybrid immunity. These findings highlight the potential for exercise to enhance immunosurveillance against previously encountered antigens, which may be linked to reductions in COVID-19 severity in physically active individuals who have previously been infected or vaccinated.

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The Immune Response in Cancer Survivors: New Cells, Alternative Approaches and Standardized Techniques

Cancer treatments accelerate age-related declines, including alterations in body composition, inflammation, fatigue, and physical function, that collectively contribute to reduced quality of life. A side effect that has received considerably less attention yet is relevant cancer recurrence and overall health is the immune system. Radiation and chemotherapy decrease cell counts and cytokine production, which contributes to age-related immunosenescence and poor regenerative capacity. This delayed recovery of the immune system is linked with higher rates of metastasis. Exercise is widely recommended throughout the cancer continuum to systemically target the adverse effects of treatment, including the immune system. Over the past ~30 years, initial evidence supporting the beneficial role of exercise on immune function within oncology populations has been established-with breast cancer, natural killer cells, and aerobic exercise featuring most prominently. As the field continues to expand, studies now include additional cancer types and treatments, different exercise modes, and unique cell populations that possess anti-tumor roles such as unconventional T cells (e.g., gamma delta, mucosal associated invariant, and natural killer T cells). However, several important considerations for future investigations remain. Presently, acute and chronic exercise have been examined separately. Emerging data have started to combine these approaches to identify age- or cancer-related dysfunction that is less apparent at rest. In breast cancer survivors, exercise training may attenuate the reductions in immune cell mobilization seen with following a single bout of activity. Additionally, including age-matched non-cancer controls provides context on the effectiveness of acute and chronic exercise relative to the optimal response. Finally, standardized techniques and outcome reporting is necessary so data can be pooled, and stronger conclusions can be drawn to further advance our field.

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Physical activity and exercise as therapeutic adjuvants for human blood cancers.

This presentation will summarise different avenues through which regular physical activity and/or structured bouts of exercise are being investigated as a means of improving anti-tumour outcomes in humans with blood cancers. Firstly, a synopsis will be given of findings relating to the direct anti-tumour effects of physical activity against blood cancer growth across the cancer survivorship continuum. Particular attention will be given to the cancer immunogram – an established biomarker model predicting the successful elimination of tumour cells by the immune system – and a summary will be given of why the cancer immunogram may explain how physical activity directly affects blood cancer outcomes in humans (i.e., reduced risk of a cancer diagnosis or cancer relapse). Secondly, an overview will be given of emerging clinical research relating to the adjuvant effects of structured bouts of exercise on the efficacy of immunotherapies in humans with blood cancers. Monoclonal antibody immunotherapies against tumour cells have become a mainstay in the treatment of blood cancers but their efficacy is often limited. Thus, a summary will be given of how acute structured bouts of exercise can be harnessed to improve immune cell kinetics to enhance the mechanism(s)-of-action of monoclonal antibody immunotherapies against blood cancers in humans. A main focus will be placed on anti-CD20 monoclonal immunotherapies in chronic lymphocytic leukaemia, but opportunities relating to other monoclonal antibody immunotherapies in B cell lineage cancers will be highlighted. Thirdly, an outline will be given of possible indirect effects of physical activity on blood cancer cells, with emphasis placed on the role of adipose tissue as a putative survival niche for blood cancer cells in humans.

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Aiming high in HI-AIM; A clinical testing of exercise in cancer

Immunotherapy of cancer has experienced tremendous breakthroughs over the past few years. Thus, the well characterized capacity of the immune system to recognize and kill cancer cells, is also being exploited in the clinic. However, predictive markers for response are largely missing, but infiltration into the tumor microenvironment has been shown in several studies to correspond to response. In this regard, we and others have shown in mouse tumor models, that exercise lead to an adrenalin mediated increase in influx of T and NK cells into the tumor in turn improving the chance for response to CPI therapy. We have therefore established the clinical trial HI AIM to test this in patients. HI-AIM (NCT04263467) is a randomized controlled trial (70 patients,1:1) aimed to investigate if high-intensive training can mobilize and activate the immune system, and thereby enhance the effect of the immunotherapy in patients with lung cancer. Besides routine oncological measures, blood samples and biopsies, will form the basis for immunological measurements of various cancer and immune system markers. Preliminary data shows successful exercise-mediated mobilization of immune cells to the peripheral blood, together with increasing adrenaline and noradrenaline levels. To this end, the functional impact of β2-Adrenalin Receptor (ß2-AR) signaling on immune cells is a double-edge-sword. We show that β2-AR activation in T cells, actually inhibit T cell cytokine secretion upon stimulation with high concentration of the β-AR agonist isoprenaline, but not at physiological concentrations. We believe that the HI AIM study will produce important data in the field of exercise-oncology/immunology.

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Changes in immune parameters after 12-week high-intensity interval training in men with prostate cancer undergoing active surveillance

BACKGROUND: Low-grade prostate cancers are often indolent, managed by active surveillance, where patients can avoid immediate invasive treatment, and are regularly monitored for any sign of disease progression. Preclinical evidence supports that chronic exercise can suppress prostate tumor progression, where exercise-induced modulations in markers of immune functions may play a significant role. However, there is a lack of human studies investigating the effects of exercise, particularly aerobic high-intensity interval training (HIIT), on immune function in men with prostate cancer. We conducted the Exercise During Active Surveillance for Prostate Cancer (ERASE) Trial, and here we report the effects of HIIT on immune parameters in men with prostate cancer undergoing active surveillance. METHODS: The ERASE Trial was a single-center, prospective, randomized controlled trial. Fifty-two men diagnosed with prostate cancer on active surveillance were randomized to either exercise (HIIT; n=26) or usual care (UC; n=26) groups. The HIIT intervention consisted of progressive, supervised, aerobic HIIT at an intensity of 85-95% VO2peak for 28-40 minutes per session performed thrice weekly for 12 weeks. Blood samples were collected after 12 hours of fasting and a minimum of 48 hours post-exercise. Immune cell phenotyping was conducted on freshly collected peripheral blood mononuclear cells using fluorescently labeled monoclonal antibodies followed by flow cytometry. Natural killer (NK) cell cytotoxicity was analyzed using the antibody-dependent cell cytotoxicity assay which involved lactate dehydrogenase (LDH) measurement using spectrophotometer. Proportions of CD3+, CD4+, CD8+, CD16+, and CD56+ in PBMC and cytotoxic NK cells were analyzed and reported as %. Analysis of covariance was used to determine between-group mean differences adjusted for baseline values and covariates. RESULTS: Average participants age was 63.4±7.1 years. The majority had the tumor stage of T1c (90%) and Gleason grade of 6 (96%). Blood data were obtained from 49/52 (94%) participants at postintervention and adherence to HIIT was 96%. Compared to UC, HIIT significantly increased NK cell cytotoxic activity (adjusted between-group mean difference, 2.7%; 95% confidence interval [CI], 0.1 to 5.3; p=0.039). Proportion of CD56+ in PBMC showed a trend to increase after HIIT compared to UC, but the difference did not reach statistical significance (2.1%; 95% CI, -0.1 to 4.2; p=0.064). No significant changes were found in the proportion of CD3+, CD4+, CD8+, and CD16+ cells in PBMC. CONCLUSION: A 12-week HIIT increased NK cell cytotoxicity and induced a meaningful trend of increase in NK cell proportion in men with low-grade prostate cancer undergoing active surveillance. Further research is warranted to identify whether the improvements in NK cell proportion and function can mediate the potential suppression of prostate cancer progression in active surveillance settings.

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Differences in exercise-induced immune response to melanoma models in mice

Advanced melanoma is a deadly cancer for which exercise may be a particularly useful therapeutic adjuvant. Immunotherapy has shown remarkable promise for treating patients with melanoma. Yet, a substantial portion of melanomas are immunologically cold, with a low neoantigen burden, and are resistant to immunotherapy. We hypothesized that aerobic exercise would improve the immune response to both immunologically cold and hot melanoma in mice, providing evidence that exercise may be an important adjuvant to immunotherapy for the treatment of melanoma. We used moderate treadmill running, initiated after the development of tumors, to treat mice bearing either B16F10 (immunologically cold) or YUMMER1.7 (immunologically hot) tumors for two weeks. Exercise increased the number of CD8+ T cells, as well as CD8 T cells expressing CD69 and PD-1, in YUMMER tumors. Excitingly, single cell RNA sequencing also identified changes in tumor myeloid cells which support an anti-tumor immune response in response to exercise. A decrease in M2 macrophages and MDSCs in YUMMER tumors from exercised mice was confirmed by flow cytometry. Contrary to our hypothesis, exercise was not sufficient to overcome the “cold” status of B16F10 and these effects were not seen in B16F10 tumors. These results as well as data which supports potential reasons for the differences in the effect of exercise in B16F10 and YUMMER models will be presented.

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Exercise in Pediatric Cancer

Pediatric cancer is a leading cause of death among children. Despite considerable improvements in survival rates in the last decades, therapeutic protocols often induce toxicities and long-lasting side effects. Furthermore, cancer might relapse as a refractory and metastatic cancer even during intense treatment protocols. Therefore, a deeper understanding of the biology of the different pediatric tumors, as well as of causes for relapse and metastasis, is required for developing less toxic and more effective treatments. In this context, recent advancements in immunotherapies and targeted therapeutic approaches represent an important step. Given its numerous benefits at the multisystem level—including immune function—another promising option is physical exercise, as explained below.

On the one hand, there is growing evidence for a protective association of regular physical activity and the risk of many prevalent adult cancers. A growing number of preclinical studies are providing insight into the biological mechanisms underlying the antitumoral effects of exercise, notably improved cancer immunosurveillance—which represents a quite important finding because evading immune destruction is a main hallmark of cancer and immunotherapy is reshaping cancer treatment in recent years. On the other hand, strong evidence has accumulated over the last two-three decades supporting the role of exercise practice as a co-adjuvant treatment to attenuate tumor/treatment side effects, notably cancer-related fatigue. Yet, many questions remain open in the context of pediatric cancer. The tumor biology indeed differs compared to most adult malignancies—among other differences, childhood tumors often develop in the context of an immature immune system—which raises alternative, fascinating questions. On the other hand, the preventive effects of an active lifestyle are likely to be less important than in adults given the very early occurrence in life of these tumors. Yet another problem is that a young survivor faces a whole lifetime of potential side effects aggravated by inactivity.

In my presentation as an international speaker in the 15th ISEI Symposium entitled ‘Exercise in pediatric oncology’, I will summarize the evidence accumulated over the years—including preclinical and clinical research—regarding the effects of exercise on the pediatric cancer continuum, with a special emphasis (but not only) on children’s immune function: from the first, pioneer study published in 1999 by Shore and Shephard, who assessed exercise training effects on the number and cytotoxic capacity of peripheral blood mononuclear cells in just three children with cancer (leukemia) receiving chemotherapy; to most recent efforts by international consortia, such as the recent EU-funded FORTEe (Get strong to fight childhood cancer) project, a multicenter exercise intervention for dozens of children and adolescents undergoing anti-cancer treatment against many types of malignancies around Europe, where patients’ physical fitness and health status (including immune function) will be studied in depth. I will also try to identify research caveats and the main questions to be addressed in future research.

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Human lymphocytes mobilized with exercise have an anti-tumor transcriptomic profile and exert enhanced graft-versus-leukemia effects in xenogeneic mice

BACKGROUND: Every bout of exercise mobilizes and redistributes large numbers of effector lymphocytes with a cytotoxic and tissue migration phenotype. The frequent redistribution of these cells is purported to increase immune surveillance and play a mechanistic role in reducing cancer risk and slowing tumor progression in physically active cancer survivors. Our aim was to provide the first detailed single-cell transcriptomic analysis of exercise-mobilized lymphocytes and test their effectiveness as a donor lymphocyte infusion (DLI) in xenogeneic mice engrafted with human leukemia. METHODS: Peripheral blood mononuclear cells (PBMCs) were collected from healthy volunteers at rest and at the end of an acute bout of cycling exercise. Flow cytometry and single-cell RNA sequencing were performed to identify phenotypic and transcriptomic differences between resting and exercise-mobilized cells using a targeted gene expression panel curated for human immunology. PBMCs were injected into the tail vein of xenogeneic NSG-IL-15 mice and subsequently challenged with a luciferase-tagged chronic myelogenous leukemia cell line (K562). Tumor growth (bioluminescence) and xenogeneic graft-versus-host disease (GvHD) were monitored bi-weekly for 40-days. RESULTS: Exercise preferentially mobilized NK-cell, CD8+ T-cell and monocyte subtypes with a differentiated and effector phenotype, without significantly mobilizing regulatory T-cells. Mobilized effector lymphocytes, particularly effector-memory CD8+ T-cells and NK-cells, displayed differentially expressed genes and enriched gene sets associated with anti-tumor activity, including cytotoxicity, migration/chemotaxis, antigen binding, cytokine responsiveness, and alloreactivity (e.g. graft-versus-host/leukemia). Mice receiving exercise-mobilized PBMCs had lower tumor burden and higher overall survival (4.14E+08 photons/s and 47%, respectively) at day 40 compared to mice receiving resting PBMCs (12.1E+08 photons/s and 22%, respectively) from the same donors ($p<0.05$). Human NK-cell and CD3+/CD4-/CD8- T-cell engraftment was largest in K562 challenged mice receiving exercise-mobilized lymphocytes, 1-2 weeks after DLI. No differences in GvHD or GvHD-free survival were observed between groups either with or without the K562 challenge. CONCLUSION: Exercise in humans mobilizes effector lymphocytes with an anti-tumor transcriptomic profile and their use as DLI extends survival and enhances the graft-versus-leukemia (GvL) effect without exacerbating GvHD in human leukemia-bearing xenogeneic mice. Exercise may serve as an effective and economical adjuvant to increase the GvL effects of allogeneic cell therapies without intensifying GvHD.

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Effect of a single bout of aerobic exercise on NK cell mobilization and infiltration in tumor tissue in prostate cancer patients

BACKGROUND: Initial preclinical studies have shown that physical exercise mobilizes IL6 sensitive natural killer cells (NK cells) to the tumor tissue thereby reducing tumor development and growth. Here we investigate in a first in human study whether these results can be transferred to the clinical setting. METHODS: For this purpose, in a randomized controlled trial, 22 patients suffering from prostate cancer who were scheduled for radical prostatectomy were divided into an intervention group (IG) and a control group (CG). While the CG remained inactive, the IG performed an aerobic exercise on a cycle ergometer for 30 minutes at 75% of the individual's peak oxygen consumption the evening before surgery. Blood samples were taken before (t1), directly after (t2) and twelve hours after the exercise intervention (t3). Besides the determination of IL-6 in blood serum, isolation of peripheral blood mononuclear lymphocytes was performed. Furthermore, CD56 positive NK cells were stained in the paraffin-embedded tumor tissue samples using immunohistochemistry. RESULTS: In addition to a twofold increase in IL6 in IG, we detected a redistribution and mobilization of NK cells in response to an acute bout of physical exercise. Subset analysis showed that especially NK cells with a cytotoxic phenotype (CD56dim) responded to exercise, in line with preclinical models. There was, however, no increase in the number of NK cells in tumor tissue samples. Notably, CD56dim NK cell counts determined immediately before surgery (t3) were associated with increased NK cell tumor infiltrates, whereas increased circulating pre surgical CD56bright NK cells were associated with decreased NK cell tumor infiltrates. CONCLUSION: Being one of the possible key mechanisms in exercise-induced tumor control, future studies should investigate a range of other tumor entities in the context of NK cell migration, in addition to an optimized study design, also including chronic exercise interventions.

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Effects of exercise on factors influencing the tumor microenvironment; Some Evidence, More Questions

The behavior of the Tumor Micro Environment (TME) can contribute to or inhibit the development and progress of a tumor and the likelihood of progression to metastasis. The elements of the TME include cells, the extracellular matrix, and blood vessels - elements that are likely influenced by inflammation, hormones, and oxidative stress. There are multiple factors that influence the TME that might be targets for exercise as therapy, including resolution of hypoxia, balancing redox status, hormonal alterations, and reduced inflammation. The TME contributes to metabolic activity of the tumor and is influenced by factors altered by exercise training. Tumor metabolism is of great interest to cancer researchers as a potential target for therapies. Multiple compounds, such as Gemcitabine, Enasidenib, and 5-Fluorouracil have already been tested for the inhibition of tumor metabolism and new approaches are being developed targeting metabolism of TME elements such as stromal or immune cells. The goal of this presentation will be to review the evidence as well as the potential for future research on exercise effects on factors influencing the tumor microenvironment.

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Gut Microbiota and Short-chain Fatty Acids in TLR5 Gene-deficient Mice

Toll-like receptors (TLRs) are receptors that play an important role in innate immune responses through the recognition of pathogen-associated molecules. TLR5, which is highly expressed in the intestinal tract, recognizes bacterial flagellar protein flagellin. Although TLR5-deficient mice develop metabolic disorders such as insulin resistance and obesity, exercise resolves them, and this might induce changes in the gut microbiota. Therefore, in this study, attempts were made to screen the bacteria and also examine short-chain fatty acids derived from gut microbiota. TLR5-deficient (KO5, n=16) and wild-type (WT, n=16) male mice (C57BL/6, 4 weeks old) were treated to exercise (W) or rest (C) for 20 weeks, respectively. Gut microbiota were identified from feces, and the short-chain fatty acids in the cecum were measured. The volcano plots method was used to visualize gut microbiota. KO5C mice had a higher rate of weight gain than WTC mice, and exercise significantly suppressed weight gain. The diversity of the gut microbiota was higher in KO5 mice and did not differ between mice with and without voluntary exercise. Diversity also reflected genetic influences. In short-chain fatty acids from gut bacteria, acetic acid and propionic acid were higher in KO5 mice and significantly lower in exercised ones, while butyric acid showed no difference. When attempts were made to extract species-level bacteria from the volcano plots method, Parabacteroides distasonis was extracted, which is known to induce anti-inflammatory cytokines, inhibit secretion of inflammatory cytokines, stabilize the gut microbiota, induce T reg, suppresse TLR4/Akt signaling, and reduce obesity in both obese patients and animal studies. The protective effect of spontaneous exercise on metabolic diseases in TLR5-deficient mice is accompanied by P. distasonis, which is involved in metabolism and immunity, as a significantly altered gut microbiota.

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Effect of training status and acute endurance exercise on metabolic signatures of CD4+ cells

BACKGROUND: Exercise is known as a physiological stressor for the body's metabolism. Moreover, it is a stimulus for the adaptive immune system. We tested if acute endurance exercise and training status have an effect on immunometabolic responses of CD4+ cells. METHODS: Fifteen healthy male participants (age: 24 ± 4; VO2max: 52.6 ± 5.7 ml/min/kg) were recruited. The subjects were tested for their maximal oxygen uptake (VO2max) and performed a treadmill run for 45-minutes at an intensity of 70% of individual VO2max. Intensity was controlled by adjusting the running speed via VO2. Before and 3 hours after exercise blood samples were taken to analyze leukocyte numbers and calculate inflammation indices. Freshly isolated CD4+ cells were incubated for 4 hours in serum, which was taken before and 3 hours after exercise. Mitochondrial respiration of CD4+ cells was measured using Oroboros O2k-Oxygraph. T cell subsets were analyzed by flow cytometry. Transcriptional profiles of CD4+ T-cells were examined by RNA-sequencing. RESULTS: Systemic inflammation index increased after exercise ($p<.05$). There were no significant differences in maximal cell respiration of CD4+ cells before and after exercise ($p>.05$). Participants VO2max showed a positive correlation to maximal electron-transfer-capacity ($r =.965$; $p =.014$). No significant differences in the composition of the CD4+ cell populations were found ($p>.05$). Several transcriptional programs related to mitochondrial energy metabolism were up-regulated in participants with higher VO2max. Moreover, transcription of genes related to NF-kappa B and p53 signaling pathways were suppressed. CONCLUSION: While acute exercise has no significant effect on CD4+ cell mitochondrial respiration, a clear association between mitochondrial respiration and cardiovascular fitness was found. The underlying reason for this does not appear to be a different composition of the cell population, but rather involves molecular adaptations of oxidative metabolism of CD4+ cells, which may also have consequences on T cell function and inflammation.

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Cutaneous in vivo immunity as a clinically relevant measure of respiratory infection burden in otherwise healthy young adults

BACKGROUND: Identifying clinically relevant measures of immune function is an important challenge for stress immunologists. Skin patch testing (contact hypersensitivity) with the novel antigen diphenylcyclopropenone (DPCP) has promise as research shows this method is sensitive to the influence of stressors. However, the clinical relevance of skin patch testing with DPCP, specifically with regards to respiratory infection, remains unknown. METHODS: In a prospective design, 53 healthy adults (55% males) were recruited during the Autumn-Winter and monitored daily for upper respiratory tract infection (URTI) symptoms for 13-weeks. After one-week without URTI, participants received a sensitizing dose of DPCP on the lower back, and two-weeks later, also when healthy, the strength of immune reactivity was quantified by measuring the summed dermal thickening and erythema responses to a low dose-series challenge with DPCP on the upper inner arm. Low and high DPCP responders were determined by median split. URTI incidence, severity, duration and symptom score (severity x duration) were determined. Excluded from analysis were N=7 who suffered URTI during the DPCP sensitization and recall time-period and N=5 who withdrew. RESULTS: Half of participants who completed the monitoring period reported URTI (N=20 of 41). Although there was no difference in URTI incidence, low DPCP responders suffered 54% more days with URTI, reported 21% more severe URTI symptoms and 70% greater URTI symptom score than high DPCP responders ($P < 0.05$). Significant negative relationships were observed between DPCP responses and URTI severity ($r = -0.37$) and URTI symptom score ($r = -0.39$). DPCP response was also lower in those reporting severe compared with mild URTI symptoms during the monitoring period (43%; severe: 3.1 ± 2.5 mm vs mild: 5.4 ± 3.5 mm; $P < 0.05$). CONCLUSION: These findings provide preliminary support for skin patch testing using DPCP as a clinically relevant measure of respiratory infection burden.

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Impact of genetically modified Lactobacillus Paracasei probiotic designed to express Angiotensin (1-7) combined with exercise training in an aging male rat model: evidence for altered neuro-remodeling and inflammation gene expression

Angiotensin (1-7) [Ang (1-7)] is a bioactive peptide of the renin-angiotensin system that modulates relevant signaling pathways associated with vascular and cellular inflammation, vasoconstriction, hyperplasia and fibrosis in many organs. Still, current pharmacokinetics properties limit its applicability in clinical care. Therefore, we developed a gut microbiota-targeted therapeutic method, a genetically modified probiotic (GMP) designed to express Ang (1-7), and tested it as an adjunct therapy to exercise training to enhance physical and cognitive function in an aging rat model. Our goal is to determine if combining our GMP with moderate exercise training enhances host gut health and modulates local and peripheral transcriptional responses in several regulatory organs. This 3x2 preclinical trial randomized sixty-three F344BN male rats aged 24-months to one of three treatments: (i) buffer (n= 25); (ii) a probiotic- Lactobacillus Paracasei (LP; n= 22); and to, (iii) a GMP- LP engineered to express Ang (1-7) (n= 17). Treatment groups were orally gavage with 2x1011 CFU/kg body weight of probiotics or an equal volume of buffer (3x/week). These groups were further randomized to a moderate treadmill exercise intervention (5 days/week) or to a control group (n= 8-13/group). After 12-weeks intervention, blood, feces, prefrontal cortex, liver and skeletal muscle were collected for multiomics analysis. Microbiome analysis revealed that our GMP altered α diversity while exercise training enhanced β-diversity across groups. Our GMP reduced the relative abundance of 3 genera. Transcriptomics analysis showed that our multimodal intervention upregulated gene expression of inflammation signaling pathways on prefrontal cortex and liver (FDR <0.10 & Log2FoldChange> 1.0). Our findings suggests that our GMP enhances gut health by altering the abundance of endotoxic generas and upregulating anti-inflammatory gene expression on pre-frontal cortex and liver. Further research is needed to determine the exact mechanism of gut-microbiota-brain crosstalk modulated by our combined intervention.

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Acute exercise increases NK cell mitochondrial respiration and effector functions under hypoxic conditions

Triple-negative breast cancer (TNBC) is an aggressive, highly metastatic malignancy with, high recurrence rates. One hallmark of the TNBC tumor micronenvironment is hypoxia, which promotes tumor growth, while impairing NK cell cytotoxic functions. Although acute exercise improves NK cell function under normoxic conditions, it is unknown if exercise increases NK cell function under hypoxic conditions. Method: Thirteen inactive healthy women (mean ± SD: age 26.9±4.5 y) completed 30 minutes of cycling at power outputs corresponding to 10% above their lactate threshold. Resting and post-exercise NK cells were isolated, and co-cultured with TNBC cells in either hypoxic (1% of O2) or normoxic conditions (21% of O2) for 4 hours. Following incubation, mitochondrial respiration and H2O2 production rates of the TNBC-activated NK cells were measured via high-resolution respirometry and specific lysis of TNBC was measured by flow cytometry. Results: Under hypoxia, post-exercise NK cells exhibited greater killing of TNBC than resting NK cells (10:1 E-T ratio hypoxia pre-exercise:7.80±5.27 % vs. hypoxia post-exercise:10.67±7.63%; $p<0.05$). Further, post-exercise NK cells were more likely to kill TNBC under hypoxia, compared to normoxic conditions. Routine mitochondrial respiration of TNBC-activated NK cells was greater in post-exercise cells than resting cells under normoxic conditions (pre-exercise:8.94±3.80 pmols/s/million vs. post-exercise: 11.33±1.84 pmols/s/million; $p<0.001$), but not under hypoxia ($p>0.05$). Acute exercise was also associated with reduced mitochondrial H2O2 production in both conditions ($p<0.01$). Discussion: This is the first study to identify the interrelationship between hypoxia and exercise-induced changes in NK cell function against TNBC cells, and how acute exercise modulates NK cell mitochondrial bioenergetic functions. Specifically, NK cell O2 and H2O2 flow (pmols/s/million) changes in response to 30min cycling suggest that exercise primes NK cell tumor killing by reducing mitochondrial oxidative stress, and thus rescuing their function when exposed to harsh hypoxic environments as observed in the microenvironment of breast solid tumors.

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Sex-based differences in leukocyte, endothelial, and platelet derived extracellular vesicles in healthy adults

Extracellular vesicles (EVs) are implicated in inter-cellular/organ crosstalk mediating the adaptive responses to exercise. An important first step towards understanding exercise-induced EV responses is to determine if there are biological sex differences in EV subpopulations. Using contemporary EV isolation techniques and nano-flow cytometry, our objectives were to: i) optimize a protocol to accurately characterize circulating leukocyte, endothelial cell, and platelet derived EVs; ii) determine if sex differences exist; and iii) explore the influence of acute exercise.

Fasted blood samples were obtained from healthy males (n=16; age=29±6 years, BMI=25±2 kg/m2) and females (n=16; age=27±5 years; BMI=23±2 kg/m2) in sodium citrate tubes, centrifuged at 2,500 x g for 15 minutes at 4°C to obtain platelet-depleted plasma and stored at -80°C for batch analysis. Samples were thawed, debris removed, and stained with antibodies (CD3, CD14, CD16, CD31, CD41, CD45, CD62E) prior to size-exclusion chromatography using 70 nm columns. Samples were then diluted 120-fold and analyzed on a CytoFLEX-S nano-flow cytometer using the 405nm violet side-scatter configuration. A proof-of-concept study in males (n=3) obtained blood samples immediately before and after a 15-minute cycling time trial and measured EVs using identical techniques.

Independent samples T-tests revealed no significant differences in EVs between males and females, though CD14+ and CD41+ EVs in the 200–900 nm range, and CD31+/CD62E+ EVs in the sub 200 nm range tended to be higher in females (all $P<0.11$) with medium effect sizes ($d=0.52$-0.7). In the proof-of-concept exercise study, all three participants experienced robust changes in CD3+ (~2-fold), CD14+ (~2.1-fold) and CD16+ (~3.4-fold) EVs following the 15-minute cycling time trial, supporting the sensitivity of our methods for detecting expected changes in circulating EVs.

There were no observable differences between healthy males and females in EV subpopulations at rest. Future research using these techniques is warranted to explore the influence of exercise.

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Metabolic regulation of innate immunity by exercise-derived metabolites

There is a growing recognition that immune responses are coordinated by cellular metabolic pathways, and that immune cells respond to stresses such as infection and inflammation by reprogramming their metabolism. Preferential usage of specific catabolic pathways for ATP production has been demonstrated for a variety of immune cells, with reprogramming towards glycolytic metabolism during pro-inflammatory activation probably the most well-characterized. However, it is now understood that immune function is also modulated by both intracellular and extracellular metabolites, which act as signaling molecules to affect immune cell function. Several of these are highly relevant to exercise, including lactate and succinate among others. Our laboratory has demonstrated glycolytic reprogramming of monocytes under stimulation by proteins from the recent pandemic SARS-CoV-2. Glycolytic activation can be suppressed by lactate, which also shifts gene expression of cytokines toward a more anti-inflammatory state. Additionally, disruption of the TCA cycle through inhibition of succinate dehydrogenase suppresses inflammation in treated monocytes, suggesting an anti-inflammatory state during succinate accumulation. As high-intensity exercise promotes increases in both lactate and succinate, systemic increases in exercise-derived metabolites are a plausible explanation for transient post-exercise immune suppression seen in some (but not all) experimental paradigms involving intense exercise. Exercise-derived metabolites may suppress inflammatory responses through a variety of mechanisms, including regulation of metabolic enzymes as well as epigenetic changes.

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Exercise and Immunometabolism in Inflammation and Obesity. The role of metabolic sensors and physical fitness in immune cells

BACKGROUND: Immunometabolism is an emergent research field focused in understanding of the metabolic pathways in immune cells, and how the energetic status can modify proliferation, differentiation and function of immune cells. Metabolic sensors as AMPK, mTORc and PPAR-γ are pivotal in the control of metabolism of these immune cells and currently we observed interaction between these sensors, immune cells fate decision and function. The excess of nutrients, for example, can induce metabolic reprogramming by chronic activation of mTORc1 and inhibition of AMPK in immune cells that induce the classical activation of macrophages and Th1 and Th17 differentiation of T cells. Furthermore, the fatty acids are the main regulators of PPAR-γ activation in immune cells and this balance between metabolic sensors are crucial to determinate the polarization and function of immune cells. On the other hand, the regular physical activity is well-known by an anti-inflammatory milieu and considered a non-pharmacological therapy. Hypothesis: our hypothesis is that the acute and chronic exercise are capable to induce different metabolic adjustments in immune cells and promote modification in AMPK, mTORc and PPAR-γactivation, mitigating the effects of obesity and sedentarism. AIM: Our group has been focused in explore the molecular mechanisms associated with the better immunometabolic response in athletes and as this can be relieving the side effects of obesity over the immunity. METHODS: We have been using animal models and human studies to investigate the role of physical fitness and how acute and chronic exercise modify the immunometabolic response and how the overweight and obesity affect the metabolism and function of immune cells. CONCLUSION: Until now, both physical fitness and obesity have shown effects on metabolic sensors and in immune responses. Still, more studies based on the effect of exercise and the role of each metabolic sensor in immunometabolic response are needed.

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Adipose tissue as a determinant of inflammation and insulin resistance in obesity and aging

Adipose tissue is a metabolically active endocrine organ that plays an important role in overall metabolic health. Adipose tissue inflammation, which is characterized by the infiltration and activation of leukocytes and the production and secretion of pro-inflammatory cytokines, is proposed to lie at the nexus of many metabolic derangements through both local and systemic processes. Within adipose tissue, inflammation impairs adipocyte differentiation and inhibits insulin signaling. Acting as an endocrine organ, the secretome of inflamed adipose tissue can affect peripheral tissues. Our lab has identified significant adipose tissue inflammation in older adults and in individuals with obesity; populations that also often exhibit systemic inflammation and insulin resistance. Further, our recent observations demonstrate strong associations between adipose tissue macrophage burden and whole-body insulin sensitivity and systemic inflammation in individuals with obesity. Once considered an inert storage depot for fat, adipose tissue is increasingly recognized as a highly metabolically active tissue and an important endocrine organ that affects peripheral tissue through the release of adipose-derived extracellular vesicles (ADEVs), adipokines, cytokines and lipids. Understanding the effects of aging, obesity, and physical activity on adipose tissue will inform our understanding of the causes of inflammation and metabolic dysfunction and could lead to the identification of therapeutic targets for improving metabolic health.