Hotel Albuquerque at Old Town Albuquerque, USA

March 20, 2024

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Geroscience Translational Clinical Trials / ICFSR TASK FORCE

* **Translational Research on Mitochondria Aging Muscle, Sarcopenia and Frailty: from Biological Assessment to Drug Development**

* **Patient-Reported Outcomes in Frailty and Sarcopenia**

Luigi Ferrucci (USA)
Roger Fielding (USA)
Bruno Vellas (France)

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ICFSR
International Conference on Frailty & Sarcopenia Research

GEROSCIENCE / ICFSR TASK FORCE
Translational Research on Mitochondria Aging Muscle, Sarcopenia and Frailty: from Biological Assessment to Drug Development
&
Patient-Reported Outcomes in Frailty and Sarcopenia

March 20, 2024, Albuquerque (New Mexico - USA)

PROGRAM

7.00 am — **Welcome coffee and networking**

8.00 – 8.15 am — **Introduction:** *Luigi Ferrucci* (Baltimore, MD, USA), *Roger Fielding* (Boston, MA, USA), *Bruno Vellas* (Toulouse, France, Albuquerque NM, USA), *Mark McCormick* (Albuquerque, NM, USA), *Debra Waters* (Albuquerque, NM, USA and Otago, New Zealand), *Nathan LeBrasseur* (Rochester, MN, USA)

MITOCHONDRIA

Moderators: Luigi Ferrucci[1], Bruno Vellas[2]
1. National Institute on Aging *(Baltimore, MD, USA)*
2. IHU HealthAge CHU Toulouse *(Toulouse, France)*

8.15 – 8.30 am — Overview on Mitochondria and Aging from Biomarkers to Therapies
Luigi Ferrucci
National Institute on Aging (NIA) *(Baltimore, MD, USA)*

8.30 – 8.45 am — Energizing Aging Research: Mitochondrial Bioenergetics for Biomarker and Target Discovery in the Inspire-T Cohort
Laurent Martinez
Institute of Metabolic and Cardiovascular Diseases *(Toulouse, France)*

8.45 – 9.00 am — Longevity Intervention in Nematodes and Mice models
Mark McCormick
University of New Mexico *(Albuquerque, NM., USA)*

9.00 – 9.30 am — **Discussion**
Chaired by: Luigi Ferrucci, Bruno Vellas
with Task Force Participants*: Amos Baruch *(San Francisco, USA)*, Angelo Parini *(Toulouse, France)*, Ann Beliën *(Diepenbeek, Belgium)*, Carla Delannoy *(Vevey, Switzerland)*, Francesco Landi *(Rome, Italy)*, Jamie Justice *(Winston-Salem, USA)*, Jérome Feige *(Vevey, Switzerland)*, Laure Rouch *(Toulouse, France)*, Luis Miguel Gutierrez Robledo *(Mexico City, Mexico)*, Marco Canevelli *(Rome, Italy)*, Mylène Aubertin *(Montreal, Canada)*, Nuria Barcons *(Barcelona, Spain)*, Philipe Barreto *(Toulouse, France)*, Ruitai Shao *(Beijing, China)*, Sandrine Andrieu *(Toulouse, France)*, Stefanie Rau *(Germany)*, Suzette Pereira *(Columbus, USA)*, Cendrine Tourette *(Paris, France)*, Waly Dioh *(Paris, France)*, Susanna Del Signore *(London, United Kingdom)*, Mark Roithmayr *(New York, USA)*, Heike Bischoff-Ferrari *(Toulouse,*

France), Sophie Guyonnet *(Toulouse, France)*, Gary Rosenberg *(Albuquerque, USA)*, Mariá Nunes Pinto *(Brazil)*, Reshma Merchant *(Singapore)*, Rob van Maanen *(Paris, France)*, John Muscedere *(Kingston, Canada)*, Anne Newman *(Pittsburgh, USA)*, Ara Khachaturian *(Rockville, USA)*, Mark Roithmayr *(New York, USA)*, Heike Bischoff-Ferrari *(Toulouse, France)*, Sophie Guyonnet *(Toulouse, France)*, Gary Rosenberg *(Albuquerque, USA)*, Mariá Nunes Pinto *(Brazil)*, Brian Rash *(Miami, USA)*, Aubrey de Grey *(Culver City, USA)*, David Furman *(Novato, USA)*, Felipe Court *(Santiago, Chile)*

MITOCHONDRIA continued

Moderators: Rafael de Cabo, Felipe Sierra

1. National Institue on Aging *(Baltimore, MD, USA)*
2. Hevolution Foundation *(Boston, MA, USA)*

9.30 – 9.45 am — Mitochondria function and aging what we have learned so far from mice cohort
Rafael de Cabo
National Institute on Aging *(Baltimore, MD, USA)*

9.45 – 10.00 am — Muscle mitochondrial energetics and human aging: the Study of Muscle, Mobility and Aging (SOMMA)
Paul Coen
Translational Research Institute for Metabolism and Diabetes, Advent Health *(Orlando, FL, USA)*

10.00 – 10.15 am — Therapeutically targeting skeletal muscle mitochondrial bioenergetics to improve physical function and reduce fatigability
Daniel Forman
Department of Medicine, Cardiology, Geriatrics, University of Pittsburgh *(Pittsburgh, PA, USA)*

10.15 – 10.45 am — **Discussion**
Chaired by: Rafael de Cabo, Felipe Sierra, Cédric Dray
with Task Force Participants*

MITOCHONDRIA continued

Moderators: Gustavo Duque[1], John Newman[2]

1. Research Institute of the McGill University Health Centre *(Montreal, QC, Canada)*
2. Buck Institute for Research on Aging *(Novato, CA, USA)*

10.45 – 11.00 am — Mitochondria and stem cells in the treatment of aging frailty
Brian Rash
Longeveron Inc. *(Miami, FL, USA)*

11.00 – 11.15 am — A Geroscience approach to musculoskeletal disease: Can we treat two birds with one stone?
Gustavo Duque
Research Institute of the McGill University Health Centre *(Montreal, QC, Canada)*

11.15 – 11.25 am — Results of a safety and tolerability pilot study of a randomized, parallel group, double-blind, placebo-controlled trial of a novel ketone ester targeting frailty via immunometabolic geroscience mechanisms.
John Newman
Buck Institute *(Novato, CA, USA)*

11.25 – 11.35 pm — Pathologic mitophagy in local neurites induces mitochondrial plaques in Alzheimer's disease
Xiuli Dan
University of Minnesota *(Minneapolis, MN, USA)*

11.35 – 11.45 pm Inhibition of arachidonic acid conversion is a novel senolytic target
Johannes Grillari
University of Natural Resources and Life Sciences and Center for Biomedical Research and Translational Surgery, Medical University of Vienna *(Vienna, Austria)*

11.45 – 12.15 pm **General discussion**
Chaired by: Gustavo Duque, John Newman
with Task Force Participants*

12.15 – 1.15 pm Lunch

PATIENT-REPORTED OUTCOMES

Moderators: Roger Fielding[1], Yves Rolland[2]
1. Research Institute of the McGill University Health Centre *(Montreal, QC, Canada)*
2. IHU HealthAge CHU Toulouse *(Toulouse, France)*

1.15 – 1.30 pm Overview of Patient-Reported Outcomes for Frailty and Sarcopenia
Roger Fielding
Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts, University Boston Claude D. Pepper Older Americans Independence Center *(Boston, MA, USA)*

1.30 – 1.45 pm Patient-reported and performance outcomes relevant to sarcopenia
David Cella
Northwestern Medicine, Feinberg School of Medicine, Northwestern University *(Chicago, IL, USA)*

1.45 – 2.00 pm Patient-reported outcomes in Sarcopenia
Charlotte Beaudart
NARILIS (NAmur Research Institute for LIfe Sciences), Namur University *(Namur, Belgium)*

2.00 – 2.30 pm General discussion
Chaired by: Roger Fielding, Yves Rolland
with Task Force Participants*

Task Force Participants*: Amos Baruch *(San Francisco, USA)*, Angelo Parini *(Toulouse, France)*, Ann Beliën *(Diepenbeek, Belgium)*, Carla Delannoy *(Vevey, Switzerland)*, Francesco Landi *(Rome, Italy)*, Jamie Justice *(Winston-Salem, USA)*, Jérome Feige *(Vevey, Switzerland)*, Laure Rouch *(Toulouse, France)*, Luis Miguel Gutierrez Robledo *(Mexico City, Mexico)*, Marco Canevelli *(Rome, Italy)*, Mylène Aubertin *(Montreal, Canada)*, Nuria Barcons *(Barcelona, Spain)*, Philipe Barreto *(Toulouse, France)*, Ruitai Shao *(Beijing, China)*, Sandrine Andrieu *(Toulouse, France)*, Stefanie Rau *(Germany)*, Suzette Pereira *(Columbus, USA)*, Cendrine Tourette *(Paris, France)*, Waly Dioh *(Paris, France)*, Susanna Del Signore *(London, United Kingdom)*, Reshma Merchant *(Singapore)*, Rob van Maanen *(Paris, France)*, John Muscedere *(Kingston, Ontario, Canada)*, Anne Newman *(Pittsburgh, USA)*, Ara Khachaturian *(Rockville, USA)*, Mark Roithmayr *(New York, USA)*, Heike Bischoff-Ferrari *(Toulouse, France)*, Sophie Guyonnet *(Toulouse, France)*, Gary Rosenberg *(Albuquerque, USA)*, Mariá Nunes Pinto *(Brazil)*, Brian Rash *(Miami, USA)*, Aubrey de Grey *(Culver City, USA)*, David Furman *(Novato, USA)*, Felipe Court *(Santiago, Chile)*

3.00 pm **ICFSR Conference**

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SHORT PARTICIPANT PRESENTATIONS

Andrieu Sandrine

Sandrine Andrieu is physician and professor of public health, chair of the clinical epidemiology and public health department at the Toulouse University Hospital and adjunct professor at the University New Mexico (USA). Since 2009, she's responsible of aging research team in the center for Epidemiology and research in population health. She served as director of the research center for Epidemiology and research in population health (UMR1027 Inserm University Paul Sabatier now CERPOP UMR1295 Inserm) from 2011 to 2020. She published more than 300 international papers and book chapters in the field of aging. She was involved in large prevention studies in the field of neuro-degenerative disease (GuidAge, MAPT) and in European projects (HATICE study, MIND-AD, PRODEMOS study). Her main topic of research is prevention of age-related loss of functions, and healthy aging. She's past-president of the French National Society of Geriatrics and Gerontology. As a member of IHU HealthAge, she's responsible of a large preventive trial to demonstrate ICOPE efficacy.

Aubertin-Leheudre Mylène

Dr. Aubertin-Leheudre is a full professor-researcher at UQAM/CRIUGM and holds a Tier 1 Canada Research Chair (CIHR). She is also Associate Director of Clinical Research at the Centre de Recherche de l'Institut Universitaire de Gériatrie (CRIUGM) and Scientific Advisor to the FRQS (Fonds de Recherche en Santé du Québec). She holds more than $6 million in grants as a nominated PI and has published more than 150 articles. Since 2009, her research program aims to understand better how muscle function can be improved and maintained throughout the lifespan. Her empirical work focuses on 1) changes in muscle function & mobility that occur with normal aging and; 2) identifying the determinants of muscle function & mobility across the lifespan (e.g., lifestyle habits, physical fitness, chronic diseases, nutritional supplementation, adipose tissue etc.). Overall, her research examines the effects of adapted physical activity training and sedentary behavior on muscle function in older adults across the lifespan.

Barcons Núria

Núria Barcons is a Registered Dietitian Nutritionist (RND) and holds a bachelor's degree in Human Nutrition and Dietetics from the University of Navarra (Spain). She works as a Global Medical Affairs Lead for Adult Medical Care at Nestlé Health Science. She is responsible for Medical Leadership, Medical education and Communication, and Real World Evidence generation for the Oral Nutritional Supplements (ONS) and Dysphagia portfolios at a global level. She has more than 20 years of experience in the pharmaceutical industry as a Medical Affairs in the field of disease-related malnutrition.

Baruch Amos

Dr. Amos Baruch earned his Ph.D. in Biochemistry and Cell Biology from Tel Aviv University in 1998. Following his graduation, he relocated to the United States for postdoctoral research, first at the Scripps Research Institute and then at the Department of Biochemistry and Biophysics at UCSF. His career progressed at Celera Genomics, where he headed the Chemical Proteomics Group. In 2006, Dr. Baruch's career took a pivotal turn when he joined KAI Pharmaceuticals. There, he led preclinical research efforts that culminated in the discovery of Parsabiv® (etelcalcetide), which is now a treatment for end-stage renal disease. Dr. Baruch spent the next decade at Genentech, leading Translational Medicine efforts and advancing Biomarker Development in cardiovascular disease, metabolism, and neurodegeneration. Currently, Dr. Baruch is at the helm of the Biomarker Department at Calico Life Sciences in South San Francisco, CA, where his team is dedicated to pioneering Biomarker Science for the study of aging and age-related diseases in humans.

Beaudart Charlotte

Dr. Charlotte Beaudart, PhD in public health (2016), is full-time lecturer of Clinical Research at the University of Namur, Belgium. She is currently affiliated to the Department of Biomedical Sciences within the Research Institute for Life Sciences (NARILIS) at the Faculty of Medicine, University of Namur, Belgium. Over the past 11 years, her primary focus has revolved around the intricate aspects of aging, delving into areas such as sarcopenia, frailty, and intrinsic capacities. Beyond those research acumen, Dr. Beaudart has cultivated expertise in various methodological domains including patient preference studies and cost-effectiveness analyses but also meta-synthesis, encompassing systematic reviews, network meta-analysis and individual participant data meta-analysis. Her mastery extends to Patient Reported Outcome Measures, where she focuses on the development, validation, and statistical analysis of psychometric properties. Dr. Beaudart is renowned for developing the SarQoL, the world's first quality of life questionnaire tailored specifically for sarcopenia. She currently has a publication record of over 150 scientific publications, including 35 as first author, and

an h-index of 39. Dr. Beaudart is also a member of the WHO Collaborating Center for Epidemiology of Musculoskeletal Health and Aging, housed within the Division of Public Health, Epidemiology, and Health Economics at the University of Liège, Belgium. Furthermore, she serves as a board member of the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis, and Musculoskeletal Disease (ESCEO).

Beliën Ann

Dr. Ann Beliën founded Rejuvenate Biomed in 2017, where she currently functions as CEO. Under her leadership, Rejuvenate Biomed transitioned from a discovery start-up to a clinical-stage biotech company. Ann has successfully attracted international investors, securing funds from seed stage to series B, and built a dedicated and capable team that shares her vision. Together, they are committed to developing safe combination drugs to improve the lives of patients with age-related diseases and promote healthy aging. Ann brings more than 2 decades of experience in drug development, covering the entire journey from the laboratory bench to the market. She gained this extensive experience through a range of international assignments in the United States, the Netherlands, and Belgium. Ann evolved from scientific roles to operational and strategic positions in various therapeutic areas, including oncology, neurology, immunology, and infectious diseases. She has also been actively involved in external and open innovation, with a focus on therapeutics and prevention. During her career, Ann served as a due diligence representative for R&D at Johnson & Johnson (J&J). She was also a member of the management board of Janssen Prevention Center for a period of five years. She joined J&J in 2000, after completing her postdoctoral research at ETH in Zürich, Switzerland. Ann holds a PhD from the University of Irchel in Zürich, Switzerland, and a master's degree from the Free University of Brussels (VUB), Belgium. In summary, Dr. Ann Beliën has a wealth of experience in drug development and has played pivotal roles in the growth and success of Rejuvenate Biomed, where her focus is on improving the lives of patients with age-related diseases and promoting healthy aging.

Canevelli Marco

Marco Canevelli is Assistant Professor of Neurology at the Department of Human Neuroscience, Sapienza University of Rome, Researcher at the Italian National Institute of Health, and Visiting Assistant Professor at the Aging Research Center, Karolinska Institutet. He is member of the Scientific Committee of the Italian Society for the Study of Dementia (SINdem), secretary of the Italian Society of Neurogeriatrics, and Member of the Italian Dementia National Plan Working Group. He is the principal investigator of the «Dementia in immigrants and ethnic minorities living in Italy: clinical-epidemiological aspects and public health perspectives» (ImmiDem) project. He is the Editor-in-Chief of the Journal of Frailty and Aging, and member of the editorial board of the Journal of Alzheimer's disease, JAMDA, and Journal of Nutrition Health & Aging. His main research interests deal with the epidemiology of cognitive disorders, frailty in dementia and other neurological diseases, and dementia in migrants.

Cella David

David Cella, PhD is Professor and Founding Chair of the Department of Medical Social Sciences at Northwestern University Feinberg School of Medicine. He is an elected member of the National Academy of Medicine (NAM) and the Academy of Behavioral Medicine Research, and a fellow of the American Society of Clinical Oncology. Dr. Cella has led development of the Functional Assessment of Chronic Illness Therapy (FACIT) Measurement System, the NIH Patient Reported Outcome Measurement Information System (PROMIS), the Neurology Quality of Life (Neuro-QoL) Measurement System, and the Emotional Health domain of the NIH Toolbox. He studies quality-of-life in clinical trials, cross-cultural equivalence of quality of life measurement, and healthcare quality. He has published more than 1,000 peer-reviewed articles, most of which focus on the unique contribution that the patient perspective has upon the evaluation of health and health care. Dr. Cella's work brings the patient voice into consideration of value and opportunities for improvement on the healthcare system. He was awarded the NAM Gustav O. Lienhard Award for Advancement of Health Care in 2016 and received the 2023 Northwestern Tripartite Legacy Faculty Prize in Translational Science and Education, recognizing excellence in translational research, teaching, and leadership.

Coen Paul

Dr. Paul Coen is an Associate Investigator at the Translational Research, AdventHealth Orlando with a 15-year track record of translational research in the areas of aging, mitochondrial energetics and skeletal muscle metabolism. The primary focus of his research is to understand the mechanisms for the loss of muscle function with aging and disuse, as well as identify novel therapeutic targets. He has broad experience in clinical translational research in aging from acute/chronic exercise and bed rest interventions to the technical aspects of state-of-the-art human metabolic phenotyping, including glucose clamps, calorimetry, echocardiography, body composition (MRI, DXA), and cardiopulmonary fitness testing. Dr. Coen is also on the investigator team for large multisite studies, including the Study of Muscle Mobility and Aging (SOMMA) and the NIH Common Fund Consortium project MoTrPAC. Dr. Coen has served as an ad-hoc reviewer for NIH CSR Study Sections (ASG, SMEP) numerous times, serves on the American College of sports Medicine's strategic health initiative on aging (SHI-A) and has been invited to give talks at national and international

meetings (ADA ACSM, ECSS, ICFSR). Dr. Coen's work to-date has been published in journals including the Journal of Clinical Investigation, Diabetes, and Aging Cell.

Dan Xiuli

Dr. Dan is a highly self-motivated researcher interested in understanding the nature of aging and aging-related neurodegenerative diseases from the aspect of mitochondrial dysfunction. After Ph.D. training in Biomedical Sciences at the Chinese University of Hong Kong, Dr. Dan undertook postdoctoral studies under the mentorship of Dr. Vilhelm A Bohr at National Institute on Aging, National Institutes of Health, where she became interested in mitochondrial dysfunction in aging, premature and neurodegenerative diseases. She then joined the laboratory of Dr. Paul. D Robbins at the University of Minnesota where she held the position of senior research fellow and developed further interest in mitochondrial dysfunction in Alzheimer's disease (AD) and cellular senescence.

De Cabo Rafael

After receiving his B.S. and M.S. from the University of Cordoba, Spain, Dr. de Cabo earned his Ph.D. in 2000 from the Department of Foods and Nutrition at Purdue University. Upon completing his graduate education, he received a postdoctoral position in the Laboratory of Neurosciences at the National Institute on Aging in Baltimore, Maryland. In 2004, he was appointed as a tenure-track investigator in the Laboratory of Experimental Gerontology. He is now a senior investigator and Chief of the Translational Gerontology Branch at NIA. His research has focused on the effects of nutritional interventions on basic mechanisms of aging and age-related diseases and on improving our understanding of the molecular mechanisms for the effects of caloric restriction on aging and pharmacological interventions for healthy aging. Ultimately his research aims to identify interventions that will improve healthspan and lifespan with translational potential to benefit human aging. He is the author or co-author of 350 publications with an h index of 112. Dr. de Cabo's has received multiple honors and awards including most recently the Irving Wright from AFAR and the Denham Harman Award (2023) of the American Aging Association, Dr de Cabo is Deputy Editor in Chief, the Journal of Gerontology Biological Sciences and serves on the editorial boards of Aging Cell, BBA-Molecular Mechanisms of Disease, Aging Research Reviews, Longevity & Healthspan, Impact Aging, AGE and is one of the founding editors of Microbial Cell.

de Grey Aubrey

Dr. Aubrey de Grey is a biomedical gerontologist based in Silicon Valley, California, USA, and is the founder, President and Chief Science Officer of LEV Foundation, a biomedical research and advocacy charity focused on repairing the molecular and cellular damage of aging. He received his BA in computer science and Ph.D. in biology from the University of Cambridge. His research interests encompass the characterisation of all the types of damage that constitute mammalian aging and the design of interventions to repair and/or obviate that damage. Dr. de Grey is a Fellow of both the Gerontological Society of America and the American Aging Association, and sits on the editorial and scientific advisory boards of numerous journals and organisations. He is a highly sought-after speaker who gives frequent invited talks at scientific conferences, universities, companies in areas ranging from pharma to life insurance, and to the public.

De Souto Barreto Philipe

Philipe de Souto Barreto is Professor of Gerontology (Université Paul Sabatier Toulouse 3) and coordinates the Institute on Aging at the Gerontopole, Toulouse University Hospital (WHO Collaborating Center on Frailty, Clinical & Geroscience Research & Geriatric Training). PhD in Bio-cultural Anthropology, he has leaded and participated in international taskforces, particularly on topics related to exercise and frailty. Philipe contributed to several national and international research projects as PI, local PI, and co-investigator (including the INSPIRE platform on Geroscience). Dr Barreto has been invited speaker at national and international congresses and has published hundreds of papers in prestigious Journals. He is Editor-in-Chief of the Journal of Nutrition, Health & Aging»

Del Signore Susanna

Susanna is an M.D., holding a certificate in internal medicine. She is expert in designing and conducting clinical trials in older adults, from phase1 to phase3. Since 2006, she engaged against the exclusion of older adults from confirmatory studies. On behalf of the European Medicines Agency, she triggered and contributed to the revision of ICH E7 guidance on Geriatrics. On behalf of Sanofi R&D she launched the Physical Frailty & Sarcopenia IMI call, later becoming the SPRINTT project1. Former CMO of Biophytis, she launched the SARA program2. In 2015 with Gianluca Zia and Stefania Del SIgnore, she founded Bluecompanion, a UK based company focused on the design and implementation of e-health services, of digital platforms of clinical trials and to facilitate academia-driven collaborative projects 3,4. 1. Multicomponent intervention to prevent mobility disability in frail older adults: randomised controlled trial (SPRINTT project). Bernabei R, Landi F, Calvani R, Cesari M, Del Signore S, Anker SD, Bejuit R, Bordes P, Cherubini A, Cruz-Jentoft AJ, et al; SPRINTT consortium. BMJ. 2022 May 11. ;377:e068788. 2. A Phase 1 study for safety and pharmacokinetics of BIO101 (20-hydroxyecdysone) in healthy young and older adults. Dioh W, Tourette C, Del Signore S, et al; J Cachexia Sarcopenia Muscle. 2023 Apr 13. 3. Moni-

toring COVID-19 vaccine use in Italian long term care centers: The GeroCovid VAX study. Abbatecola AM, Incalzi RA, Malara A, Palmieri A, Di Lonardo A, Fedele G, Stefanelli P, Borselli G, Russo M, Noale M, Fumagalli S, Gareri P, Mossello E, Trevisan C, Volpato S, Monzani F, Coin A, Bellelli G, Okoye C, Del Signore S, Zia G, Bottoni E, Cafariello C, Onder G; GeroCovid Vax Working Group. Vaccine. 2022 Apr 1;40(15):2324-2330. doi: 10.1016/j.vaccine.2022.02.064. 4.Promoting and Building Long-Term Care Health Research Networks: GeroCovid Observational and Gerocovid Vax Initiatives. GeroCovid Observational and GeroCovid Vax group. J Am Med Dir Assoc. 2023 Jun;24(6):926-927.e2. doi: 10.1016/j.jamda.2023.01.026

Delannoy Carla

Food engineer from Catholic University, Porto (Portugal) with a PhD in Biology-Physics from Université d'Orsay, Paris (France). Carla started working for Nestlé since more than 20 years in different R&D facilities with multiple responsibilities and with international experience. Carla Delannoy is a Research & Development Global Manager at Nestlé Health Science since more than 7 years, where she manages the Innovation pipeline for the Medical Nutrition Adult Care Category, including oral nutritional supplement solutions for the elderly population suffering from loss of physical and cognitive autonomy. She has led innovations for brands like BOOST, RESOURCE, CLINUTEN, RENUTRYL, MERITENE, and BRAINXPERT among others.

Dioh Waly

Chief Operating Officer. Biophytis, Paris, France

Dray Cédric

Dr. Dray is an associate professor at Toulouse University and working as a head laboratory (METABOLINK) at RESTORE Institute (Toulouse France). He obtained his PhD in 2009 in the Philippe Valet's laboratory (Toulouse, France) with the discovery of a new role of apelin in the field of metabolism and diabetes related to obesity. Today, this finding is transposed to a human clinical trial in phase 2. After his PhD, Dr Dray achieved a post doc in New-York (Weill Cornell Medical School) working on metabolism and cancer and came back in France to develop an "Aging" axis. Now, Dr Dray drives a 35 peoples laboratory with main concerns dealing with the role of tissues (muscle, adipose and liver) communication and age-related loss of function through the study of cytokines and metabolite. Recently, Dr Dray team put in light the role of apelin in the field of sarcopenia (Vinel et al. Nature Medicine 2018).

Duque Gustavo

Professor Gustavo Duque, MD, Ph.D., FRACP, is a geriatrician and biomedical scientist with a research interest in the mechanisms, potential therapies, and biomarkers for age-related bone loss, osteoporosis, sarcopenia, osteosarcopenia, and frailty in older persons. He is also looking at the effect of vitamin D, exercise, and proteins on bone and muscle mass. His initial training included Internal Medicine at Javeriana University (Colombia) and Geriatric Medicine, which he completed at McGill University in Montreal (Canada). Subsequently, he obtained his Ph.D. at McGill University in 2003 with a thesis entitled 'Molecular Changes of the Aging Osteoblast' under the supervision of Dr. Richard Kremer. Between 2003 and November 2007, he joined the McGill University Medical School faculty as a member of the Division of Geriatric Medicine and as a Researcher at the Lady Davis Institute for Medical Research. In November 2007, he moved to Australia to join the Faculty as Associate Professor and Head of the Division of Geriatric Medicine and Director of the Musculoskeletal Ageing Research Program at Sydney Medical School Nepean -University of Sydney. In 2012, he was promoted to Professor of Medicine at the University of Sydney. Between 2015 and 2022, Professor Duque held the positions of Chair of Medicine and Director of the Australian Institute for Musculoskeletal Science at the University of Melbourne. In 2022, Prof. Duque assumed the roles of Full Professor, Dr. Joseph Kaufmann Chair in Geriatric Medicine, Director - RUISSS McGill Centre of Excellence for Sustainable Health of Seniors/ Simone & Edouard Shouela (CE-Durable), and Principal Investigator at the Bone, Muscle & Geroscience Group of the Research Institute of the McGill University Health Centre (MUHC). He is also the Editor-in-Chief of the Journal of Gerontology: Biological Sciences, one of the official journals of the Gerontological Society of America. As a Geriatrician and Clinician-Investigator, Prof. Duque has implemented several Falls and Fractures clinics (the most recent ones at the MUHC and the Jewish General Hospital in Montreal) where patients are comprehensively assessed for falls and fracture risk. His clinical trials unit conducts several trials testing the effect of pharmacological and non-pharmacological treatments for age-related musculoskeletal diseases. He is the author of more than 280 peer-reviewed articles and multiple book chapters and has edited five books in the aging and musculoskeletal fields (two on osteosarcopenia).

Feige Jerome

Dr Jerome N. Feige is the head of the Physical Health department and vice-director of the Nestlé Institute of Health Sciences in Lausanne, Switzerland, and a recognized expert in muscle and aging biology. He holds a degree in Bioengineering and a PhD in Biology from the University of Lausanne. Dr Feige performed post-doctoral research at the Institute of Genetics, and Molecular and Cellular Biology in Strasbourg, France on the molecular regulation of energy

metabolism. He subsequently worked as laboratory head at the Novartis Institute of Biomedical Research in Basel, Switzerland, where he performed drug discovery for muscle diseases and contributed to the development of new therapies. Since 2012, Dr Feige has held increasing responsibilities in the Nestlé Institute of Health Sciences where he established a research program studying muscle biology and a translational department developing nutritional therapies to support the Musculo-Skeletal system. His research programs have lead to the commercialization of several products for infant and medical nutrition, and to the creation of 2 start-ups. Dr Feige is also an adjunct lecturer at the Ecole Polytechnique Fédérale de Lausanne (EPFL) where he teaches nutrition and entrepreneurship, and trains PhD students in biomedical science.

Ferrucci Luigi

Dr. Luigi Ferrucci is a geriatrician and an epidemiologist who conducts research on the causal pathways leading to progressive physical and cognitive decline in older persons. He has made major contributions in the design of many epidemiological studies conducted in the U.S. and in Europe. Dr. Ferrucci received a Medical Degree and Board Certification in 1980, Board Certification in Geriatrics in 1982 and Ph.D. in Biology and Pathophysiology of Aging in 1998 at the University of Florence, Italy. Between 1985 and 2002 he was Chief of Geriatric Rehabilitation at the Department of Geriatric Medicine and Director of the Laboratory of Clinical Epidemiology at the Italian National Institute of Aging. In September 2002, he became the Chief of the Longitudinal Studies Section at NIA. From 2002 to 2014 he was the Director of the Baltimore Longitudinal Study on Aging. Dr. Ferrucci is currently the Scientific Director of NIA, since May 2011.

Fielding Roger

Roger A. Fielding, Ph.D. serves as Team Lead and Senior Scientist of the Nutrition, Exercise Physiology, and Sarcopenia (NEPS) Team at the Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University. He is also Professor of Nutrition at the Friedman School of Nutrition Science and Policy, Professor of Medicine at Tufts University School of Medicine and the Associate Director of the Boston Claude D. Pepper Older Americans Independence Center. Dr. Fielding is an internationally known researcher who studies the underlying mechanisms contributing to the age-associated decline in skeletal muscle mass, the resultant impact on function, and the potential role of exercise, nutrition, physical activity and other therapies on attenuating this process. He has published over 250 peer-reviewed papers(H-index 101). Dr. Fielding has a strong record of extramural funding including support from the NIH, USDA, foundations and industry. He is an Deputy Editor of the Journals of Gerontology Medical Sciences, and Calcified Tissues International and Musculoskeletal Research. He has also served as a reviewer on numerous NIH study sections and was elected to the NIH/CSR College of Reviewers. In 2015, he received the Olof Johnell Science Award from the International Osteoporosis Foundation and in 2021 he received the Herbert Fleisch Medal from the same organization.

Forman Daniel

Dr. Daniel Forman is a Professor of Medicine at the University of Pittsburgh in the Divisions of Cardiology and Geriatrics. He has faculty appointments at the University of Pittsburgh Medical Center (UPMC) and the VA Pittsburgh Health System (VAPHS). At UPMC, he is Chair of Geriatric Cardiology and Associate Director of Translational Research at the University of Pittsburgh's Aging Institute. At the VAPHS, he is the Director of Translational Research of the Pittsburgh Geriatrics Research, Education, and Clinical Center (GRECC) as well as Director of Transitional Care with related leadership as Director of its Cardiac Rehabilitation and Gerofit programs. Dr. Forman receives funding from the National Institutes of Health and the Veterans Health Affairs with research interests that center on physical function in older adults with cardiovascular disease. A National Institute on Aging grant focuses on nitrite supplementation to enhance skeletal muscle mitochondrial bioenergetics in older sedentary adults, and related bioenergetic and functional gains. Both National Institute on Aging and Veterans Health Administrative grants focus on novel implementation strategies of cardiac rehabilitation for older adults. In related studies, he is studying the benefit of inspiratory muscle training to improve skeletal muscle energetics and clinical outcomes in older adults with heart failure. Dr. Forman has prominent leadership roles in the field of Geriatric Cardiology, with significant impact in the American College of Cardiology and the American Heart Association to shift research, guidelines, and practice management to incorporate scientific principles and outcome metrics pertinent to an older patient population.

Furman David

Dr. David Furman is Director of the Stanford 1,000 Immunomes Project at Stanford School of Medicine, Associate Professor at the Buck Institute for Research on Aging and Chief of the AI Platform at the same institute. He obtained his Doctoral degree in immunology (summa cum laude) from the School of Medicine, University of Buenos Aires, Argentina, for his work on cancer immune-surveillance. During his Postdoctoral training at the laboratory of Professor Mark M Davis (Stanford), he conducted cutting-edge research in Data Science and Systems Immunology to predict clinical outcomes using multi-omics technologies in large human cohorts. The aim was to answer scientific questions with strong potential for translational medicine, including the effect of immunity in age-related disease and longevity. Dr. Furman moved to University of Bordeaux, France, where he was appointed as Visiting Scientist and investigated the involvement

of the endocrine and immune systems in human aging and in kidney transplantation. After France, Dr. Furman helped create the Systems Biology Department at the Sidra Medical Research Center in Doha, Qatar. Dr. Furman was then re-appointed at the Stanford School of Medicine to assume the role of Consulting Professor at the Institute for Immunity, Transplantation and Infection (ITI), and his work involved the use of high-bandwidth/high throughput technologies to measure immune function in humans and Machine Learning tools to better define the role of the immune system in disease and longevity.

Goetz Laura

Dr. Laura Goetz is the Medical Deputy for the XPRIZE Healthspan Competition. She is a board-certified General Surgeon and Preventive Medicine physician. In addition to seeing patients, she designs novel N-of-1 research protocols using precision medicine technologies for disease prevention and healthspan promotion. She is overseeing safety aspects of the Competition.

Grillari Johannes

Dr. Grillari is director of the Ludwig Boltzmann Institute for Traumatology. The Research Center in cooperation with AUVA and associate Professor at the Dept. of Biotechnology at the University of Natural Resources and Life Sciences in Vienna. Dr. Grillari's research interest is on improving our understanding of the molecular and physiological changes that occur during cellular aging, their impact on organismal aging and tissue regeneration. His work has pioneered the role of miRNAs in cellular senescence, bone and skin regeneration, showing that extracellular vesicles and their cargo, especially their miRNA cargo are inhibitors of regeneration when from senescent cells, while they have therapeutic effects when coming from mesenchymal stroma cells. He was also instrumental in designing targeting EVs for regenerative medicine purposes. He has authored and co-authored more than 200 SCI publications and 15 patents. He is also co-founder of 4 companies, Evercyte, TAmiRNA, Phoenestra and Rockfish Bio.

Gutiérrez Robledo Luis Miguel

He graduated as a medical doctor from La Salle University and trained in Internal Medicine at the National Institute of Medical Sciences and Nutrition «Salvador Zubirán» in Mexico. In France he obtained the Specialty in Geriatrics at the University of Grenoble and has a PhD in public health and epidemiology from the University of Bordeaux. He founded the Geriatrics Department of the National Institute of Medical Sciences and Nutrition «Salvador Zubirán» and headed it for 20 years. He was the Founding Director of the National Institute of Geriatrics (INGER) at the National Institutes of Health from 2009 to December 2022. He is currently researcher and head of the WHO collaborating center on integrated care at INGER, and PAHO and WHO consultant and member of the Steering Committee of the Clinical Consortium on Aging of the International Association of Gerontology and Geriatrics and WHO since 1996. He has more than 280 publications in scientific journals and chapters in books (H index 48, more than 15,000 citations in Google scholar), as well as 27 edited books, most related to research in clinical geriatrics, Alzheimer's disease, nutrition of the older adult and the epidemiology of aging.

Justice Jamie

Dr. Jamie Justice, PhD, is Executive Director of XPRIZE Healthspan Prize and EVP of Health Domain at XPRIZE Foundation, and an Adjunct Professor in Internal Medicine Section on Gerontology and Geriatric Medicine, and Sticht Center on Healthy Aging and Alzheimer's Prevention at Wake Forest University School of Medicine (WFUSM). Jamie completed graduate and postdoc training at University of Colorado Boulder and WFUSM. At WFUSM Jamie was director the Biogerontology Lab, and co-leader the Integrative Biology Core (IBC) of the WF Claude D. Pepper Older Americans Independence Center (OAIC), and an MPI of the National Institute of Aging-supported Geroscience Education. Jamie was the recipient of the Jarrahi Research Scholars Fund in Geroscience Innovation, the 2022 Vincent Cristofalo Rising Star in Aging Research, and the 2022 NIA Nathan W Shock Awardee. Jamie is dedicated to geroscience which that advances the hypothesis that by targeting the basic biology of aging the incidence of multiple age-related diseases can be delayed or prevented. Her training background allowed her lead translational research to test the geroscience hypothesis in humans. This included: 1) serving as Co-I on large multicenter prospective cohort studies like the Study of Muscle Mobility and Aging (SOMMA), and the NIH Cell Senescence (SenNet) Buck Institute Tissue Mapping Center for skeletal muscle; 2) leading proof-of-concept senolytics trials; and 3) designing trials of testing therapeutics that target biological age in older adults. In her new role as Executive Director of the $101M XPRIZE Healthspan she operates a $101 million global competition to drive teams to develop innovative solutions that make healthy human aging possible, for everyone.

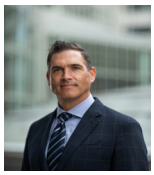
Khachaturian Ara

Ara S. Khachaturian, Ph.D. is the Executive Vice-President of the Campaign to Prevent Alzheimer's Disease. Presently, Dr. Khachaturian is leading the Brain Watch Coalition. This public-private coalition aims to assure accurate, affordable, and equitable access to brain health care and treatments that maximally extend a person's vitality, autonomy, and independence. He is also editor-in-chief of Vitality, Medicine & Engineering, a newly launched journal that links public health, public policy, medicine, and engineering technologies to produce actionable and translational knowledge. Dr.

Khachaturian is a Senior Research Fellow at the University of Nevada Las Vegas Institute for High-Performance Computing and is the founding Chair of the International Neurodegenerative Disorders Research Center Scientific Advisory Board based in Prague, Czech Republic. He is the founding Executive Editor of the Alzheimer's & Dementia journal family. Dr. Khachaturian is a neuroepidemiologist trained at the Bloomberg School of Public Health at the Johns Hopkins University.

Landi Francesco

Francesco Landi is Professor of Internal Medicine at the Catholic University of Rome, School of Medicine. He is the chief of the Geriatric Internal Medicine Unit at the A. Gemelli University Hospital in Rome, Italy. He has been a visiting Assistant Professor at Brown University School of Medicine, Department of Community Health. Contributions to advance scientific knowledge and medical practice include active involvement in research and the application to patient care. Main research interests are in geriatric assessment, nutritional problems, sarcopenia, models of health services for elderly care, and geriatric pharmaco-epidemiology. Prof. Landi serves as a President of the Scientific Committee of the Italian Geriatric Society, on the Editorial Board of several international geriatric journals, and as a peer reviewer for numerous international medical journals. He has acted as the Principal Investigator in many multicenter national and international trials. In addition, he is a member of national and international expert groups that work on guidelines in the field of nutrition, sarcopenia and functionality in older adults. Prof. Landi has over 500 peer-reviewed original papers in international medical journals, many of which are in the area of frailty and functional status of older people. He is particularly interested in the role of nutrition as part of the integrated care of older adults, and participated in the development of the European consensus on sarcopenia definition and diagnosis.



LeBrasseur Nathan

Nathan LeBrasseur, PT, PhD, is a Professor in the Department of Physical Medicine and Rehabilitation and has a joint appointment in the Department of Physiology and Biomedical Engineering at Mayo Clinic. Dr. LeBrasseur is the Director of the Robert and Arlene Kogod Center on Aging, the Co-Director of the Paul F. Glenn Center for Biology of Aging Research, and Scientific Director of the Office of Translation to Practice at Mayo Clinic. He is the recent chair of the NIH Cellular Mechanisms in Aging and Development Study Section. Dr. LeBrasseur's research team conducts translational "bench-to-bedside" research on strategies to improve physical function, metabolism, and resilience in the face of aging and disease. His latest work has centered on cellular senescence, a fundamental mechanism of aging, and interventions to counter this process to extend healthspan. Dr. LeBrasseur has received the Glenn Award for Research in Biological Mechanisms of Aging, the Nathan W. Shock Award Lecture from the National Institute on Aging, and the Vincent Cristofalo Rising Star Award in Aging Research from the American Federation for Aging Research. He is a Fellow of the Gerontological Society of America.

Martinez Laurent

Laurent Martinez, PhD in Human Pathophysiology since 2001 (University of Toulouse), began his career with a major publication in Nature (Nature. 2003;421(6918):75-9). As a postdoctoral researcher between 2002 and 2005, he collaborated with Professor Alan Tall at Columbia University (New York City, USA) and Nobel laureate in Chemistry, John E. Walker, at the University of Cambridge, United Kingdom. Recruited by Inserm (French National Institute of Health) in 2004, Laurent Martinez advanced through the Institute to become Director of Research by 2011. Presently, he leads the LiMitAging team at the Institute of Cardiovascular and Metabolic Diseases, alongside teaching at the master's level at the University of Toulouse. Laurent Martinez is also a member of several scientific councils, including the scientific commission of Inserm, the scientific council of the University of Toulouse, and the executive committee of the Hospitalo-University Institute HealthAge. Additionally, he serves as an associate editor for the journal Atherosclerosis. His team, specialized in research on metabolic and cardiovascular pathologies and healthy aging, has been recognized with several distinctions, including the Lavoisier Prize (2001), EMBO (2004), Inserm Avenir (2006), as well as the Inserm Scientific Excellence Award (2014, 2022). Author of 72 publications, including 34 as principal investigator, his work has been cited more than 5800 times. Notably, he recently published a study on the benefits and limitations of intermittent fasting1 and was the first to identify the circulating form of the mitochondrial protein IF1 as a biomarker in the context of cardiometabolic diseases and aging2-4. Recent Publications: 1) Mérian J, Ghezali L, Trenteseaux C, Duparc T, Beuzelin D, Bouguetoch V, Combes G, Sioufi N, Martinez LO, Najib S. Intermittent Fasting Resolves Dyslipidemia and Atherogenesis in Apolipoprotein E-Deficient Mice in a Diet-Dependent Manner, Irrespective of Sex. Cells. 2023 Feb 7;12(4):533. 2) Raffin J, Rolland Y, Genoux A, Combes G, Croyal M, Perret B, Guyonnet S, Vellas B, Martinez LO*, de Souto Barreto P*. Associations between physical activity levels and ATPase inhibitory factor 1 (IF1) concentrations in older adults. J Sport Health Sci. 2023 Sep 23:S2095-2546(23)00094-7. *co-last authors; 3) da Silva JA*, Martinez LO*, Rolland Y, Najib S, Croyal M, (…), Vellas B, de Souto Barreto P. Plasma Level of ATPase Inhibitory Factor 1 (IF1) and Intrinsic Capacity in Community-Dwelling Older Adults: Prospective Data From the MAPT Study. J Gerontol A BiolSci Med Sci. 2024;79(1):glad142. *co-first authors; 4) Pires Da Silva J, Wargny M, Raffin J, Croyal M, (…), Viguerie N, Rolland Y, Barreto PS, Cariou B, Martinez LO. Plasma level of ATPase inhibitory factor 1 (IF1) is associated with type 2 diabetes

risk in humans: A prospective cohort study. Diabetes Metab. 2023;49(1):101391.

McCormick Mark

Mark McCormick, PhD. The McCormick Lab studies the basic biology of aging. We use multiple model systems to look for conserved biology that will help us understand aging and hopefully eventually delay the onset of age-related diseases in humans. Prior to joining UNM, Dr. McCormick completed a PhD in Biochemistry and Molecular Biology studying the basic biology of aging at the University of California San Francisco, and a postdoctoral fellowship at the Buck Institute for Research on Aging. He also has a BS in Mechanical Engineering and a BS in Biology from the University of Texas at Austin. labmccormick.org; @labmccormick

Merchant Reschma

Associate Professor Reshma Merchant; Head of Division Geriatric Medicine and Senior Consultant; Department of Medicine; NUS Yong Loo Lin School of Medicine. National University of Singapore; National University Health System, Singapore. She graduated from the University of Edinburgh and obtained her postgraduate qualification from the Royal College of Physicians, London, in 1999, where she worked for several years before returning to Singapore in 2001. She is a member of WHO Global Network on Long-term care (GNLTC), Clinical Consortium on Healthy Aging and recognised as a thought leader and special expert in policy, research and practice in fields associated with population ageing globally. She has won multiple clinical and teaching awards, including the NUHS-Mochtar Riady Pinnacle Master Clinician Award in 2022. She is well published and her main areas of research interests are in sarcopenia, frailty and healthy ageing in community dwelling older adults. She is currently leading the frailty prevention initiative at Health District @ Queenstown in Singapore.

Muscedere John

Dr. John Muscedere MD, FRCPC is a Professor of Medicine, Intensivist and Clinician Scientist at Queen's University and Kingston Health Sciences Center. Dr. Muscedere' s research focuses on improving outcomes by generating new evidence and knowledge translation through clinical trials, systematic reviews and meta-analyses focussing on nosocomial infections and frailty. He is the Scientific Director for the Canadian Frailty Network (CFN). CFN is dedicated to improving care for older Canadians living with frailty through the generation of new knowledge, knowledge mobilization, partnerships and training highly qualified personnel. CFN is developing public health initiatives for the prevention and mitigation of frailty through Regional Centers for Healthy Aging. For more information: www.cfn-nce.ca

Newman Anne

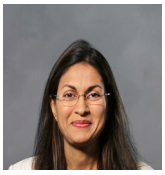
Anne B. Newman, MD, MPH is Distinguished Professor of Epidemiology and Professor of Medicine and Clinical and Translational Science in the School of Medicine. She is the Clinical Director of the Aging Institute of the University of Pittsburgh and UPMC and UPMC Chair of Geroscience. She has defined key metrics of physical functioning, frailty, and sarcopenia in epidemiology cohort studies, and has conducted clinical trials designed to prevent disability and extend health span. She currently serves as a member of the National Institute on Aging Clinical Trials Advisory Panel (CTAP), and has completed service as a member of the Board of Scientific Counselors and the National Advisory Council on Aging. She is a member of the American Federation for Aging Research(AFAR) National Scientific Advisory Council. Dr. Newman is also an Associate Editor of the Journal of Gerontology, Medical Sciences, after serving as the Editor-in Chief from 2016-2020.

Newman John

John Newman, MD, PhD is a geriatrician, basic scientist, and educator at the Buck Institute for Research on Aging and in the Division of Geriatrics at UCSF. His laboratory at the Buck Institute carries out basic science and clinical research investigating the energy and signaling functions of ketone bodies in the aging brain, Alzheimer's disease, and frailty. He also leads a clinical-translational program to understand how aging-related metabolic mechanisms drive the geriatric syndrome delirium. He is a member of the Bakar Aging Research Institute at UCSF and the UCSF Older Americans Independence (Pepper) Center, and a leader of the national Geroscience Education and Training Network

Parini Angelo

Angelo Parini is a cardiologist and professor emeritus at the Faculty of Health of Toulouse. He's co-leader of the group «Cardiometabolic remodeling: mechanisms and microenvironment» at the Institute of Metabolic and Cardiovascular Diseases in Toulouse. His research interests mainly concern the molecular mechanisms of cardiac aging and, more broadly, the molecular and functional determinants of biological age. He is responsible for the preclinical cohorts of the INSPIRE project and the IHU HealthAge.



Pereira Suzette

Dr. Suzette Pereira, Ph.D. is a Research Fellow at the Nutrition Division of Abbott. Over her 20+ year tenure at Abbott, she has conducted both clinical and pre-clinical research towards developing novel nutritional products to address muscle loss due to aging (sarcopenia), chronic disease, hospitalization, and malnutrition. Her research has fo-

cused on understanding mechanisms behind muscle loss and identifying bioactive nutritional ingredients to mitigate the same. Together with her diagnostic colleagues she has also explored the development of novel technologies to screen and identify muscle loss towards increasing awareness with consumers and health care professionals. Prior to joining Abbott, Dr. Pereira received her doctoral degree and carried out postdoctoral research in Molecular Microbiology at The Ohio State University (USA). She has coauthored over 70 peer-reviewed manuscripts and ~230 patents/patent applications.

Pierpoint Lauren

Lauren Pierpoint holds a PhD in Epidemiology from the Colorado School of Public Health. She is currently a Senior Researcher at XPRIZE, working on developing competition guidelines which govern XPRIZE Healthspan, a global competition which aims to incentivize clinical teams to develop and test therapeutics targeted at restoring function lost to age-related degradation of multiple organ systems. Prior to joining XPRIZE Lauren was the principal consultant at Pierpoint Analytics, LLC and served as the Hip Research Manager at the Steadman Philippon Research Institute. Lauren also holds an Adjunct Assistant Professor position at the University of Utah School of Medicine Department of Physical Medicine and Rehabilitation and is the Chair of the Injury Control Emergency Health Services Section of the American Public Health Association.

Rash Brian

Dr. Brian Rash received his PhD in neuroscience from the University of Chicago in 2007 and completed postdoctoral and early faculty positions at Yale University, and throughout this career trajectory has studied neuroscience, cognitive neural development, stem cells, mitochondria, and the molecular cell biology and genetics of disease. Dr. Rash transitioned to biotech (Herophilus; San Francisco) in 2019 to further induced pluripotent stem cell (iPSC) technology and develop brain organoids at scale, leading efforts to discover small molecules in the treatment of Rett syndrome and Alzheimer's disease. Working at Longeveron as VP of Research and Discovery, Dr. Rash is overseeing efforts to develop treatments for a variety of conditions with their clinical stage IND, Lomecel-B, a cell therapy with anti-inflammatory and pro-vascular therapeutic potential.

Roithmayr Mark

Mark Roithmayr is an admired nonprofit leader with four decades of experience in both start-ups and mature organizations. As Chief Executive Officer of the Alzheimer's Drug Discovery Foundation (ADDF), Mr. Roithmayr is responsible for steering the Foundation's overall strategy, focus, and business operations. His areas of expertise include venture philanthropy, strategic planning, volunteer development, and brand-building. Since joining the ADDF in 2017, the organization has transformed dramatically in impact, scale, presence, and brand. Under his leadership, ADDF's revenue has increased five-fold from $17M to an excess of $90M and mission related investing has grown over 100%. Prior to joining the ADDF, Mr. Roithmayr was Chief Relationship Officer at the Leukemia and Lymphoma Society (LLS). There, he helped launch its venture philanthropy initiative, directed its 56 national chapters, and led annual fundraising of over $200 million. Prior his time at LLS, he served for seven years as president of Autism Speaks. As that organization's first president, he shepherded its growth from a start-up into the world's largest autism research and advocacy organization. Earlier in his career, Mr. Roithmayr held several executive positions, spanning two decades, with the March of Dimes. He earned a bachelor's degree in communications at Rowan University.

Rolland Yves

Yves Rolland (MD, PhD) is Professor of Internal Medicine and Geriatrics at the IHU HealtAge of Toulouse (France) and has a postgraduate diploma in sports medicine. He is member of the CERPOP Team, UMR1295 (INSERM) at the University Toulouse III Paul Sabatier (MAINTAIN - MAintain Functions and INTrinsec capacities with Aging: Preventive and Personalized INterventional Research). He is the author of more than 300 articles indexed Pubmed. In 2023, he published "Challenges in developing Geroscience trials" in Nature Com and "Current and investigational medications for the treatment of sarcopenia" in Metabolism.

Rosenberg Gary

Dr. Rosenberg is a Professor of Neurology with joint appointments in Cell Biology, Neuroscience and Mathematics and Statistics. He joined the faculty of Neurology in 1976, and is currently the Director of the New Mexico Alzheimer's Disease Research Center (NM ADRC). He is the Founding Director of the UNM Center of Memory and Aging. From 1985 to 2015 he served as Chairman of Neurology, and has trained many neurologists. He graduated from the Albert Einstein College of Medicine and trained there in Neurology. He studied biomedical engineering at the Technion University in Haifa, Israel. His current research is on improving diagnosis in patients with dementia by the use of biomarkers and machine learning. He is an expert in vascular cognitive impairment. He has published over 168 papers and written two books. He has been continuously funded by NIH since 1983, and is now the Principal Investigator on two large NIH grants.

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Stubbs Brianna

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Challenges in developing Geroscience trials

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Geroscience is becoming a major hope for preventing age-related diseases and loss of function by targeting biological mechanisms of aging. This unprecedented paradigm shift requires optimizing the design of future clinical studies related to aging in humans. Researchers will face a number of challenges, including ideal populations to study, which lifestyle and Gerotherapeutic interventions to test initially, selecting key primary and secondary outcomes of such clinical trials, and which age-related biomarkers are most valuable for both selecting interventions and predicting or monitoring clinical responses ("Gerodiagnostics"). This article reports the main results of a Task Force of experts in Geroscience.

For over a century, continued improvements in living conditions, public health policies, and advances in medicine have led to an unprecedented increase in life expectancy across the globe. However, older adults now routinely experience multi-morbidities that are strongly associated with the aging process, including cardiovascular diseases, type II diabetes mellitus, dementias, cancers; sarcopenia, frailty, and functional decline, as well as declines in immune function and other systems[1]. Relative to life expectancy, these can result in a prolonged period of decreased health that can last over a decade. The increases in life expectancy that have outpaced increases in healthspan in some countries are characterized by increased disability, diminished quality of life, and high healthcare costs[2].

Multiple clinical conditions and pathophysiological processes have long been considered as inescapable and unmodifiable consequences of the aging process. However, these perceptions are changing, in particular with respect to how modifying factors, such as levels of physical activity, diet, social and community disadvantage, and exposure to pollution and other environmental stresses may affect the trajectory of developing age-related disabilities and diseases. Over the past few decades, research focusing on the interplay between the fundamental processes of aging and the biology of co-morbidities has given rise to the concept of Geroscience, the goal of which is to develop new biologically-based therapeutic and preventive approaches that target fundamental aging processes; thus, to decrease age-related multi-morbidities as a group and improve healthspan[3]. The beneficial effect of using Gerotherapeutic drugs to modulate the fundamental molecular, cellular, and/or genetic mechanisms of aging has been demonstrated in animal models, and offers exciting preventive and even curative therapeutic translational opportunities in humans[4–9]. However, Geroscience trials face numerous methodological challenges in their study design regarding demonstrating clinical effectiveness successfully in humans[10–12]. One critical challenge is that the usual design of therapeutic clinical trials is centered on disease-specific diagnosis and physiopathology, whereas Geroscience trials aim to target mechanisms of aging in order to delay or prevent the onset or reduce the progression of multiple age-related diseases, geriatric syndromes, and potentially alleviate or treat such conditions.

We present here the recommendations by the Geroscience Clinical Trial International Task Force, which met on March 24 and 25, 2022 in Toulouse, France. Design methodologies of future randomized controlled trials in the field of Geroscience were considered, including the most appropriate target populations and key clinically relevant primary, secondary, and exploratory endpoints.

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What are potential outcomes of Geroscience clinical trials?

Indications for treatment are defined by governmental agencies, such as the Food and Drug Agency (FDA) or European Medicine Agency (EMA) as conditions, usually a disease or manifestation of disease—which affect the life quality and functioning of an individual in the opinion of patients, physicians, and experts in the field (https://www.fda.gov/drugs/development-approval-process-drugs). As such, it is unlikely that regulatory agencies will recognize aging as a treatable indication. Thus, defining approvable indication(s) for Geroscience compounds currently under development is an essential task.

The EMA and the FDA have high concordance (91–98%) in decisions on marketing approvals[13], but the arrival of gerotherapeutic drugs will challenge both agencies to define the terms of marketing approval in the context of Geroscience. Being an emergent discipline, Geroscience will challenge some of the established protocols for fast approval of new drugs and biomarkers needed to meet the challenges of an aging society. Although some differences may exist between FDA and EMA, these agencies have been dialoguing and cooperating in the past two decades in order to align Europe and the US on decisions on market authorizations[13]. In general, FDA or EMA approve drugs for treating diseases; however, aging by itself is not currently considered as a "disease", but as the major risk factor for multiple morbidities. Basic scientists, clinicians, and drug agency officials already interact so that the concept behind Geroscience is understood and shared. A scale for evaluating FDA-approved drugs for their Gerotherapeutic potential has been proposed[4]. In this context, it is important to highlight that the design of the TAME (Targeting Aging with MEtformin) trial has been approved by the FDA; TAME aims to delay mortality and the onset of several age-related diseases (e.g., myocardial infarction, stroke, cancer, dementia) and conditions (e.g., major decline in mobility or cognitive function) rather than targeting a single disease[14]. The TAME trial may serve as a proof of concept that proves to the medical agencies that aging can be a therapeutic indication in itself. This result would favor conditions for defining new marketing approval, type of approval, and approved indication for new or already approved drugs and will be incentive for pharmaceutical companies to invest in research on Geroscience. Diet and physical exercise are prevention strategies targeting multiple age-related conditions in humans that are already recognized by all international recommendations for healthy aging. It is demonstrated that both diet and physical exercise influence the hallmarks of aging. Other lifestyle modifications such as the use of probiotics could also be relevant and safe and various drugs, safe, and already on the market, such as metformin or SGLT − 2 inhibitors could be considered to prevent the degradation of the hallmarks of aging.

Experts agree that chronic pathologies that become prevalent in middle-age and older adulthood (i.e. age-related diseases such as type II diabetes mellitus, arthritis, osteoporosis, heart failure, dementias, cancers) share, at their root causes, metabolic, genetic, and cellular dysfunction collectively termed the "hallmarks of aging"[15]. These hallmarks of aging are also thought to underlie various geriatric conditions such as frailty, which is characterized by declines in the domains of intrinsic capacity, including mobility and cognition[12]. A Geroscience trial can be defined by its targeting one or more hallmarks of aging. By acting directly on fundamental aging mechanisms, Geroscience therapeutic candidates are intended to postpone occurrence of multiple age-related diseases, target a single disease, maintain/improve function(s) (Table 1), or improve healthspan and survival (Table 2). Below, the panel of on-going trials presented during the task force meeting illustrates the heterogeneity of study outcomes across the field of Geroscience. Some trials focus on the onset of clusters of diseases (TAME study), some target specific age-related diseases (such as Alzheimer's disease, AD), while others target very prevalent age-related physical/biological conditions (such as loss of mobility, delirium, or immuno-senescence in frail subjects, or loss of intrinsic capacity with advancing age). Outcomes using composite scores are not without limitations and permissive effects. An intervention study could achieve its main objective on a composite outcome by having efficacy on only one of the items and thus find a broad indication even though the molecule is only effective on a single biological mechanism of a disease and not on the biological mechanisms of aging. The rating scale proposed by ref. [4] should reduce this potential bias.

Geroscience trial to collectively prevent age-related diseases

The TAME study aims to demonstrate that by targeting the cellular hallmarks of aging in humans, the onset of several age-related diseases may be delayed. TAME holds the potential to be the first study that could lead to considering aging, or at least multimorbidity, as a therapeutic indication[14]. TAME aims at investigating the effect of a molecule already approved by the FDA and can be considered as a model for the design of future studies evaluating other drugs that are repurposed with an indication of targeting multimorbidity, aging, or age-related dysfunction[4]. Metformin is a generic drug used for its ability to reduce hepatic insulin resistance and hyperglycemia in patients with type 2 diabetes. Metformin has also been demonstrated to prevent the onset of type 2 diabetes mellitus in those with impaired glucose tolerance. Recently, basic research has demonstrated its involvement in many biological pathways of aging and the prevention of age-related diseases[14,16]. Metformin has a pleiotropic mode of action including suppression of inflammation, activation of nutrient sensor AMPK, inhibition of mitochondrial functioning, lowering adipocyte senescence with reduction of SASP, induction of autophagy and favorable shifts in the gut microbiota[17]. Epidemiological studies have indicated that metformin is associated with a reduced incidence of multiple age-related diseases, including cancers and Alzheimer's disease[14], as well as all-cause mortality, effects which have been observed not only in individuals diagnosed with diabetes, but also in non-diabetics, thus supporting the hypothesis that metformin can have geroprotective effects[18,19]. TAME will be a six-year randomized controlled trial, conducted in 14 research institutes in the United States, studying the effects of metformin on the incidence of chronic diseases in 3000 subjects. Participants must be between 65 and 80 years old and either have a walking speed of 0.4 to 1 meter per second or have an age-related disease such as cardiovascular disease, cancers, or Mild Cognitive Impairment (MCI) at the start of the study. The primary endpoint of TAME is the time to incidence of any of 5 major age-related conditions (myocardial infarction, stroke, cancer, heart failure, mild cognitive impairment (MCI)/dementia), or death. The hypothesis is that by targeting one or more hallmarks of aging, metformin will delay the development and severity of chronic diseases.

Geroscience trials to prevent functional limitations and geriatric syndromes

Another clinical trial related to the Geroscience hypothesis involved intervention the geriatric syndrome, frailty[20], using bone marrow-derived allogeneic Mesenchymal Stem Cells (MSCs, branded as Lomecel-B). The depletion of stem cells compromises tissue regeneration and repair and is the main rationale for stem cell-based replacement strategy. Allogeneic MSCs offer promise as a Gerotherapeutic drug candidate through multiple mechanisms of action that can address multiple mechanism of aging. Among these are anti-inflammatory, anti-fibrotic, and pro-vascular activities, and ability to stimulate intrinsic and pro-regenerative and repair mechanisms[21,22]. The clinical-stage biotechnology company, Longeveron, *Inc*., reported the results of its multicenter phase IIb randomized clinical trial involving 148 participants aged 70 to 85 with a mild to moderate frailty score (Canadian Study on Health & Aging [CSHA] Clinical Frailty Scale score 5–6), a walking distance of 200 to 400 meters on the 6-min walk test (6MWT), and a low-level inflammatory state (defined by serum tumor necrosis factor TNF-α ≥ 2.5 pg/mL). The study evaluated the

Table 1 | Outcomes

Outcome	Example of clinical outcome
Diseases	Incidence of new age-related disease, Cardio-vascular events, Infectious disease, Dementia, Sarcopenia, Osteoporosis, unexplained anemia of aging. Progression rate of the diseases
Geriatric syndrome	Delirium, Falls, Frailty, Incontinence, Undernutrition (anorexia of aging)
Physical and biological function	Disability, Physical performance (SPPB, walking speed), Decline of Intrinsic Capacity and its domains (mobility, mood, vitality, hearing, vision, cognition), Immunity
Healthspan and mortality	See Table 3: Summary of studies investigating the effects of candidate Gerotherapeutic drugs on healthspan and mortality in human (Adapted from Kulkarni et al., 2022)

Table 2 | Target population

Target population in Geroscience trial	Definition	Potential indications
Subjects at risk of age-related diseases	Age-related diseases: Defined as disease with increased incidence in old age and generated by chronic impairment of the hallmark of aging	Atherosclerosis, cardio-vascular disease, cancer, osteo-arthritis, osteoporosis, type 2 diabetes, hypertension, cataract, Alzheimer's disease, pre-eclampsia, others
Subjects with accelerated aging-like states	Accelerated aging disease: Genetic disorder that result in accelerated aging-like states	Down syndrome, progeria, Werner syndrome
Subject facing an accelerated aging-like condition	Accelerated aging condition: Clinical condition that results in accelerated phenotypic or biological aging	Immobilization, radiation, chemotherapy, exposure to toxins (tobacco, alcohol...), surgery, cardiopulmonary bypass surgery, hypoxia, prematurity, space flight, others
Subjects at risk of geriatric syndromes	Geriatric syndrome: Group of age-related acute or chronic common health condition that are associated with poor resilience	Delirium, fall, functional limitation, undernutrition, frailty, sarcopenia, cognitive impairment, depression, others
Subjects with (or at risk of) declining Intrinsic capacity (IC)	Intrinsic capacity: Concept that represents the composite of all physical and mental capacities	Older adult with abnormal IC domains (mobility, sensory, mood, cognition, vitality) as defined by WHO

effect of 4 doses of MSCs (single intravenous infusion of 25, 50, 100, or 200 million [M] cell) vs. placebo. The primary objectives were (i) to show a difference in the 6MWT between the treatment groups *vs.* the placebo group at 6 months and (ii) to establish the potential dose-response effect of MSCs on the 6MWT. The authors reported a statistically significant dose-response effect with a gain in walking distance of around 63 meters at an MSC dose of 200 M cells by 9 months after a single infusion. This physical performance improvement is greater than the distance of 32 meters considered clinically relevant in chronic heart failure patients[23] or the 19 to 22 meters of improvement deemed clinically relevant in elderly subjects living in the community[24]. This study also reported a dose-dependent decrease in soluble Tie2 (sTie2), a receptor tyrosine kinase expressed on the surface of endothelial cells, consistent with pro-vascular activity. While these promising results support MSCs as a gerotherapeutic candidate, the ability to simultaneously address multiple mechanisms of aging presents a unique challenge in drug development that will need to be addressed in follow-up studies. In particular, developing mechanistic-related biomarkers of efficacy may be challenging given the number of potential targets involved, and may ultimately require a composite biomarker approach to assess effect and effect duration to guide follow-up treatment. Further complicating this is the fact that principal targets may not be uniform across all patients, e.g., patients with age-related frailty versus disease-related frailty may require unique (and again, possibly composite) biomarkers for effect.

Geroscience trials to treat or prevent specific age-related diseases

Cellular senescence is a complex cell fate that becomes more frequent with age and occurs in the context of inducers, such as reactive oxygen species, telomere attrition, deoxyribonucleic acid (DNA) damage, or oncogene activation. Cellular senescence can entail to changes in expression of multiple molecular mediators, such as $p16^{INK4a}$ or $p21^{CIP1/WAF1}$, that induce essentially permanent cell cycle arrest, resistance to apoptosis; metabolic changes, such as β-galactosidase accumulation in lysosomes; and cell morphological changes. Most senescent cells develop a senescence-associated secretory phenotype (SASP). The SASP varies depending on the cell type that became senescent, how senescence was induced, how long the cell has been senescent, and its microenvironment. The SASP can entail secretion of growth factors, chemokines, metalloproteases (MMPs), cytokines, non-coding nucleotides (e.g., microRNA's), and other bioactive molecules (e.g., prostanoids, bradykines, ceramides, ROS), which contribute to organ dysfunction, including dysfunction of the brain[25–28]. Neurons, but also glial and brain endothelial cells, have been reported to develop a senescent phenotype[29–32]. Interestingly, several basic and animal research studies support the idea that lower senescent cell abundance is linked to improved healthspan[6,33–36], including neurodegenerative disorders[37]. Musi et al. reported in mice that senolytic treatment (biweekly administration of Dasatinib and Quercetin for 12-weeks) reduced brain atrophy, decreased white matter pathology, and rescued aberrant cerebral blood flow[37]. These findings support the idea that reducing senescent cell burden in the brain may reduce neurodegeneration in humans[38] and pave the way to new therapeutic interventions, such as drugs targeting senescent cell anti-apoptotic pathways, senolytics[39,40]. Directly testing the impact of senescence-targeting therapies in a neurodegenerative state, Mitzi Gonzales, et al. have recently reported the first results of the SToMP-AD trial, a pilot clinical trial of senolytic treatment in early-stage AD[41]. Results show that the combination of Dasatinib and Quercetin is safe, penetrates the central nervous system (CNS), and well-tolerated in humans. This pilot study has provided evidence for proceeding with a multisite Phase II clinical trial to evaluate the safety and feasibility of senolytic therapy in AD.

Longeveron also reported results from its Phase 1 Trial for subjects with Alzheimer's Disease[42] at the meeting. Thirty-three participants were enrolled who were between 50 and 80 years old with mild AD. Participants were randomized into three groups, receiving a single intravenous infusion of 20 M allogenic MSCs, 100 M allogenic MSC's or placebo, and were followed-up for 26 weeks post-infusion. Safety was the primary endpoint. No adverse events (AEs) or serious AE (SAEs) were attributed to the product, thus the safety stopping rule was not

triggered (meeting the primary endpoint). With the caveat that the trial was not powered for efficacy, statistically significant improvements were observed in vascular endothelial growth factors (VEGF), and inflammation-related biomarkers (Il-4, Il-6, sIl-2α, Il-10, Il-12), and imaging outcomes (left hippocampus volume). In this case, a potential composite biomarker for effect may be plausible that encompasses both fluid-based and imaging readouts. In addition, cognitive decline (measured by the Mini-Mental State Exam) progressed more slowly in the 20 M MSCs arm compared to placebo, although these findings must be considered with caution given the small sample size.

The above paragraph illustrates the point for Alzheimer disease, a very prevalent condition during aging, but there is also a growing number of Geroscience trials designed to treat or prevent specific age-related diseases. For example, Guanabenz, an alpha-2 adrenergic agonist used to treat hypertension, also targets the loss of proteostasis and has been approved by FDA in patients with amyotrophic lateral sclerosis[43]. In a phase 1 clinical trial, oral Nicotinamide Riboside that targets disabled macroautophagy in Parkinson's disease patients has been reported to improve clinical symptoms and reduced inflammatory markers in the cerebrospinal fluid and blood[44]. In an open-label phase 2/3 randomized clinical trial, elamipretide, that targets mitochondrial dysfunction, has been reported to improve physical performance and muscle strength on Barth syndrome[45]. In a small sample size phase 1 clinical trial Justice, et al. have reported that Dasatinib + Quercetin, a senolytic drug combination that targets cellular senescence, improved physical performance and reduce inflammatory markers in patients with pulmonary fibrosis[46]. These senolytics have also been reported to reduce the inflammatory profile of patients with diabetic kidney disease[47]. Data from the CANTOS study suggests that a treatment targeting the interleukin-1β innate immune pathway with Canakinumab, aimed to reduce chronic inflammation, reduces the incidence of and mortality from lung cancer. In this Phase 3 clinical trial, 10,061 patients with atherosclerosis who had a myocardial infarction and without previous cancer and high C-reactive protein (hsCRP) levels at baseline were randomized with different doses of Canakinumab or placebo. Incident lung cancer was significantly less frequent in the canakinumab group[48]. Overall, these data related to interventions targeting the mechanisms of aging in the context of human diseases suggest that gerotherapeutic drugs could improve the prognosis or even prevent these diseases, and extend healthspan and lifespan. The multiple ongoing studies will certainly bring new data to the field of gerotherapeutic drugs in the short-to-medium term.

Geroscience trials targeting Intrinsic Capacity (IC)

Recently the World Health Organization (WHO) introduced the concept of age-related decline in IC to ICD-11, defining IC as the composite of all physical and mental capacities that a person can draw on, including biological reserve (https://www.thelancet.com/journals/lanhl/article/PIIS2666-7568(22)00102-7/fulltext https://doi.org/10.1016/S2666-7568(22)00102-7). This paves the way for a possible drug approval to treat IC from the EMA and FDA. The construct of IC has been operationalized through assessing five major functional domains: cognition, psychological, locomotion, vitality, and sensory function[49]. IC has been proposed as a metric to assess function in older adults and could prove to be a relevant primary outcome for Geroscience drug trials. Previous work in AD clinical research led to the development of CDR sum boxes (a composite cognitive score) which has recently been recommended by the FDA for Alzheimer's prevention trials[14]. A similar composite score model could be developed for IC to bring it into use as an endpoint in clinical trials. For the WHO, healthy aging is defined by the ability to maintain function and to continue to be and to do what we value[50]. By manipulating biological mechanisms of aging, Geroscience innovations may help to slow down the loss of IC and to maintain healthy aging. Maintaining function by increasing or preventing the decline in IC associated with aging as well as preventing the onset of frailty in older adults is the main objective of the WHO Integrated Care for Older People (ICOPE) initiative[51]. ICOPE's goal is that care for older people worldwide maintains and restores intrinsic capacity and functional capacity and help to promote healthy aging. This preventive approach is already implemented in Occitanie (France)[52,53] with more than 20,000 community-dwelling participants followed digitally. The key preventive strategies for these older adults currently emphasize healthy lifestyle behaviors (e.g., physical activity, nutrition); new strategies may be added or substituted when specific drugs become available to maintain their IC.

An IC score for clinical research could be used to monitor IC trajectories over time and to predict disability in a manner similar to that of the cognitive composite score for AD. The composite IC measure will have to be predictive of functional ability outcomes (e.g., care dependency) and sensitive to changes over time compared to single measures of function. Depending on its reliability, this might help reduce sample sizes for clinical trials.

Geroscience-based interventions, Gerotherapeutics, appear to delay, prevent, alleviate, or treat not only specific clinical disorders in older adults, but can also impact a broad range of biological processes and multiple diseases and disorders. For example, the process of immune dysfunction that occurs with age (so-called immunosenescence) is closely related to infections, autoimmune diseases, and malignant tumors. It has been reported that upregulation of interferon-induced antiviral responses in older adults with a low dose of an mTOR inhibitor may substantially reduce the severity of viral respiratory tract infections in older adults[54]. Targeting immune function is a major area of clinical study in Geroscience.

Studies investigating the effect(s) of candidate Gerotherapeutic drugs on healthspan and mortality in humans

Mortality and longevity are outcomes that are difficult to apply in randomized controlled trials because they require long-term follow-up and large sample sizes. A study with the sole objective of lifespan extension would take decades and would be very expensive. Therefore, most clinical projects in progress employ composite outcomes monitoring for the development of diseases in addition to death. Recent synopsis by ref. [4] identified studies (in rodents or human) performed on drugs already approved by the FDA which might have geroprotective effects, particularly those potentially improving healthspan and extending lifespan. The authors propose a standardized process for evaluating FDA-approved medications for their gerotherapeutic potential. The process proposed is a 12-point rating scale assigning points based on results of robust preclinical and clinical trials for each drug. Six points are related to the results of pre-clinical trials and are attributed when attenuation of the biological mechanisms of aging is achieved or when the extension of lifespan is demonstrated. The six remaining points of the rating scale are related to clinical trials and consider the effects of the drug beyond the targeted disease (the drug has effects on a disease that it was not intended to treat) and are attributed on the reduction of overall mortality or mortality unrelated to the targeted disease. Table 3 gives outcomes of these studies investigating the effects of candidate gerotherapeutic drugs on healthspan and mortality in humans.

What is the target population for Gerotherapeutic clinical trials?

Table 3 summarizes potential target populations for Gerotherapeutics trials. The field of clinical trials in Geroscience research goes far beyond the prevention or treatment of age-related disease. Indeed, the concepts of Geroscience potentially apply to the entire life course and open up therapeutic perspectives beyond geriatric medicine[6]. The fundamental biological mechanisms of aging start early in adulthood or even before, as indicated by changes in muscle, brain, and cardiovascular function that can be observed as young as 30 years of age in

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Table 3 | Summary of studies investigating the effects of candidate Gerotherapeutic drugs on healthspan and mortality in human. (Adapted from Kulkarni et al., 2022)

Gerotherapeutics	References	Primary outcome(s)
SGTL-2 inhibitors	Packer et al.[78]	A composite of cardiovascular death or hospitalization for worsening heart failure.
SGTL-2 inhibitors	Perkovic et al.[79]	A composite of end-stage kidney disease (dialysis, transplantation, or a sustained estimated GFR of <15 ml per minute per 1.73 m2), a doubling of the serum creatinine level, or death from renal or cardiovascular causes.
SGTL-2 inhibitors	Heerspink et al.[80]	A composite of a sustained decline in the estimated glomerular filtration rate (GFR) of at least 50%, end-stage kidney disease, or death from renal or cardiovascular causes.
SGTL-2 inhibitors	Neal et al.[81]	A composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke.
SGTL-2 inhibitors	Zinman et al.[82]	A composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke.
SGTL-2 inhibitors	McMurray et al.[83]	A composite of worsening heart failure (hospitalization or an urgent visit resulting in intravenous therapy for heart failure) or cardiovascular death.
Metformin	Knowler et al.[84]	Diagnosis of diabetes.
Metformin	UKPDS Group[85]	Any diabetes-related clinical endpoint (sudden death, death from hyperglycemia or hypoglycemia, fatal or non-fatal myocardial infarction, angina, heart failure, stroke, renal failure, amputation [of at least one digit], vitreous hemorrhage, retinopathy requiring photocoagulation, blindness in one eye, or cataract extraction); diabetes-related death (death from myocardial infarction, stroke, peripheral vascular disease, renal disease, hypoglycemia, or hyperglycemia, and sudden death); and all-cause mortality.
Metformin	Hong et al.[86]	A composite of cardiovascular events, death from a cardiovascular cause, and death from any cause.
Metformin	Luchsinger et al.[87]	The co-primary clinical outcomes were changes from baseline to 12 months in total recall of the Selective Reminding Test (SRT) and the score of the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog). The secondary outcome was change in relative glucose uptake in the posterior cingulate-precuneus in brain fluorodeoxyglucose positron emission tomography.
Metformin	Cryer et al.[88]	The primary end point was the incidence of serious adverse events (SAEs), death, and hospitalization.
Acarbose	Holman et al.[89]	To assess whether acarbose could reduce the frequency of cardiovascular events in Chinese patients with established coronary heart disease and impaired glucose tolerance, and whether the incidence of type 2 diabetes could be reduced.
Acarbose	Chiasson et al.[90]	The primary endpoint was development of diabetes on the basis of a yearly oral glucose tolerance test (OGTT).
Acarbose	Chiasson et al.[91]	To evaluate the effect of decreasing postprandial hyperglycemia with acarbose, an alpha-glucosidase inhibitor, on the risk of cardiovascular disease and hypertension in patients with impaired glucose tolerance (IGT).
Rapamycin/Rapalogs	Mannick et al.[92]	To evaluate whether the mammalian target of rapamycin (mTOR) inhibitor RAD001 ameliorated immunosenescence (the decline in immune function during aging) in elderly volunteers, as assessed by their response to influenza vaccination.
Rapamycin/Rapalogs	Mannick et al.[93]	To determine whether low-dose mTOR inhibitor therapy enhanced immune function and decreased infection rates in 264 elderly subjects given the study drugs for 6 weeks.
Rapamycin/Rapalogs	Kraig et al.[94]	To determine the safety and tolerability of RAPA in older human subjects.
Methylene Blue	Wishick et al.[95]	The primary outcome was change on the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog) at 24 weeks relative to baseline severity.
Angiotensin-converting enzyme inhibitor and angiotensin receptor blocker (ACEi/ARB)	NAVIGATOR study group[96]	Three coprimary outcomes: the development of diabetes; an extended composite outcome of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, hospitalization for heart failure, arterial revascularization, or hospitalization for unstable angina; and a core composite outcome that excluded unstable angina and revascularization.
ACEi/ARB	Lithell et al.[97]	The primary outcome measure was major cardiovascular events, a composite of cardiovascular death, non-fatal stroke and non-fatal myocardial infarction.
ACEi/ARB	Ravid et al.[98]	To evaluate the effect of prolonged ACE inhibition on renal function and albuminuria in patients with type 2 diabetes.
ACEi/ARB	Onder et al.[99]	The aim was to see whether ACE inhibitors also prevent reduction in physical performance and in muscle strength in older women who do not have congestive heart failure (CHF).
ACEi/ARB	Lithell et al.[100]	Primary: major cardiovascular events (cardiovascular mortality, non-fatal stroke or non-fatal myocardial infarction).
Dasatinib + Quercetin	Justice et al.[46]	The primary endpoints were retention rates and completion rates for planned clinical assessments. Secondary endpoints were safety and change in functional and reported health measures. Associations with the senescence-associated secretory phenotype (SASP) were explored.
Dasatinib + Quercetin	Hickson et al.[47]	Senescent cell and macrophage/Langerhans cell markers and circulating SASP factors.
Dasatinib + Quercetin	Martyanov et al.[101]	Primary objectives were safety and pharmacokinetics. Secondary outcomes included clinical assessments, quantitative high-resolution computed tomography (HRCT) of the chest, serum biomarker assays and skin biopsy-based gene expression subset assignments. Clinical response was defined as decrease of >5 or >20% from baseline in the modified Rodnan Skin Score (MRSS).

healthy individuals[55,56]. Genetic disorders which show early onset of aging phenotypes such as Down syndrome, which begins with aging of the oocyte before conception and which is linked to cellular senescence, may also be a target population and used in Geroscience as models of accelerated ageing and help develop geroprotective molecules[57,58] Cellular senescence has been associated with adverse pregnancy outcomes and modulating this hallmark of aging with gerotherapeutic drugs to prevent preterm birth is currently being considered[59]. The study of hallmarks of aging during the perinatal period and their postnatal and long-term effects also represents a new research path in maternal-fetal medicine and its consequences during later childhood or in adults such as asthma related to cellular senescence caused by perinatal hyperoxia[60]. It also appears that surviving cancer at a young age is associated with early onset of age-related chronic diseases including AD, diabetes mellitus, osteoporosis, or sarcopenia, probably due to an acceleration of the biological processes of aging[61,62]. Furthermore, certain acute infections such as COVID-19 induce cellular senescence thereby promoting the entry of the virus into healthy cells[26,63]. Clinical trials of Gerotherapeutics are therefore not restricted to the older adult population but may extend from frail older adults to childhood cancer or even astronauts exposed to radiation[6,64].

A currently unanswered question is the age at which an individual would begin taking a Gerotherapy in order to prevent aged-related diseases. This question is important because, according to the theory of pleiotropic antagonism, certain biological mechanisms improve health early in life but impair health later in life[65]. For example, some observational data suggest that young subjects with a high level of insulin-like growth factor 1 (IGF-1) are protected against chronic disease, while elderly subjects with a high level of IGF-1 have an increased incidence of age-related disease and death[66]. This points to the possibility that Gerotherapeutic drugs such as metformin, senolytics, IGF-1, and others could be beneficial when one is old but deleterious when one is young. To date, nothing justifies their use in healthy young subjects. However, certain conditions leading to accelerated aging, such as obesity, forced inactivity (e.g., bed rest), and chemotherapy could serve as early-stage indications for Gerotherapeutic drugs. The synergistic or antagonistic effect of Gerotherapeutic drugs should also

be studied. For example, in the MASTER trial, Walton, et al. hypothesized that metformin might enhance muscle gain during progressive resistance exercise training by reducing the inflammatory response. However, the authors observed a significantly greater gain in muscle mass in the placebo group[67]. Some data also suggest that metformin reduces the beneficial effects of physical training on endurance and strength capacities[68] but other data suggest that muscle quality is preserved with metformin[16].

Some Gerotherapeutic drugs, such as metformin, have been safely used for more than 60 years. Other more recently discovered molecules, such as sodium-glucose cotransporter-2 inhibitors (SGLT-2) or bisphosphonates, are already being widely used and are deemed safe[69,70]. However, our knowledge about potential long-term effects of other Gerotherapeutic drugs remains partial and fragmented. Due to the poorly-understood risks for these novel compounds, trials investigating innovative Gerotherapeutic drugs are currently focusing on target populations with more severe diseases for which there is no appropriate treatment, e.g., patients with idiopathic pulmonary fibrosis[46] or advanced cancers[71,72]. The results of these trials will help indicate whether Gerotherapeutic drugs can not only prevent but also treat diseases, even at an advanced stage.

Geroscience clinical trial task force discussion

The concept of Geroscience is that, by modulating one or more biological mechanisms of aging, it may be feasible to influence the functional loss/pathophysiology of a multitude of organs and thus prevent various diseases and clinical conditions. Given this concept, a clinical trial focused on outcomes that summarize the pleiotropic effects of a geroprotective molecule and its ability to prevent multi-morbidity would dramatically contribute to individual and public health. While this approach could validate the concept of Geroscience more than studies targeting one single function (e.g., strength or cognition) or a disease (e.g., Alzheimer's, or osteoarthritis), experts from the group recognized that in practice and as a first step, targeting a single disease or a function is more feasible approach initially and has the potential to more imminently benefit human health. Focusing on single outcomes such as cognition also have an easier regulatory path forward. Designing a disease-centric trial remains the only way to date to gain approval from the FDA or EMA, each of which still adheres to the "one disease, one drug" model. The regulatory constraints required for a new drug to be brought to patients and the extent to which the patients benefit from it must also be taken into consideration when designing a trial. However, targeting a single pathology in a clinical trial is not without risk either. Diagnostic criteria change over time, in particular with the emergence of biomarkers, not-withstanding that most diseases of ageing are of complex etiology, resulting from (still poorly understood) interactions between non-modifiable factors (including age, sex, and genetic predisposition) and modifiable factors, related to environmental and other exposures, lifestyle factors, etc. Moreover, it should be emphasized that some Gerotherapeutic drugs could have a very modest and difficult to demonstrate effect in organs evaluated separately, but have a clinically significant overall effect due to their action on the whole organism, and the alternative also exists that a study using a composite score might fail to capture substantial changes within just one domain if not statistically powered for that endpoint alone. A trial centered on only one function or disease is the current conventional approach but is probably not appropriate for certain molecules such as metformin, for which effects are pleiotropic, acting on multiple organs and through multiple biological mechanisms[73]. Demonstrating an effect of SGTL-2 inhibitors or rapamycin on cognition or heart failure alone would probably be very difficult to demonstrate because this would likely require an unrealistic number of participants in a clinical trial. Defining the therapeutic purpose of a molecule, therefore, needs to be considered on a case-by-case basis. The development of Geroscience research also requires partnership with governmental drug-regulating agencies such as the EMA and FDA so that drug indications evolve and can be validated outside the currently restricted environment.

By definition, the effect of a Gerotherapeutic drug on any given organ may correlate with its effect on other organs given that Gerotherapeutic drugs affect the common underlying mechanisms of aging shared by all organs. Gerotherapeutic drug trials are thus exemplified by trials such as the ones for Lomecel-B[42] targeting frailty and cognition and the rationale behind the design of the TAME study[14] to target multiple diseases. A key challenge for current Gerotherapeutic drug studies is to design studies that provide a better understanding of the mechanisms through which a Gerotherapeutic drug acting on one organ can at the same time act on the whole organism, as opposed to attempting to determine which clinical trial design might be best for Gerotherapeutic drugs overall. The group additionally stressed the importance of systematically collecting a dataset of common clinical tests and biological samples, whatever the primary outcome of the study, to facilitate cross-study comparability and foster progress in the understanding of the biology of aging.

A limitation of current Geroscience clinical trials is that most trials are small and carried out over a short period of time. Demonstrating progression in clinical phenotypes, such as the transition from robust to frail, is not feasible with small study population and short follow-up. Therefore, it is important to assay variables that change rapidly over time and predict long-term clinical effects. One option is to use validated biomarkers of aging, as has been done with cholesterol to validate the value of statins in preventing cardiac events. Therefore, the identification of valid and easily measurable biomarkers of biological aging is a fundamental issue. The ease of using new techniques such as unbiased omics approaches should rapidly advance research in the field. Although the search for such biomarkers of aging has been very active, currently there are no consensually accepted biomarkers of aging. Biomarkers of aging capable of predicting the rate of aging would make it possible to stratify the individual risk, to develop prevention strategies, and eventually to monitor the response to the treatments implemented. In a narrative review, Gonçalves, et al.[74], reported many promising biomarkers of frailty within each key biological determinants of the aging process[15] but none has demonstrated its superiority. It is therefore more likely that a set of biomarkers (such as a set of components of SASP, GDF15, epigenetic clock, telomerase activity…), rather than a single biomarker, would be the most appropriate approach to measure the rate of aging. Biomarkers are likely to be a way in the future to better define the criteria by which a target population for a given treatment may be identified. The hierarchy of hallmarks of aging as proposed by ref. [75] in three categories (primary, antagonistic, and integrative hallmark) is controversial but suggests that some biomarkers of aging could be used preferentially to assess and follow the early aging phase (primary biomarkers). Other biomarkers may represent a response to damage at a later stage of aging or in different clinical conditions (antagonistic biomarkers). Finally, the global rate of aging could be assessed by other biomarkers (integrative biomarkers). Further investigation to identify biomarkers to aid Gerotherapeutic drug study recruitment and define early change are needed. For this, pre-clinical studies play a critical role in building the design of clinical trials. An alternative to identification of such biomarkers to define the study population could be to conduct studies targeting the acute resilience framework, e.g., clinical situations such as disability associated with hospitalization, delirium, or acute loss of muscle mass after surgery. In this context, a Gerotherapeutic drug could have a significant effect over a very short period of time, thus providing the proof-of-concept for new molecules. A caveat is the difficulty in this clinical setting to include and collect data prior to the acute event (hip fracture, infection, etc.), making these trials difficult to conduct. In addition, there is also the difficulty of the potential study population's heterogeneity in this clinical setting. The underlying

hypothesis behind the use of gerotherapeutic drugs is that they act simultaneously on different aging mechanisms. Biomarkers of aging would make it possible to limit the problems of heterogeneity of the population. They could also make it possible to better understand which are the mechanisms of aging that are favorably influenced by the gerotherapeutic drug. Nevertheless, it cannot be ruled out that a composite of many outcomes may challenge identification of mechanisms due to the many mechanisms potentially integrated in the multiple outcomes.

Combinatorial therapy, whether multiple Gerotherapeutic drugs or Gerotherapeutic drugs combined with other drugs—even drugs that failed in phase 3 for lack of clinically significant improvement—should also be investigated. A change in the health paradigm from being focused on the treatment of a single disease to focusing on the development of treatments to address aging mechanisms would pave the way for designing novel therapeutic approaches and trial designs. At present, a large number of on-going research approaches are focused on the development of a new class of pleiotropic molecules collectively called Gerotherapeutic drugs. A collective reflection of patient associations, the pharmaceutical/biotech industry, researchers, and drug agencies must be carried out in parallel with the development of these molecules such that the greatest number of individuals can benefit from these therapeutic advances without delay.

Geroscience brings the hope of an increased life expectancy at birth, and a compression of morbidity in late life. The duty of social justice is to lead everyone to be able to access the innovations brought about by advances in Geroscience[76]. The indication of preventive drugs could concern a very large proportion of the population. If Gerotherapeutic drugs are expensive and only accessible to the richest, its consequences would be to accentuate social inequalities. The life expectancy of the richest is currently higher than that of the poorest mainly due to social and environmental factors. Gerotherapic drugs accessible to the greatest number would reduce this inequity. The reflection around Gerotherapeutic drug' development and their reimbursement must consider these economic, societal and ethical dimensions.

Inequity currently exists in routine care and clinical research where minority populations, particularly older subjects, and subjects most at risk of experiencing poorer outcomes are often excluded from clinical trials. Future treatments in the field of Geroscience are likely to concern a considerable number of subjects with different clinical profiles. Geroscience clinical trials should ensure access to the innovation for all individuals who can benefit from it; that will contribute to detect differences in responses to interventions according to subgroups and enhance the generalizability of the conclusions.

The dream of eternal youth must not lead to drifts in the sale of molecules whose undesirable effects are not known or the thoughtless initiation of research projects raising ethical questions. The credibility of the field of Geroscience depends on it. Independent organizations, such as the Nuffield Council on Bioethics[77], can be of assistance in addressing the ethical issues raised by Geroscience and providing informed comments to policy makers on emerging issues[76].

At present, further research is required to better understand the mechanisms through which Gerotherapeutic drugs produce their benefits, to define the most appropriate outcomes for assessing the effects of Gerotherapeutics, to delineate target populations, and to demonstrate the safety and tolerability of these molecules. The science of aging may need to extend beyond its focus on older adults, and shift to include young individuals and, to do so, it will be necessary to develop sensitive biomarkers which accurately characterize aging trajectories. The field of Geroscience is at its infancy, but it provides a promising basis for the management and prevention of age-related diseases, accelerated aging conditions, and geriatric syndromes with a potentially transformative impact on public health.

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Competing interests

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