Accreditation of the program has been received from the Dutch Institution ‘Accreditatie Bureau Algemene Nascholing (ABAN)’ with a total of 11 points under ID number 299155.
- Thursday, November 9, 2017: 1 point.
- Friday, November 10, 2017: 6 points.
- Saturday, November 11, 2017: 4 points.
# Contents

<table>
<thead>
<tr>
<th>Subject</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contents</td>
<td>2</td>
</tr>
<tr>
<td>Introduction</td>
<td>3</td>
</tr>
<tr>
<td>Conference directors</td>
<td>4</td>
</tr>
<tr>
<td>Program directors</td>
<td>5</td>
</tr>
<tr>
<td>Chair Poster Session / Planning Committee</td>
<td>6</td>
</tr>
<tr>
<td>Program</td>
<td>7</td>
</tr>
<tr>
<td>Faculty</td>
<td>10</td>
</tr>
<tr>
<td>Session Chairs</td>
<td>13</td>
</tr>
<tr>
<td>Alliance for Healthy Aging Members</td>
<td>18</td>
</tr>
<tr>
<td>Maps</td>
<td>19</td>
</tr>
</tbody>
</table>

**Thursday, November 9, 2017**

*Opening, Keynote Lecture, Buffet* .................................................. 21

**Friday, November 10, 2017**

*Topic I Mitochondria, ROS & NAD* ..................................................... 24
*Topic II Metabolism and Cell Senescence* .......................................... 31
*Topic III Nutrient sensing* .............................................................. 37

**Saturday, November 11, 2017**

*Topic IV Systems Biology* ................................................................. 42
*Topic V Metabolism and stem cell ageing* ............................................ 49

Abstracts (Oral/Posters) ................................................................. 55

Participants ................................................................. 91
Introduction

8th Annual Alliance for Healthy Aging Conference
*A partnership of the Mayo Clinic Robert and Arlene Kogod Center on Aging, The University Medical Center Groningen, and Newcastle University Institute for Ageing*

The Alliance for Healthy Aging was founded by the Mayo Clinic Robert and Arlene Kogod Center on Aging (Rochester, Minnesota, USA) and, from the Netherlands, the University Medical Center Groningen (Groningen), the University of Groningen, the Noaber Foundation (Lunteren) and Vita Valley (Ede). Since 2015, Newcastle University (Newcastle, UK) joins in the organisation of the conferences. The Alliance is holding a series of annual meetings dedicated to translational research on aging with the objective to bring together scientists, clinicians and engineers, providing a forum for the exchange of ideas.

History: In June 2010, the first meeting, The Next Step in Aging Research: From Bench to Bedside: A Forum for Collaboration between Clinicians and Researchers, focused on the basic biology of ageing and its relationship to clinical practice. It was a resounding success. In October 2011, the second meeting was held in Groningen, entitled Healthy Aging and Independent Living: Countering Frailty and Maintaining Independence. In November 2012, the conference was held back at the Mayo Clinic in Rochester, with conference topic Senescence and Healthspan. The 2013 conference topic in Groningen was on Molecular Mechanisms of Age-Related Multi Morbidity and the 2014 conference in Rochester was on Frailty and Healthspan: Bench to Bedside to Home. Newcastle University Institute for Ageing hosted the 6th Annual Conference on Interventions to Slow Down Ageing in 2015 at Slaley Hall in the North of England. The 7th Annual Conference, Highlights of Aging Research, was scheduled to take place in Jacksonville, Florida. Unfortunately, the conference had to be cancelled due to hurricane Matthew.

Present: The 8th Annual Alliance for Healthy Aging Conference, entitled Metabolism & Ageing, with conference topics: I Mitochondria, ROS & NAD; II Metabolism and Cell Senescence; III Systems Biology; IV Nutrient Sensing; and V Metabolism and Stem Cell Ageing, will be held at the University Medical Center Groningen, Groningen, The Netherlands from November 9-11, 2017.

Benefits: The meeting will foster research collaborations, act as a springboard for new research grants and directions, and accelerate the translation of scientific discoveries to clinical practice by bringing together an expert and interdisciplinary panel with unique clinical, scientific, and commercial perspectives.

Program Description: Sessions will be organized around key topics. Each session will have a chair and co-chair. Presentations by invited speakers will consist of a 25 minute talk and 5 minutes of discussion. To encourage participants to engage across different areas of research and focus, the meeting will not have concurrent sessions. In an effort to promote attendance by junior investigators, students, and clinical trainees, we will offer travel awards for outstanding abstracts. To be considered for a travel award an abstract must be submitted and a scientific poster displayed/presented at the poster session.

Ruud Krom Fund: The organisation of the 8th Alliance for Healthy Aging is very grateful for the support by the Ruud Krom Fund.
Conference directors

Marian Joëls, PhD

Prof. Marian Joëls (Amsterdam, 1956) studied Biology at the University of Amsterdam. She graduated in 1984 and started her career as researcher and was appointed Professor of Zoology in 1997 at the University of Amsterdam. In 2009 she was appointed Professor of Neurosciences at the University of Utrecht and became Director of the Research Institute Brain Center Rudolf Magnus at the University Medical Center Utrecht. Since September 2016 Professor Joëls acts as Dean and Member of the Board of Directors of the University Medical Center Groningen, Groningen, The Netherlands. Marian Joëls is an internationally renowned scientist who closely connects laboratory and clinic in her work. Her research focus is mainly on stress and the brain.

James L. Kirkland, MD, PhD

James L. Kirkland, M.D., Ph.D., is the director of the Robert and Arlene Kogod Center on Aging at Mayo Clinic and Noaber Foundation Professor of Aging Research. Dr. Kirkland’s research is on cellular senescence, age-related adipose tissue and metabolic dysfunction, and development of agents and strategies for targeting fundamental aging mechanisms to treat age-related chronic diseases and disabilities. He published the first article about drugs that clear senescent cells – senolytic agents. He is a scientific advisory board member for several companies and academic organizations. He is a member of the National Advisory Council on Aging of the National Institutes of Health, President-Elect of the American Federation for Aging Research, and past chair of the Biological Sciences Section of the Gerontological Society of America. He holds honorary appointments at Boston University and the University of Groningen in the Netherlands. He is a board certified specialist in internal medicine, geriatrics, and endocrinology and metabolism.

Thomas von Zglinicki, PhD, Dr nat.habil.

Dr. von Zglinicki, Professor of Cell Gerontology, is a founding member of the basic biology branch of the Newcastle Ageing Institute and its present scientific director. His principal research interest is in understanding the cellular and molecular signaling pathways connecting DNA damage responses (specifically emanating from dysfunctional telomeres) with mitochondrial function and metabolism, thus causing and maintaining cell senescence, and how these contribute to mammalian ageing. He was the first to discover oxidative stress and resulting DNA damage as a major cause of telomere shortening and to propose telomere length as a biomarker of ageing in humans. Dr. von Zglinicki chaired the 2004 Gordon Research Conference on Biology of Aging. He chairs the Scientific Advisory Board (SAB) of the Leibniz Institute for Environmental Medicine Dusseldorf (Germany) and is a member of the Mayo Clinic Robert and Arlene Kogod Center on Aging SAB. He is a Trustee of the Seneca Award for Aging Research of the Industry Club Dusseldorf and serves on the editorial boards of Aging Cell, Aging (Albany) and other journals in the field. He published over 200 papers on cell and molecular biology of ageing, resulting in an h-index of 64 (Google Scholar).
Program directors

Barbara Bakker, PhD
Barbara Bakker studied biochemistry at the University of Amsterdam and did her PhD in systems biology ‘avant la lettre’ at the VU University Amsterdam. During her PhD and postdoc period she also worked at the De Duve Institute in Brussels, the Biozentrum in Frankfurt, and the Delft University of Technology. Subsequently, she became Assistant (2000) and Associate Professor (2003) at the VU University Amsterdam. Since 2009 she is a group leader in Groningen.

Eduardo Chini, MD, PhD
Professor of Anesthesiology, Mayo Clinic Robert and Arlene Kogod Center on Aging and Mayo Clinic Cancer Center, Rochester, Minnesota, USA. Eduardo Nunes Chini, MD, PhD, received his MD and PhD from the federal university of Rio de Janeiro in Brazil, and did a fellowship in basic research and residency in Anesthesiology at the Mayo Clinic in Rochester. Dr. Chini activities at the Mayo Clinic include clinical and academic, and administrative duties. He dedicates 50% of his time to patient care and 50% to research and his academic and administrative activities.

Thomas von Zglinicki, PhD, Dr nat.habil.
Chair Poster Session

Tamara Tchkonia, PhD

Tamar Tchkonia’s research is focused on the role of senescent cells in aging and disease. She is one of the four co-inventors of a mouse model where senescent cells can be removed selectively and a named inventor on seven patent applications related to therapeutic approaches for targeting senescent cells in aging and disease. Recently, in collaboration with Dr. Kirkland and others she identified first senolytic agents that are effective in eliminating senescent cells both \textit{in vitro} and \textit{in vivo}. Our group first demonstrated that clearance of senescent cells pharmacologically improves healthspan in chronologically aged mice.

Planning Committee

Ann Boer

Ann Boer is staff member for the Healthy Ageing Team and for the Center for Development and Innovation, Office of the Dean of Research, University Medical Center Groningen, P.O. Box 30.001, HPC LB43, 8th floor De Brug, room 8.17, NL-9700 RB Groningen.

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Sharon Denley

Sharon Denley is Institute Manager at Newcastle University Institute for Ageing, Campus for Ageing and Vitality, Newcastle upon Tyne NE4 5PL, United Kingdom.

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http://www.ncl.ac.uk/ageing/

http://www.ncl.ac.uk/nica/

Julie L. Sokoloski

Julie Sokoloski is program coordinator for the Robert and Arlene Kogod Center on Aging at Mayo Clinic, Rochester, Minnesota, USA.

Sokoloski.julie@mayo.edu
Program

Thursday, November 9, 2017

Location Registration Desk: next to the Fonteinpatio and nearby ‘Entrance Oostersingel - 11’
14.00  Registration open

Location: Blauwe Patio / Blue Patio
14.00  Poster mounting open

Location: Blauwe Zaal / Blue Room
17.30  Opening & Welcome by the conference directors
      Marian Joëls, PhD, Dean/Board of Directors University Medical Center Groningen
      James L. Kirkland, MD, PhD, Mayo Clinic Robert and Arlene Kogod Center on Aging
      Thomas von Zglinicki, PhD, University Ageing Biology Centre, Newcastle University

17.35  Announcement by the President of the University of Groningen
      Sibrandes Poppema, MD, PhD

17.45  Keynote lecture
      Genetic mapping of targets in mitochondria, metabolism and ageing
      Johan Auwerx, MD, PhD, Professor at the Ecole Polytechnique Fédérale, Laboratory of Integrative
      and Systems Physiology, Lausanne, Switzerland

18.45  Drinks and Dinner buffet
      The drinks (reception) are offered to you by the University of Groningen, the Municipality of
      Groningen and the Province of Groningen

Friday, November 10, 2017

Location: Rode Zaal / Red Room
08.00  Registration Open

Topic I Mitochondria, ROS & NAD
08.20  Opening by program director Barbara Bakker (UMCG) and chairs Gabriele Saretzki
      (Newcastle University) & Ellen Nollen (UMCG)
08.25  The NAD metabolome – Bioenergetics, signalling and emerging therapeutic applications
      Mathias Ziegler, MD, PhD, Professor at the University of Bergen, Head of the Department of
      Biomedicine, Faculty of Medicine, Bergen, Norway
08.55  Ketone bodies: Signaling metabolites that affect aging and memory
      John Newman, MD, PhD, Assistant Professor of Geriatrics, UCSF, San Francisco USA; Visiting
      Scientist, Buck Institute for Research on Aging, Novato USA
09.25  Mitochondrial DNA methylation
      Marianne C. Rotz, PhD, Professor of Molecular Epigenetics, Department of Pathology and
      Medical Biology, University Medical Center Groningen, Groningen, the Netherlands
09.55  CD38: from mechanism to therapy for aging-related metabolic decline
      Eduardo Chini, MD, PhD, Professor of Anesthesiology, Mayo Clinic Robert and Arlene Kogod
      Center on Aging and Mayo Clinic Cancer Center, Rochester, Minnesota, USA
10.25  Summary Topic I by chairs
Location: Blauwe Patio / Blue Patio

10.30  Coffee break

**Topic II Metabolism and Cell Senescence**

11.00  **Opening by chairs** Nathan LeBrasseur (Mayo Clinic, Rochester, Minnesota) & Folkert Kuipers (UMCG)

11.05  **Cellular Senescence: At the Nexus between Obesity and Metabolic Dysfunction**  
**James L. Kirkland**, MD, PhD, Noaber Foundation Professor of Aging Research, Director Mayo Clinic Robert and Arlene Kogod Center on Aging, Rochester, Minnesota, USA

11.35  **Nuclear to Mitochondrial DNA damage signaling in Neurodegeneration and Aging**  
**Vilhelm A. Bohr**, MD, PhD, Senior investigator, Laboratory of Molecular Gerontology, National Institute on Aging, Baltimore, USA

11.45  **Pharmacological inhibition of mitochondrial complex I reduces senescence and reverses aging-related regulation of gene expression in mice**  
**Eugenia Trushina**, PhD, Associate Professor, Mitochondrial Neurobiology and Therapeutics Laboratory Mayo Clinic, Rochester, Minnesota, USA

12.05  **Senescence in post-mitotic cells: a telomere-centric story**  
**João Passos**, PhD, Associate Professor, Newcastle University Institute for Ageing and Institute for Cell and Molecular Biosciences, Newcastle University, UK

12.30  **Summary by chairs**

13.00  **Poster Pitch by**

13.25  **Ana Patricia Huerta Guevara**, University Medical Center Groningen, Groningen  
**Selma Osmanagic-Myers**, University of Natural Resources and Life Sciences, BOKU, Vienna  
**Mariana Tarrago**, Mayo Clinic

Location: Blauwe Patio / Blue Patio

13.30  **Lunch, Poster viewing and discussion**

**Topic III Nutrient sensing**

15.30  **Opening by chairs** Cor Calkhoven (UMCG) & Diana Jurk (Newcastle University)

15.35  **Nutritional modulation of nonhuman primate aging**  
**Rozalyn Anderson**, PhD, Associate Professor, Department of Medicine, SMPH, University of Wisconsin-Madison, USA

16.05  **Mechanistic insights into mTORC1 and autophagy in cell senescence**  
**Viktor Korolchuk**, PhD, Associate Professor, Institute for Cell and Molecular Biosciences, Newcastle University Institute for Ageing, Newcastle University, UK

16.30  **Systems approaches to the mammalian target of rapamycin (mTOR) network**  
**Kathrin Thedieck**, PhD, Associate Prof of Biochemistry & Molecular Biology, Department of Paediatrics, University Medical Center Groningen, Groningen, the Netherlands

17.05  **Developing tools to monitor changes in metabolism in cancer patients**  
**Hilde Jalving**, MD, PhD, Medical Oncologist, Department of Medical Oncology, University Medical Center Groningen, Groningen, the Netherlands

17.30  **Summary by chairs**

17.40  **Closing day 1 by program directors**

Location: Restaurant ’t Feithhuis

18.30  Dinner
Saturday, November 11, 2017
Location: Rode Zaal / Red Room

**Topic IV Systems Biology**

08.30 Opening by chairs Tamara Tchkonia (Mayo Clinic) & Paul Robbins (Scripps Research Institute, Jupiter, Florida)

08.35 *From the control of erythropoiesis to patient-specific anemia treatment*

_Ursula Klingmüller_ PhD, Division Head, Division Systems Biology of Signal Transduction, German Cancer Research Center (DKFZ), Heidelberg, Germany

09.05 *Systems modelling of cell signalling networks in ageing*

_Daryl Shanley_ PhD, Senior Lecturer, Institute for Cell and Molecular Bioscience, Newcastle University, UK

09.35 *Multilevel regulation of mitochondrial metabolism during muscle ageing*

_Barbara Bakker_ PhD, Professor of Medical Systems Biology, Department of Pediatrics and Systems Biology Center for Energy Metabolism and Ageing, University Medical Center Groningen, Groningen, the Netherlands

10.05 *Saccharomyces cerevisiae goes through distinct metabolic phases during its replicative life*

_Matthias Heinemann_ PhD, Professor of Biochemistry & Molecular Biology, Microbiology, Faculty of Science and Engineering, University of Groningen, Groningen, the Netherlands

10.35 **Summary** by chairs

Location: Blauwe Patio / Blue Patio

10.40 **Coffee break**

**Topic V Metabolism and stem cell ageing**

11.10 Opening by chairs Laura Niedernhofer (Scripps Research Institute, Jupiter, Florida, USA) & Gerald de Haan (UMCG)

11.15 *Mitochondrial Metabolic Checkpoint, Stem Cell Aging and Rejuvenation*

_Danica Chen_, PhD, Professor of Nutritional Sciences and Toxicology, Department of Nutritional Sciences & Toxicology, Berkeley University of California, USA

11.45 *Epigenetic stress response and stem cell aging*

_K. Lenhard Rudolph_, MD, Head of the research group on ‘Stem cell aging’ and Scientific Director Leibniz Institute on Aging – Fritz Lipmann Institute, Jena, Germany

12.15 *Using stem cells to understand and model age related macular degeneration*

_Majlinda Lako_, PhD, Professor of Stem Cell Science, Institute of Genetic Medicine, Newcastle University, UK

12.45 *Mitochondrial and senescence mechanisms in lung disease: aging at birth?*

_Y.S. Prakash_, MD, PhD, Chair of Physiology and Biomedical Engineering, Mayo Clinic Robert and Arlene Kogod Center on Aging, Rochester, Minnesota, USA

13.15 **Summary** by chairs

Location: Blauwe Patio / Blue Patio

13.20 **Conference closing by conference and program directors followed by Closing lunch**
Faculty

Rozalyn Anderson, PhD
Associate Professor, Department of Medicine, SMPH, University of Wisconsin-Madison, USA

Johan Auwerx, MD, PhD (keynote)
Professor at the Ecole Polytechnique Fédérale, Laboratory of Integrative and Systems Physiology, Lausanne, Switzerland

Barbara Bakker, PhD
Professor of Medical Systems Biology, Department of Pediatrics and Systems Biology Center for Energy Metabolism and Ageing, University Medical Center Groningen, Groningen, the Netherlands

Vilhelm A. Bohr, MD, PhD
Senior investigator, Laboratory of Molecular Gerontology, National Institute on Aging, Baltimore, USA

Cornelis F. Calkhoven, PhD
Principal investigator at the European Research Institute for the Biology of Ageing (ERIBA), University Medical Center Groningen, Groningen, the Netherlands

Danica Chen, PhD
Professor of Nutritional Sciences and Toxicology, Department of Nutritional Sciences & Toxicology, Berkeley University of California, USA

Eduardo Chini, MD, PhD
Professor of Anesthesiology, Mayo Clinic Robert and Arlene Kogod Center on Aging and Mayo Clinic Cancer Center, Rochester, Minnesota, USA

Gerald de Haan, PhD
Scientific Director of the European Research Institute for the Biology of Ageing (ERIBA), University Medical Center Groningen, Groningen, the Netherlands

Matthias Heinemann, PhD
Professor of Biochemistry & Molecular Biology, Microbiology, Faculty of Science and Engineering, University of Groningen, Groningen, The Netherlands

Hilde Jalving, MD, PhD
Medical Oncologist, Department of Medical Oncology, University Medical Center Groningen, Groningen, the Netherlands

Marian Joëls, PhD
Professor of Neuroscience, Dean/Board of Directors University Medical Center Groningen, Groningen, the Netherlands

Diana Jurk, PhD
Principal Investigator, Newcastle University Institute for Ageing (NUIA), Institute for Cell & Molecular Biosciences (ICaMB), Newcastle Universitair, Newcastle upon Tyne, United Kingdom

James L. Kirkland, MD, PhD
Noaber Foundation Professor of Aging Research, Director Mayo Clinic Robert and Arlene Kogod Center on Aging, Rochester, Minnesota, USA

Ursula Klingmüller, PhD
Division Head, Division Systems Biology of Signal Transduction, German Cancer Research Center (DKFZ), Heidelberg, Germany

Viktor Korolchuk, PhD
Associate Professor, Institute for Cell and Molecular Biosciences, Newcastle University Institute for Ageing, Newcastle University, UK
Folkert Kuipers, PhD  
Professor of Pediatrics, head Laboratory of Pediatrics, University Medical Center Groningen, the Netherlands

Majlinda Lako, PhD  
Professor of Stem Cell Science, Institute of Genetic Medicine, Newcastle University, UK

Nathan LeBrasseur, PT, PhD  
Consultant, Associate Professor and Co-Chair of Research in the Department of Physical Medicine and Rehabilitation, Mayo Clinic, Rochester, Minnesota, USA

John Newman, MD, PhD  
Assistant Professor of Geriatrics, UCSF, San Francisco USA; Visiting Scientist, Buck Institute for Research on Aging, Novato USA

Laura Niedernhofer, MD, PhD  
Associate Professor in the Department of Molecular Medicine and the Center on Aging at The Scripps Research Institute in Jupiter, Florida, USA

Ellen Nollen, PhD  
Principle investigator at the European Research Institute for the Biology of Aging (ERIBA), University Medical Center Groningen, Groningen, the Netherlands

João Passos, PhD  
Associate Professor, Newcastle University Institute for Ageing and Institute for Cell and Molecular Biosciences, Newcastle University, UK

Sibrandes Poppema, MD, PhD  
President of the University of Groningen, Groningen, the Netherlands

Y.S. Prakash, MD, PhD  
Chair of Physiology and Biomedical Engineering, Mayo Clinic Robert and Arlene Kogod Center on Aging, Rochester, Minnesota, USA

Paul D. Robbins, PhD  
Professor of Molecular Medicine at The Scripps Research Institute (TSRI) in Jupiter, Florida and Director of the TSRI Center on Aging, USA

Marianne G. Rots, PhD  
Professor of Molecular Epigenetics, Department of Pathology and Medical Biology, University Medical Center Groningen, Groningen, the Netherlands

K. Lenhard Rudolph, MD  
Head of the research group on 'Stem cell aging' and Scientific Director Leibniz Institute on Aging – Fritz Lipmann Institute, Jena, Germany

Gabriele Saretzki, PhD  
Lecturer, University Ageing Biology Centre, Newcastle upon Tyne, United Kingdom

Daryl Shanley, PhD  
Senior Lecturer, Institute for Cell and Molecular Bioscience, Newcastle University, UK

Tamara Tchkonia, PhD  
Mayo Clinic Robert and Arlene Kogod Center on Aging, Rochester, Minnesota, USA

Kathrin Thiedieck, PhD  
Associate Professor of Biochemistry & Molecular Biology, Department of Paediatrics, University Medical Center Groningen, Groningen, the Netherlands
Eugenia Trushina, PhD  
Associate Professor, Mitochondrial Neurobiology and Therapeutics Laboratory Mayo Clinic, Rochester, Minnesota, USA

Thomas von Zglinicki, PhD  
Professor of Cell Gerontology, Director The ABC-Newcastle, University Ageing Biology Centre, Newcastle upon Tyne, United Kingdom

Mathias Ziegler, MD, PhD  
Professor at the University of Bergen, Head of the Department of Biomedicine, Faculty of Medicine, Bergen, Norway
Session Chairs

Cornelis F. Calkhoven, PhD

Dr. Calkhoven is principal investigator at the European Research Institute for the Biology of Ageing (ERIBA). He studied biology and chemistry at the University of Groningen, where he also received his PhD-degree in 1996. As a Marie Curie Postdoctoral fellow he then moved to the Max Delbrück Center for Molecular Medicine (MDC) in Berlin, where in 2000 he was rewarded with a Helmholtz fellowship to start his own research group. At the MDC he identified factors and mRNA-regulatory elements that control translation of key factors in cellular differentiation and cancer. In 2005 he moved to the Leibniz Institute on Aging - Fritz Lipmann Institute (FLI) in Jena where he established a research program to study common regulatory mechanisms in ageing, metabolism and cancer. The current focus is on understanding the mechanisms of gene-regulation that are under control of the nutrient and energy sensitive mTORC1 signaling pathway and its involvement in health- and lifespan determination.

Gerald de Haan, PhD

Gerald de Haan received his MSc (1990) and PhD (1995) from the University of Groningen. As a graduate student he was employed by the University of Cologne, working on the regulation of blood cell production by growth factors. He became a postdoc at the University of Kentucky with Gary Van Zant where he worked on stem cell aging, and returned to the Netherlands as a fellow of the Royal Netherlands Academy of Sciences. He established his own lab at the Department of Cell Biology, where he was appointed full professor in 2005. He was awarded a VICI grant by the Netherlands Organization of Scientific Research in 2007. From October 2016 Gerald holds the position of Scientific Director of the European Research Institute for the Biology of Ageing. The general scope of studies in his Laboratory is to further improve the understanding of mechanisms that specify normal stem cell functioning. Studies focus on hematopoietic stem cells, largely because superior technical tools and invaluable functional assays exist to study stem cells in this particular tissue. Gerald's group is interested in the unique genetic and epigenetic program that distinguishes stem cells from non-stem cells.

Diana Jurk, PhD

Diana Jurk studied Natural Sciences at TU Bergakademie Freiberg (Germany) and completed her PhD at the Institute for Ageing and Health at Newcastle University under the supervision of Prof Thomas von Zglinicki, Prof Derek Mann and Prof Chris Day. She received her PhD degree in 2012 on the basis of her work on “The role of cell senescence and inflammation in mouse ageing”. Dr Jurk, as part of her PhD, was the first to demonstrate that ageing mice neurons show multiple hallmarks of cell senescence, which has led to the recent proposal of a redefinition of senescence as a phenotype not exclusive to proliferation competent cells. She demonstrated how
cellular senescence induced by genotoxic or oxidative stress depends on chronic DNA-damage signalling from irreparable damage to telomeres and how nfkb1−/− mice develop chronic systemic inflammation which aggravates cell senescence in various tissues, inducing an accelerated ageing phenotype and decreasing lifespan. Recently, she and her group showed that senescence drives age-dependent hepatic steatosis (NAFLD) and that clearance of senescent cell can reduce fat accumulation in hepatocytes and restore liver function. At the moment she is investigating the mechanisms by which cellular senescence contributes to brain ageing and neurodegeneration. She was a Faculty Fellow of Newcastle University (2015-2017) and has started her own research group as Principal Investigator in 2017.

**Folkert Kuipers, PhD**

Folkert Kuipers is Professor of Pediatrics and head of the Laboratory of Pediatrics (www.labpediatricsrug.nl) at the University Medical Center Groningen (UMCG) and holds the Healthy Life Alliance professorship at the University of Groningen, Groningen, The Netherlands. From September 2008-March 2016 he served as Dean of the Faculty of Medical Sciences and Vice-Chairman of the Board of Directors of the UMCG. He studied biology/biochemistry at the University of Groningen and received his PhD degree in the Faculty of Medical Sciences, University of Groningen, in 1987. His research program deals with regulation and development of lipid and cholesterol metabolism and transport in liver and intestine and with the interactions between carbohydrate and lipid metabolism in metabolic disorders associated with obesity and ageing. He is one of the initiators of the Alliance for Healthy Aging, a transatlantic network organization. He is (co-) author of >320 peer-reviewed publications and has supervised >25 PhD theses. Currently, he is a member of the Supervisory Board of the Healthy Ageing Network Northern Netherlands (HANNN, www.hannn.eu), the Dutch Permanent National Committee Large Research Infrastructures and of the External Advisory Boards of the Pasteur Institute in Lille (France), the Well Living Lab, Mayo Clinic and Delos Ventures, and the Robert & Arlene Kogod Center for Aging Research at the Mayo Clinic (Rochester, MA, USA).

**Nathan LeBrasseur, PT, PhD**

Nathan LeBrasseur is a Consultant, Associate Professor, and the Co-Chair of Research in the Department of Physical Medicine and Rehabilitation at Mayo Clinic. He received an M.S in physical therapy and his Ph.D. in applied anatomy and physiology from Boston University and conducted postdoctoral studies in molecular medicine and integrative physiology at Boston Medical Center. His laboratory conducts translational “bench-to-bedside” research on strategies to improve physical performance, metabolism, and resilience in the face of aging and disease. Dr. LeBrasseur directs the Healthy Aging and Independent Living Program and the Healthspan Assessment Laboratory in the Robert and Arlene Kogod Center on Aging, and the Muscle Performance and Physical Function Core in the Center for Clinical and Translational Sciences. He is also an Associate Director of the Glenn Laboratories for Senescence Research at Mayo Clinic.
Laura Niedernhofer, MD, PhD

Laura Niedernhofer is an Associate Professor in the Department of Molecular Medicine and the Center on Aging at The Scripps Research Institute in Jupiter, Florida. She has a Bachelor of Sciences in Chemistry from Duke University and completed the Medical Scientist Training Program at Vanderbilt University. She followed this with post-doctoral training at the Erasmus Medical Center in Rotterdam, the Netherlands, under the mentorship of Jan Hoeijmakers. There she discovered a new progeroid syndrome caused by a defect in DNA repair, cementing a link between DNA damage and aging. She began her independent career at the University of Pittsburgh in the Department of Microbiology and Molecular Genetics. Dr. Niedernhofer’s current research program is focused on discovering the mechanism by which DNA damage promotes aging and age-related diseases. She primarily works with murine models of human genome instability disorders and has a drug discovery program aimed at extending healthy aging. She has been awarded the Hillman Family Foundation and PNC Bank for innovative cancer research, the Mentorship Award at Scripps, and the Hart Family Foundation Award for her advocacy work. Laura was an Ellison Medical Foundation New Scholar in Aging, an Outstanding New Environmental Scientist with NIEHS, a recipient of the Glenn Award for Research in Biological Mechanisms of Aging, and elected to the American Society for Clinical Investigation for her translational research. She has served on the Board of Directors for the Federation of American Societies for Experimental Biology since 2009 and is a standing member of Cellular Mechanisms of Aging and Development for NIA.

Ellen Nollen, PhD

Ellen Nollen is a principle investigator at the European Research Institute for the Biology of Aging (ERIBA) in Groningen, leading the Molecular Neurobiology of Aging group. Her studies focus the molecular basis of aging-associated neurodegenerative diseases, in particular on role of toxic aggregation prone-proteins. Her group aims to identify cellular mechanisms that drive protein toxicity during the aging process. These mechanisms can then be further explored as candidate targets to treat neurodegenerative diseases. Ellen Nollen received her PhD from the University of Groningen in 2000. Her postdoctoral training she obtained at Northwestern University, Evanston, USA and at the Hubrecht Institute, Utrecht, the Netherlands. Ellen Nollen was the first researcher to be awarded a Rosalind Franklin Fellowship at the UMCG. In 2011 she was awarded a EUR 1.5 million European ERC grant for her research and was named as an EMBO Young Investigator.

Paul D. Robbins, PhD

Paul Robbins is a Professor of Molecular Medicine at The Scripps Research Institute (TSRI) in Jupiter, Florida and Director of the TSRI Center on Aging. Previously he was a Professor of Microbiology and Molecular Genetics, Director of Basic Research for the Molecular Medicine Institute and Co-Director of the Paul Wellstone Cooperative Muscular Research Center at the University of Pittsburgh School of Medicine as well as Interim Director of Molecular & Cellular Oncology at the University of Pittsburgh Cancer Institute. He received his B.A. from Haverford College, his Ph.D. from the University of California at Berkeley and worked as a post-doctoral fellow in the
laboratory of Dr. Richard Mulligan at the Whitehead Institute for Biomedical Research at MIT. He has co-authored over 325 peer-reviewed manuscripts and 175 book chapters and reviews and has edited four books. He was a member of the NIH PathB Study Section, Chair of the Italian Telethon Scientific Review Committee and a member of the Telethon Scientific Advisory Board. He also was a member of the Scientific Review Board of National Gene Vector Laboratory and the Board of Directors of the American Society of Gene Therapy and currently is a member of the Interventions Testing Program Steering Committee for the National Institute on Aging. He has co-founded three biotechnology companies and currently serves on the Scientific Advisory Boards of five companies. Dr. Robbins’ research is focused on developing therapeutic approaches, including small molecules, biologics and stem cells, to extend healthspan and reduce frailty in mouse models of aging.

Gabriele Saretzki, PhD

Gabriele Saretzki graduated from St. Petersburg (Russia) State University in 1982 in Genetics. She then went on to the department of Genetics at Humboldt-University Berlin where she got her PhD in 1990 in Molecular Biology with a thesis in Virology (HBV). In 1989 she got her first post-doc position in the Institute for Pathology (Rudolph Virchow Institute) at the Charité Berlin working on the detection of opportunistic infections during HIV infection. There she also got interested in ageing research teaming up with Thomas von Zglinicki working on telomeres and oxidative stress. She was involved in establishing telomeres as sensitive structures for oxidative stress in human cells. Soon after she also started working on telomerase as an important enzyme associated with cancer cells. From 1993-1994 she got a Fellowship from the Jung Foundation in Hamburg and worked 1 year in Munich on microsatellite instabilities in ovarian tumours. In 1996 she spend 3 months at Geron Corporation in California on oxidative stress and telomerase-inhibition related projects. From 1999-2000 she worked in Freiburg (Germany) on telomerase inhibition in cancer cells. In 2001 she came to the Institute for Ageing and Health lead by Prof. Tom Kirkwood at Newcastle University where she continued her work on telomeres and telomerase, oxidative stress and ageing. In 2002 she got her lectureship in Ageing where the focus of her group was mainly on the non-telomeric function of the telomerase protein TERT in mitochondria resulting in decreased oxidative stress, apoptosis and DNA damage in cells under stress, thus promoting cellular survival. Over the last 15 years she established a collaboration with a group working on embryonic and iPS cells characterising oxidative stress and DNA damage in various disease-associated models. However, her main focus over the last 10 years was shifted to non-canonical functions of the telomerase protein TERT in the brain during ageing and in neurodegenerative diseases. Her group characterised mitochondrial localisation of TERT in the brain during dietary restriction in mice and in Alzheimer’s disease (AD) in human archived brain material. Based on these novel findings she established a collaboration with TA Sciences Inc. (USA) applying telomerase activators to old mice as well as a mouse model of Parkinson’s disease (PD) which showed promising results ameliorating motor as well as non-motor symptoms of PD. She currently aims to translate these results into a clinical trial on PD patients using the plant-derived telomerase activator TA-65. She published more than 80 peer-reviewed papers and is associated editor of PLoS one, Oxidative stress and Longevity and BMC Biology.
Tamar Tchkonia, PhD

Tamar Tchkonia’s research is focused on the role of senescent cells in aging and disease. She is one of the four co-inventors of a mouse model where senescent cells can be removed selectively and a named inventor on seven patent applications related to therapeutic approaches for targeting senescent cells in aging and disease. Recently, in collaboration with Dr. Kirkland and others she identified first senolytic agents that are effective in eliminating senescent cells both in vitro and in vivo. Our group first demonstrated that clearance of senescent cells pharmacologically improves healthspan in chronologically aged mice.
Alliance for Healthy Aging Members

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university of groningen

noaber foundation

VitaValley
Maps

Conference locations - UMCG
Main Entrance at the Hanzeplein 1 - walk to the Fonteinpatio and turn right to ‘Winkelstraat 1’.
- Blue Room (ground floor); Blue Patio (first floor); Red Room (second floor).
Dinner location (Friday)
Restaurant ’t Feithhuis
Martinikerhof 10
9712 JG Groningen
Phone: +31 (0)50-3135335
Thursday, November 9, 2017

Location: Blauwe Zaal / Blue Room
17.30 Opening & Welcome by the conference directors
   Marian Joëls, PhD, Dean/Board of Directors University Medical Center Groningen
   James L. Kirkland, MD, PhD, Mayo Clinic Robert and Arlene Kogod Center on Aging
   Thomas von Zglinicki, PhD, University Ageing Biology Centre, Newcastle University

17.35 Announcement by the President of the University of Groningen
   Sibrandes Poppema, MD, PhD

17.45 Keynote lecture
   Genetic mapping of targets in mitochondria, metabolism and ageing
   Johan Auwerx, MD, PhD, Professor at the Ecole Polytechnique Fédérale, Laboratory of Integrative and Systems Physiology, Lausanne, Switzerland

Location: Fonteinpatio / Fountain Patio
18.45 Drinks and Dinner buffet
Sibrandes Poppema, MD, PhD

Sibrandes Poppema was born in Emmen, the Netherlands, and studied Medicine at the University of Groningen. He specialized in Pathology and defended his PhD thesis on the Immunopathology of Hodgkin’s disease in 1979. He obtained postdoctoral positions at the University of Kiel (Germany) and at the Massachusetts General Hospital, Harvard Medical School. In 1985 he was appointed on the J.K. de Cock chair in Immunopathology at the University of Groningen. From 1987 till 1995 he was Professor of Pathology and Oncology at the University of Alberta and Director of Laboratory Medicine at the Cross Cancer Institute in Edmonton, Alberta, Canada.

In 1995 he returned to Groningen to become the chairman of the Department of Pathology and Laboratory Medicine. In 1999 he was appointed dean of the Faculty of Medical Sciences at the University of Groningen. He introduced the problem based, competency oriented curriculum G2010 in 2003, forged the merger of Faculty and Academic Hospital into the University Medical Center Groningen in 2005 and became vice-president of the UMCG. In 2006 he initiated the Healthy Ageing focus of UMCG with the flagship projects LifeLines and ERIBA. In 2008 he took over as president of the University of Groningen and in 2014 was re-appointed till 2018. Under his guidance the university introduced the three focus areas Healthy Ageing, Energy & Sustainability, and Sustainable Society. In 2016 the Energy Academy Europe, a zero emission education and research building was completed. During his tenure the study success rate of the students improved by more than 25 percent and the University of Groningen progressed to place 59 in the Academic Ranking of World Universities.

Professor Poppema is an expert on Hodgkin’s disease and published around 240 articles that have been cited more than 12,000 times and has an H-index of 60. He obtained several patents on CD45 and Galectin and founded two biotech companies.

He was awarded a Knighthood in the Order of the Netherlands Lion for his scientific achievements in 2007 and is a member of the Netherlands Academy of Technology and Innovation. In 2011 he received an appointment as Honorary Consul General for the Republic of Korea in the Northern Netherlands. He is vice president of the Netherlands Association of Research Universities VSNU.

Professor Poppema serves on a wide range of committees and boards, such as the supervisory board of the health care group Treant, the Energy Academy Europe and the Carbohydrate Competence Center, and internationally on the Supervisory Board of the European Medical School Oldenburg, Germany, the Supervisory Board Alliance for Healthy Ageing (with Mayo Clinics), the International Advisory Board Manipal Global Group of Universities, India, the Scientific Advisory Board Berlin Institute of Health, Germany, the Board of the Arab European University Association (AEUA), the Advisory Board Institute for Cultural Diplomacy ICD in Berlin, Germany, and the Council of Confucius Institute Headquarters, Beijing, China.
Johan Auwerx, MD, PhD

Johan Auwerx is Professor at the École Polytechnique Fédérale in Lausanne, Switzerland, where he occupies the Nestle Chair in Energy Metabolism. Dr. Auwerx has been using molecular physiology and systems genetics to understand metabolism in health, aging and disease. Much of his work focused on understanding how diet, exercise and hormones control metabolism through changing the expression of genes by altering the activity of transcription factors and their associated cofactors. His work was instrumental for the development of agonists of nuclear receptors - a particular class of transcription factors - into drugs, which now are used to treat high blood lipid levels, fatty liver, and type 2 diabetes. Dr. Auwerx was amongst the first to recognize that transcriptional cofactors, which fine-tune the activity of transcription factors, act as energy sensors/effectors that influence metabolic homeostasis. His research validated these cofactors as novel targets to treat metabolic diseases, and spurred the clinical use of natural compounds, such as resveratrol, as modulators of these cofactor pathways. Johan Auwerx was elected as a member of EMBO in 2003 and has received many international scientific prizes. Dr. Auwerx received both his MD and PhD in Molecular Endocrinology at the Katholieke Universiteit in Leuven, Belgium. He was a post-doctoral research fellow in the Departments of Medicine and Genetics of the University of Washington in Seattle.

Genetic mapping of targets in mitochondria, metabolism and ageing

Our understanding of genetic mechanisms that define complex traits has been hindered by the difficulty of obtaining comprehensive omics datasets across a broad range of biological “layers”. Complete data on the genome of individuals can be readily obtained, but the full complexity of the transcriptome, proteome, metabolome, and phenome have remained largely out of reach. This is, however, beginning to change, with the development of robust multi-layered omics strategies that are pioneered in model organisms. We here profiled the healthspan and lifespan in >80 cohorts of the BXD mouse genetic reference population. Large variability was observed across all omics layers; to understand how these differences stem from genetic variance, we exploited a multilayered set of molecular phenotypes—genomics, transcriptomics, proteomics, and metabolomics. With this multi-omics strategy, large networks of proteins could be analyzed and causal variants identified in proteins involved in determination of lifespan (e.g. Mrps5, Jmjd3), glucose homeostasis (e.g. Dhtkd1), hypertension (Ubp1) and mitochondrial supercomplex formation (Cox7a2l). These new candidates were then validated using cross-species genetic strategies in C.elegans, mouse, and human. Our large-scope multi-omics measurements in mouse populations combined with cross-species validation hence provided us with robust conserved and mechanistically defined pathways that underpin complex traits involved in metabolism and aging.
Friday, November 10, 2017

Topic I Mitochondria, ROS & NAD

Location: Rode Zaal / Red Room

08.00 Registration Open

08.20 Opening by program director Barbara Bakker (UMCG) and chairs Gabriele Saretzki (Newcastle University) & Ellen Nollen (UMCG)

08.25 The NAD metabolome – Bioenergetics, signalling and emerging therapeutic applications
Mathias Ziegler, MD, PhD, Professor at the University of Bergen, Head of the Department of Biomedicine, Faculty of Medicine, Bergen, Norway

08.55 Ketone bodies: Signaling metabolites that affect aging and memory
John Newman, MD, PhD, Assistant Professor of Geriatrics, UCSF, San Francisco USA; Visiting Scientist, Buck Institute for Research on Aging, Novato USA

09.25 Mitochondrial DNA methylation
Marianne G. Rots, PhD, Professor of Molecular Epigenetics, Department of Pathology and Medical Biology, University Medical Center Groningen, Groningen, the Netherlands

09.55 CD38: from mechanism to therapy for aging-related metabolic decline
Eduardo Chini, MD, PhD, Professor of Anesthesiology, Mayo Clinic Robert and Arlene Kogod Center on Aging and Mayo Clinic Cancer Center, Rochester, Minnesota, USA

10.25 Summary Topic I by chairs

Location: Blauwe Patio / Blue Patio

10.30 Coffee break
Mathias Ziegler, MD, PhD

1980-1986  Medical University Moscow, School of Biomedicine Medical doctor, August 1986
1986-1990  Humboldt-Universität Berlin, Medical School (Charité), Institute of Biochemistry: Dr. med. (Ph.D.), June 1990
1990-1993  State University New York, Health Science Center Syracuse, Dept. Biochemistry and Molecular Biology, Post-doctoral fellow
1993-1999  Freie Universität Berlin, Department of Biochemistry: Research group leader Habilitation (Dr. scient.), July 1998
2000-2004  Assistant professor of Biochemistry in the program for students of bioinformatics (Freie Universität Berlin)
2004  Full Professor of molecular biology, University of Bergen, Dept. of Molecular Biology
2012  Program Director "Metabolism and Signaling", Dept. of Molecular Biology
Jan-Aug 2017  Head of the Dept. of Molecular Biology, Faculty of Mathematics & Natural Sciences
Sept 2017  Head of the Dept. of Biomedicine, Faculty of Medicine

The NAD metabolome - Bioenergetics, signalling and emerging therapeutic applications

NAD is a vital molecule in all organisms. It plays a major role in all cells as substrate for signal transduction and as cofactor in metabolic redox reactions, processes that undergo critical changes in aging and a variety of diseases. NAD⁺-dependent signalling pathways include poly- and mono-ADP-ribosylation, protein deacetylation by sirtuins and generation of messengers involved in Ca²⁺ signalling. They regulate fundamental events such as transcription, DNA repair, cell cycle progression and apoptosis and also contribute to the control of metabolism. Since these signalling reactions include degradation of NAD, perturbations of NAD supply can have severe consequences. Given the increasing awareness of the biological roles of NAD, the routes, molecular mechanisms and regulation of NAD biosynthesis have also become the subject of intense research. The commonly known precursors of NAD biosynthesis are nicotinic acid and nicotinamide (known as vitamin B3). However, their riboside derivatives now appear to be of similar importance. Impressive progress has been made regarding the molecular identification, functional and structural characterization as well as regulation of the human NAD biosynthetic enzymes. Both phylogenetic analyses and metabolic modelling approaches are increasingly contributing to the understanding of this complex metabolic and signalling network. Exciting therapeutic concepts have emerged, which aim at modulation of NAD availability by interfering with the biosynthetic network to prevent, reduce or reverse pathological conditions. In addition, the targeting of specific NAD-dependent regulatory processes bears great potential for the treatment of diseases associated with aging such as cancer, diabetes and neurodegenerative disorders.
John Newman, MD, PhD

John Newman, MD, PhD, is Assistant Professor in the Division of Geriatrics at UCSF and a Visiting Scientist at the Buck Institute. His Buck research studies the molecular details of how diet and fasting regulate the genes and pathways that in turn control aging. He particularly studies the ketone body beta-hydroxybutyrate, and how its molecular signaling activities involving epigenetics and inflammation regulate phenotypes of aging in mice. Dr. Newman is also a geriatrician who cares for hospitalized older adults at UCSF and the San Francisco VA Medical Center, focusing on preserving mobility and preventing delirium. He completed an MD/PhD at the University of Washington, then did his residency and fellowship training at UCSF.

Ketone bodies: Signaling metabolites that affect aging and memory
Ketogenic diets recapitulate certain metabolic aspects of dietary restriction such as reliance on fatty acid metabolism and production of ketone bodies. Ketone bodies themselves have signaling activities such as deacetylase inhibition that might suggest broad impacts on aging. We investigated whether an isoprotein ketogenic diet (KD) might, like dietary restriction, affect longevity and healthspan in C57BL/6 male mice. We find that Cyclic KD, KD alternated weekly with the Control diet to prevent obesity, reduces midlife mortality but does not affect maximum lifespan. A non-ketogenic high-fat diet (HF) fed similarly may have an intermediate effect on mortality. Cyclic KD markedly improves memory performance in old age. It also ameliorates age-related declines in cardiac function, exploration, and composite healthspan measures. Gene expression analysis identifies downregulation of insulin, protein synthesis, and fatty acid synthesis pathways as mechanisms common to KD and HF. However, upregulation of fatty acid metabolism including PPARα target genes is unique to KD, consistent across tissues, and preserved in old age. We developed a set of novel ketone ester compounds that permit the feeding of ketone bodies in a normal diet context, and allow the mechanistic study of the effects of ketone bodies in a ketogenic diet on aging phenotypes. In all, we show that a non-obesogenic ketogenic diet improves survival, memory, and healthspan in aging mice.
Marianne Rots studied Medical Biology at the University of Amsterdam, obtained her PhD at the VU Medical Center, Amsterdam in 2000 and was subsequently trained as postdoctoral fellow in the Gene Therapy Center of the University of Alabama, Birmingham, USA. In 2001, she was recruited to the School of Pharmacy in Groningen and in 2007 to the University Medical Center Groningen, to start her own research group. She combined gene therapy and epigenetics and was one of the first to establish Epigenetic Editing, for which she obtained several prestigious grants. In 2010, she was appointed professor of Molecular Epigenetics in the Department of Pathology and Medical Biology at the University Medical Center in Groningen. So far, ten PhD students graduated (of with two with the highest distinction) under her supervision. Among others, she also serves as commissioning and associate editor in the editorial board of Nature Springer Clinical Epigenetics, acts as research coordinator of an H2020-EU-ITN (www.epipredict.eu) and is vice-chair in a EU COST action (CM1406: www.epichembio.eu).

Mitochondrial DNA methylation

M.G.P. van der Wijst1,2, A. Mposhi1,3, K.N. Faber3, M.G. Rots1

1Epigenetic Editing, Dept. of Pathology and Medical Biology; 2Dept. of Genetics; 3Dept. of Hepatology and Gastroenterology, University of Groningen, University Medical Center Groningen, The Netherlands.

Mitochondrial dysfunction has been related to ageing and disease, but detailed insights into exact cause-consequence are largely lacking. As mitochondria also provide substrates for epigenetic enzymes, epigenetic processes might be involved in translating mitochondrial dysfunction into disease. Interestingly, mitochondria themselves also contain DNA and recent reports provide accumulating evidence that, like nuclear DNA, also the mitochondrial DNA (mtDNA) is subjective to DNA methylation. This evidence includes the demonstration of mitochondria-localised DNA methyltransferases and demethylases, and the detection of mtDNA methylation as well as hydroxymethylation. Moreover, in diseases associated with mitochondrial dysfunction, such as non-alcoholic steatohepatitis (NASH), diabetes and colorectal cancer, differential methylation of mtDNA has been reported. In some cases, mtDNA methylation was related to altered gene expression and mitochondrial dysfunction. Yet, the presence of mtDNA methylation is still the subject of much debate.

We decided to move beyond mere associations of mitochondrial DNA methylation and clinical phenotypes and set out to prove a direct function of mtDNA methylation by so-called Epigenetic Editing. In Epigenetic Editing, locus-specific rewriting of epigenetic marks is obtained by exploiting gene targeting systems, such as CRISPR-Cas9. First, the DNA binding tool is re-engineered to bind to a genomic (nuclear or mitochondrial) locus of interest. Next, an epigenetic writer or eraser of an intended mark, such as CpG methylation, is fused to the (nuclease-inactivated) DNA binding tool. Using this approach, we and others
have demonstrated that for nuclear DNA, methylation within promoter regions of genes is causally associated with gene repression. In order to address the question regarding the direct function of mtDNA methylation, we have designed mitochondria-targeted DNA binding proteins fused to prokaryotic DNA methyltransferases (M.Sss1 or M.CviPI).

In cancer cell lines we have shown that these fusion proteins localize to the mitochondria where they induce mtDNA methylation. Unexpectedly, upon efficient induction of CpG mtDNA methylation, mtDNA gene expression and mitochondrial function remained unchanged. Intriguingly, induction of C-methylation in the GpC context, decreased mtDNA gene expression. In the latter case, the activity of the three mtDNA promoters seemed differentially affected.

Follow-up investigations that further address the functional consequences of mtDNA methylation are necessary to progress our insights into a role of mtDNA methylation. Besides mtDNA methylation, also mtDNA hydroxymethylation and post-translational modifications of the mitochondria-localised, histone-like protein TFAM have been described. Since such epigenetic-like modifications are reversible and reprogrammable, these could provide new therapeutic targets for many of the aforementioned diseases.

This study was supported in part by NWO ChemThem (grant nr 728.011.101)

1. Mposhi A, van der Wijst MG, Faber KN, Rots MG. Regulation of mitochondrial gene expression, the epigenetic enigma. Front Biosci (Landmark Ed); 22:1099-1113, 2017
Eduardo Nunes Chini, MD, PhD, received his MD and PhD from the federal university of Rio de Janeiro in Brazil, and did a fellowship in basic research and residency in Anesthesiology at the Mayo Clinic in Rochester. Dr. Chini activities at the Mayo Clinic include clinical and academic, and administrative duties. He dedicates 50% of his time to patient care and 50% to research and his academic and administrative activities. Key awards include the Mayo Clinic Kendall award, the Duane K. Rorie, the Richard A. Theye award and the Glenn/AFAR BIG Award from the American Federation of Aging Research. Additionally, Eduardo has demonstrated an extraordinary funding history of ~$5 million in direct costs since joining the Mayo Clinic staff in 2001 (including support from the NIH and industry such as GSK, Pfizer, SIRTIS and Calico). His service has also been exceptional and is well documented in his nomination materials and includes extensive service as member of NIH study sections and as reviewer for multiple journals, and as one of the leader on the Center of Biomedical discovery at the Mayo Clinic. Very impressive is the fact that Dr. Chini is one of the first non-GI specialists at Mayo Clinic to serve as a member of the Hepatobiliary Pathophysiology Study Section, National Institute of Diabetes and Digestive and Kidney Diseases. He is a member of Association of University Anesthesiologists. Has served at the American federation of aging research and is a member of the Minnesota Minnesota Nutrition and Obesity Center and of nine different centers at the Mayo Clinic. This catalogue of achievements does not capture the full measure of their impact. Dr. Chini’s scientific achievements are vast and include the discovery of a new intracellular second messenger. Furthermore, during his initial years as an independent investigator while working with NAD derived second messengers Dr. Chini made yet another seminal discovery. In the early 2000’s Dr. Chini demonstrated that the enzyme CD38 was the main NAD degrading enzyme in mammalian tissues. NAD is a nucleotide that plays a major role as electron acceptor in multiple biological reactions and also as a signaling molecule in several pathways. This discovery is perhaps his main contribution to science and has been extensively citation in the literature and lead to impressive funding and collaborations with several pharmaceutical companies including Pfizer, Sirtris, GSK and most recently the sister Google company Calico. The impact of these discoveries has been enormous and Dr. Chini has authored over a 100 original publications, opinions and reviews in journals including PNAS, Cell Metabolism, Nature, Science, JBC, JCB, and JASN. His original publications have received a large number of citations. Dr. Chini’s work in NAD metabolism further expands to cancer biology and his laboratory was one of the first ones at the Mayo clinic to approach cancer via metabolic pathways. In particular, Dr. Chini championed studies in and metabolism in pancreatic cancer that him to be one of the project leaders in the Mayo Clinic Pancreatic Cancer SPORE. This work may lead to novel and effective metabolic base therapies for this devastation disease. In addition, Dr. Chini is an active member of the Mayo clinic Cancer Center and of C-Sig Gi center at Mayo.
CD38: from mechanism to therapy for aging-related metabolic decline

Principal Investigator: Eduardo Nunes Chini, MD, PhD, Mayo Clinic, Kogod Center on Aging and Department of Anesthesiology

Aging is characterized by the development of age-related metabolic diseases and frailty (Fig 1). Recent studies demonstrate that a decrease in levels of nicotinamide adenine dinucleotide (NAD) is a key causal factor for the development of age-related metabolic decline (Fig 1). NAD⁺ is crucial for oxi-reduction reactions and mitochondrial function. Interestingly, administration of NAD precursors such as nicotinamide mononucleotide (NMN) or nicotinamide riboside (NR) is sufficient to improve healthspan and longevity in mice. To date, the mechanisms that lead to the NAD decline during aging have not been elucidated. The prevailing hypothesis is that activation of DNA-repair enzymes such as Poly-ADP-ribose polymerases (PARPs) would consume NAD during the aging process. However, we have recently challenged this paradigm and show that CD38 is the main NADase responsible for the aging-related NAD decline.

The long-term goal of my laboratory is to understand the role of CD38 in NAD metabolism during aging. CD38 is an ecto-enzyme that is highly expressed in inflammatory cells. CD38 expression and activity in these inflammatory cells is induced by cytokines and endotoxins. Thus our main hypothesis is that NAD decline, and metabolic dysfunction during aging is mediated by infiltration/accumulation of CD38⁺ inflammatory cells in tissues, that consumes NAD. Furthermore, we propose that cytokines derived from the “chronic sterile inflammation of aging” are the main inducers of CD38 during the aging process. Finally, we propose that small molecule CD38 inhibitors (CD38i) can preserve cellular NAD levels, and augment metabolic health span in mammalians, and that CD38i will further increase the healthspan effects of NAD precursors.

In conclusion, CD38 may provide a mechanistic link between aging-related inflammation/senescence, cellular NAD decline, mitochondrial and metabolic dysfunction. Furthermore, small molecule CD38i alone or in combination with NAD precursors may improve metabolic function and health span in the elderly.
Friday, November 10, 2017

Topic II Metabolism and Cell Senescence

11.00  **Opening by chairs**  Nathan LeBrasseur (Mayo Clinic, Rochester, Minnesota, USA) & Folkert Kuipers (UMCG)

11.05  **Cellular Senescence: At the Nexus between Obesity and Metabolic Dysfunction**

*James L. Kirkland*, MD, PhD, Noaber Foundation Professor of Aging Research, Director Mayo Clinic Robert and Arlene Kogod Center on Aging, Rochester, Minnesota, USA

11.35  **Nuclear to Mitochondrial DNA damage signaling in Neurodegeneration and Aging**

*Vilhelm A. Bohr*, MD, PhD, Senior investigator, Laboratory of Molecular Gerontology, National Institute on Aging, Baltimore, USA

12.05  **Pharmacological inhibition of mitochondrial complex I reduces senescence and reverses aging-related regulation of gene expression in mice**

*Eugenia Trushina*, PhD, Associate Professor, Mitochondrial Neurobiology and Therapeutics Laboratory Mayo Clinic, Rochester, Minnesota, USA

12.35  **Senescence in post-mitotic cells: a telomere-centric story**

*João Passos*, PhD, Associate Professor, Newcastle University Institute for Ageing and Institute for Cell and Molecular Biosciences, Newcastle University, UK

13.05  **Summary**  Topic II by chairs

13.10- **Poster Pitch by**

13.25  **Ana Patricia Huerta Guevara**, University Medical Center Groningen  
**Selma Osmanagic-Myers**, University of Natural Resources and Life Sciences, BOKU, Vienna  
**Mariana Tarrago**, Mayo Clinic

*Location: Blauwe Patio / Blue Patio*

13.30  **Lunch, Poster viewing and discussion**
James L. Kirkland, MD, PhD

James L. Kirkland, M.D., Ph.D., is the director of the Robert and Arlene Kogod Center on Aging at Mayo Clinic and Noaber Foundation Professor of Aging Research. Dr. Kirkland’s research is on cellular senescence, age-related adipose tissue and metabolic dysfunction, and development of agents and strategies for targeting fundamental aging mechanisms to treat age-related chronic diseases and disabilities. He published the first article about drugs that clear senescent cells – senolytic agents. He is a scientific advisory board member for several companies and academic organizations. He is a member of the National Advisory Council on Aging of the National Institutes of Health, President-Elect of the American Federation for Aging Research, and past chair of the Biological Sciences Section of the Gerontological Society of America. He holds honorary appointments at Boston University and the University of Groningen in the Netherlands. He is a board certified specialist in internal medicine, geriatrics, and endocrinology and metabolism.

Cellular Senescence: At the Nexus between Obesity and Metabolic Dysfunction

Adipose tissue dysfunction and inflammation are associated with obesity-related insulin resistance and diabetes, but mechanisms underlying this relationship have not been clear. Although senescent cells accumulate in adipose tissue of obese humans and rodents, a direct role for these cells in the development of diabetes has remained to be demonstrated. Here we show that reducing senescent cell burden in obese mice, either by activating drug-inducible “suicide” genes driven by the p16\textsuperscript{ink4a} promoter in transgenic INK-ATTAC or p16-3MR mice or by treatment with senolytic agents, alleviates metabolic and adipose tissue dysfunction. These interventions improved glucose tolerance, reduced circulating inflammatory and insulin resistance-inducing mediators, enhanced adipogenesis, increased the ratio of subcutaneous to visceral adipose tissue, reduced muscle lipid and steatosis, and improved insulin sensitivity in obese mice. Moreover, reducing senescent cell burden prevented migration of transplanted monocytes into intra-abdominal adipose tissue and reduced adipose tissue macrophages. Our results implicate cellular senescence as a causal factor in obesity-related inflammation and metabolic derangements, and show that emerging senolytic agents hold promise for treating obesity-related diabetes and its complications.
Vilhelm A. Bohr, MD, PhD

1978-1980  Residencies in internal medicine and surgery, University Hospital, Copenhagen, Denmark
1980-1982  Postdoctoral Fellowship at the University of Copenhagen, Denmark
1982-1985  Visiting Scholar, Stanford University, and Stanford CA
1985-1986  Research Associate, Stanford University, Stanford, CA
1986-1988  Senior Staff Fellow, Laboratory of Molecular Pharmacology, Developmental Therapeutics Program, Division of Cancer Treatment, National Cancer Institute, National Institutes of Health, Bethesda, MD
1988-1992  Medical Officer, Senior Investigator, Laboratory of Molecular Pharmacology, Developmental Therapeutics Program, Division of Cancer Treatment, National Cancer Institute, National Institutes of Health, Bethesda, MD
1992-   Chief (Dept. Chair), Laboratory of Molecular Genetics, National Institutes on Aging, NIH
2008-   Adj. Prof, University of Copenhagen

Senior Associate, Johns Hopkins University School of Medicine
Professor, Dept. Structural and Molecular Biology, Aarhus University, Denmark.
Professor (adj) University of Copenhagen Medical School
Member, Editorial boards of several biomedical journals. Editor in Chief, Mech. Aging and Development
Member Danish Royal Academy of Sciences

Nuclear to Mitochondrial DNA damage signaling in Neurodegeneration and Aging

We find that some DNA repair defective diseases with severe neurodegeneration have mitochondrial defects. Our studies involve cell lines, the worm (c.elegans), and mouse models and include the conditions Xeroderma pigmentosum group A, Cockaynes syndrome and Ataxia telangiectasia. We find a pattern of hyperparylation, deficiency in the NAD and Sirtuin signaling and mitochondrial stress. We are pursuing mechanistic studies of this signaling and interventions at different steps to improve mitochondrial health and the neurodegeneration. I will discuss intervention studies in these diseases models including a new Alzheimer mouse model with NAD supplementation. NAD supplementation stimulates mitochondrial functions including mitophagy and stimulates DNA repair pathways. In AT cells, mice and nematode worms, base excision repair is stimulated. This also happens in an Alzheimers mouse deficient in DNA polymerase β, and this will be discussed. DNA Polβ affects mitochondrial functions via its nuclear role, and via a newly identified role in mitochondrial DNA repair.
Dr. Trushina is an Associate Professor in the Department of Neurology and the Department of Molecular Pharmacology and Experimental Therapeutics at the Mayo Clinic Rochester. She received her doctoral degree in organic chemistry from Saratov State University in Russia. Dr. Trushina completed her postdoctoral training at the Mayo Clinic, Rochester studying mechanisms of Huntington’s Disease (HD). Dr. Trushina scientific interests include the role mitochondria and cellular metabolism play in health and disease. She has developed a profound expertise in broad variety of techniques studying neurodegenerative processes related to HD, Alzheimer’s Diseases (AD), Parkinson’s Disease, chemotherapy-induced peripheral neuropathy, multiple sclerosis and neurodegeneration caused by exposure to environmental toxicants. To study the mechanisms of mitochondrial dysfunction, her group developed a panel of advanced techniques that allows monitoring mitochondrial dynamics and function in neurons and brain tissue from transgenic animals including mice and Drosophila, and in fibroblasts and iPS cells from patients. Application of systems biology approaches such as metabolomics, proteomics, transcriptomics and epigenetics allows monitoring changes in multiple functionally connected pathways to decipher novel aspects of mitochondria-nuclear communication in response to genetic and environmental stressors. Based on these studies, the group developed novel small molecule mitochondria-targeted therapeutics, which is now in the lead optimization and preclinical characterization stage. Dr. Trushina is a recipient of the NIH, ADDF, BrightFocus, GHR, Minnesota Partnership, and multiple Mayo Clinic Research Awards.

**Pharmacological inhibition of mitochondrial complex I reduces senescence and reverses aging-related regulation of gene expression in mice**

Mounting evidence suggests that mitochondrial dysfunction plays a significant role in aging. Yet none of clinical trials designed to enhance mitochondrial function achieved significant improvements. On the contrary, the presence of mtDNA mutations encoding subunits of mitochondrial complex I or inhibition of OXPHOS with pharmacological inhibitors including metformin prevented obesity and type II diabetes, and promoted longevity in model organisms and in humans. Recently, complex I was identified as a hub for negative correlation with lifespan where its partial inhibition prolonged lifespan and rejuvenated the transcriptome in African turquoise killifish.

We have developed small molecules partial inhibitors of complex I that penetrate the blood brain barrier and have an outstanding safety profile over an extended period of time. Chronic treatment with these compounds enhanced health span in ageing mice and survival in wild type mice fed with a high fat diet. Treatment with lead compound CP2 averted the development of cognitive dysfunction in multiple transgenic mouse models of Alzheimer’s Disease when independent cohorts of mice were treated *in utero*, at pre- and symptomatic stages of the disease. Molecular mechanism involves activation of AMPK
and downstream signaling pathways leading to increased mitochondrial biogenesis and autophagy, enhanced cellular energetics and synaptic function, and restoration of axonal trafficking. AMPK-independent mechanism includes mitohormetic ROS-dependent activation of NRF2 leading to a significant decrease in markers of senescence, inflammation and oxidative damage. Longitudinal RNA-seq analysis confirmed the rejuvenating phenotype in ageing mice treated with CP2. Our data identifies mitochondrial complex I as a small molecule-sensitive modulator of health span.
João Passos, PhD

João Passos is originally from Porto, Portugal where he studied biochemistry at the University of Porto. He was awarded a scholarship by the graduate program GABBA from the University of Porto and conducted his PhD at Newcastle University under the supervision of Prof. Tom Kirkwood. He remained in Newcastle University as a Research Associate at the BBSRC-funded Centre for Integrative Systems Biology of Ageing and Nutrition in Thomas von Zglinicki’s lab and temporarily at the Max Planck Institute for Stem Cell ageing in Ulm, Germany. In 2010, João was awarded the highly prestigious BBSRC David Phillips Fellowship which allowed him to set up his own laboratory and is currently a Reader in Molecular Biology of Ageing. His group is investigating the molecular mechanisms driving cellular ageing, with a focus on the interaction between telomeres and mitochondria.

João Passos has published more than 50 papers in leading scientific periodicals on the subject of biology of ageing. Work in his laboratory is funded by BBSRC, Medical Research Council, British Heart Foundation, European Union and Unilever. João is an editor for several journals in the ageing field, including Aging Cell. He is a member of the BBSRC pool of experts panel and deputy leader for “Understanding the Mechanisms of Ageing theme” at the Newcastle University Institute for Ageing.

Senescence in post-mitotic cells: a telomere-centric story

João Passos, PhD, Associate Professor, Newcastle University Institute for Ageing and Institute for Cell and Molecular Biosciences, Newcastle University, UK

Telomere shortening has been proposed as a major inducer of senescence. Telomeres are repetitive sequences of DNA, associated with a number of proteins which form a complex known as shelterin, which facilitates the formation of a lariat-like structure to shield the exposed end of DNA, thus serving to protect the ends of chromosomes from being recognized as DNA damage. The current dogma of telomere biology suggests that telomere shortening with each successive cell division eventually disrupts the protective cap, leading to a sustained DNA Damage response and activation of senescence. This hypothesis may explain age-related degeneration of tissues maintained by constant contribution of stem cell pools, such as the skin and hematopoietic systems; however, it is insufficient to explain how senescence contributes to ageing in primarily post-mitotic tissues.

In this talk, I will show that during ageing, human and murine post-mitotic cardiomyocytes acquire a senescent-like phenotype characterized by persistent DNA damage at telomere regions which can be driven by mitochondrial dysfunction, and occurs independent of cell-division, telomere length and telomerase activity. Telomere damage in cardiomyocytes activates the classical senescence-inducing pathways, p21^{CIP} and p16^{INK4a}, but not a typical senescence-associated secretory phenotype (SASP). Crucially, clearance of senescent cardiomyocytes in aged INK-ATTAC mice or treatment with senolytic drug navitoclax alleviates myocardial hypertrophy, a detrimental feature of cardiac ageing.

Finally, I will show data suggesting that telomere dysfunction and induction of senescence in post-mitotic cells is a much more widespread phenomenon than previously thought and discuss the implications of these observations in the context of ageing and age-related disease.
Friday, November 10, 2017

Topic III Nutrient sensing

15.30 Opening by chairs Cor Calkhoven (UMCG) & Diana Jurk (Newcastle University)

15.35 Nutritional modulation of nonhuman primate aging
   Rozalyn Anderson, PhD, Associate Professor, Department of Medicine, SMPH, University of Wisconsin-Madison, USA

16.05 Mechanistic insights into mTORC1 and autophagy in cell senescence
   Viktor Korolchuk, PhD, Associate Professor, Institute for Cell and Molecular Biosciences, Newcastle University Institute for Ageing, Newcastle University, UK

16.35 Systems approaches to the mammalian target of rapamycin (mTOR) network
   Kathrin Thedieck, PhD, Associate Prof of Biochemistry & Molecular Biology, Department of Paediatrics, University Medical Center Groningen, Groningen, the Netherlands

17.05 Developing tools to monitor changes in metabolism in cancer patients
   Hilde Jalving, MD, PhD, Medical Oncologist, Department of Medical Oncology, University Medical Center Groningen, Groningen, the Netherlands

17.35 Summary by chairs

17.40 Closing day 1 by program directors

Location: Restaurant ’t Feithhuis, Martinikerkhof 10, 9712 JG Groningen
18.30 Dinner
Rozalyn Anderson, PhD

Associate Professor (tenured), Division of Geriatrics and Gerontology, Department of Medicine, UW SMPH, and Health Science Officer, Geriatric Research, Education and Clinical Center, William S. Middleton Memorial Veterans Hospital Madison

Dr. Anderson leads the Metabolism of Aging research program at the University of Wisconsin Madison Department of Medicine in the School of Medicine and Public Health. Her work on aging and delayed aging by caloric restriction began in unicellular eukaryotes during her post-doc in Harvard Medical School, Boston MA, and extended into mammalian systems at the UW Madison Institute on Aging and at the Wisconsin National Primate Research Center. Dr. Anderson is Co-PI of the Caloric Restriction and Aging in Rhesus Monkeys study which was the first to demonstrate the translatability of mechanisms of delayed aging by caloric restriction to primate species. She is Associate Director of the UW Madison T32 Biology of Aging training grant program and Co-Director of the Cellular and Molecular Biology of Aging course. Dr. Anderson is a recipient of the Nathan Shock New Investigator Award from the Gerontological Society of America, The Glenn Award for Research in Biological Mechanisms of Aging, and a recipient of the Breakthroughs in Gerontology Award from the American Federation for Aging Research and the Glenn Foundation for Medical Research.

**Nutritional modulation of nonhuman primate aging**

An emerging paradigm in aging research identifies metabolic dysfunction as a root cause in the age-related increase in disease vulnerability. Diabetes, cancer, and neurodegeneration are among the most common diseases of aging and each has an established metabolic component. Caloric restriction (CR), a reduction in caloric intake in the absence of malnutrition, delays aging and the onset of age-related disease in diverse species. Here we report data from our studies of aging and CR in rhesus monkeys, a highly translatable nonhuman primate model. We show that rhesus monkeys on CR are significantly healthier than their control-fed counterparts, with lower indices in multiple disease-risk factors and a lower burden of age-related diseases and disorders. Molecular profiling identifies CR responsive elements in the transcriptome, proteome, and metabolome, and show that improvements in health and survival are associated with changes in metabolism in nonhuman primates. These studies demonstrate that aging can indeed be modulated through nutrition and that healthy aging is linked to metabolic status. These findings have implications for human health and suggest that metabolism may be an effective target for interventions to delay and diminish age-related disease vulnerability.
Mechanistic insights into mTORC1 and autophagy in cell senescence

The mammalian target of rapamycin complex 1 (mTORC1) is the key signalling hub that regulates cellular protein homeostasis, growth, and proliferation. Activation of mTORC1 leads to the suppression of the catabolic process of autophagy where damaged cellular components are degraded via lysosomal proteolysis. mTORC1 is also intimately linked to cellular senescence and organismal aging. Inhibition of mTORC1 is the best-known intervention to extend lifespan, and recent evidence suggests that clearance of senescent cells can also improve health and lifespan. mTORC1 is important for the development of characteristic phenotypes of senescence, although the underlying mechanisms by which mTORC1 contributes to the acquisition of senescence are not well understood.

mTORC1 is able to sense the levels of specific intracellular amino acids such as leucine and arginine. Amino acids have previously been shown to activate mTORC1 by promoting its recruitment to the lysosomal surface. We have recently identified an additional mechanism of mTORC1 activation which is specific to arginine. We found that arginine but not leucine suppresses the function of TSC complex, the negative regulator of mTORC1 mediating the input of growth factor signalling into mTORC1. As such, arginine cooperates with growth factor signalling and other amino acids to promote full activation of mTORC1. Importantly, we have found that cellular senescence induced by stress, replicative exhaustion, or oncogene activation results in the perturbation of these amino acid and growth factor sensing mechanisms. Thus, in senescent human fibroblasts mTORC1 becomes constitutively active and resistant to serum and amino acid starvation. This is driven by depolarization of senescent cell plasma membrane and a resultant failure to inhibit growth factor signalling. Furthermore, increased autophagy promoting high levels of intracellular amino acids may also contribute to the persistent mTORC1 activity in starvation conditions. Interventions that correct these phenotypes restore sensitivity of mTORC1 to growth promoting signals in senescent cells and cause their death, indicating that persistent signalling supports senescent cell survival. These findings suggest how mTORC1 signalling contributes to cellular and organismal senescence and may inform interventions aiming to delay ageing.
Kathrin Thedieck joined the University Medical Center Groningen and Oldenburg University in 2013 in the frame of the European Medical School (EMS). She studies since more than 10 years the kinase networks centered on phosphatidylinositide 3-kinases (PI3K) and the mammalian target of rapamycin (mTOR), by means of cell biology and biochemistry, omics studies and systems biology. The Thedieck lab focuses on PI3K/mTOR crosstalk with ancillary signalling and stress networks, and developed together with Daryl Shanley (Newcastle) one of the first systems approaches to study mTOR signaling.

Thedieck did her postdoctoral training with Michael N. Hall (Basel University, Switzerland), who discovered target of rapamycin, and with whom she published papers on novel interactors that control mTOR activity and cancer cell survival. These efforts grounded her for work done at Freiburg University where she started her own lab in 2008, and extended her earlier efforts to develop systems approaches to the PI3K/mTOR network. The models are patented for their use in precision medicine, and Thedieck and colleagues developed a portfolio of grants to further this work with emphasis on therapies for genetic disorders and cancer.

Selected References

Systems approaches to the mammalian target of rapamycin (mTOR) network
Hilde Jalving, MD, PhD

Hilde Jalving is a medical oncologist, based at the comprehensive cancer center, UMCG, Groningen, the Netherlands. She completed her basic medical- and specialist training in Groningen. Her PhD research (2002-2006) focussed on induction of apoptosis in gastrointestinal cancer. During her medical oncology clinical training she spent time at the clinical trials unit at the Royal Marsden Hospital in London and at the Radcliffe Hospital in Oxford. During the time in Oxford she also worked as a clinical research fellow on interactions between the EGF and IGF receptors and completed an MSc in Experimental Therapeutics at the University of Oxford. She is involved in both patient care and clinical and translational research especially focussing on tumour metabolism. She was recently granted a Young Investigator Grant by the Dutch Cancer Society for research into unraveling tumour metabolic pathways and the interaction of tumour metabolism with tumour immunogenicity in metastatic melanoma.

Developing tools to monitor changes in metabolism in cancer patients
The altered metabolic profile of malignant tumours is an attractive new therapeutic target. Many currently used anti-cancer drugs and drugs in clinical development directly or indirectly target tumour metabolism. In pre-clinical models there is a wealth of knowledge on cancer cell metabolism, metabolic networks and factors that sensitize cancer cells to metabolically targeted therapies. However, there is little knowledge of tumour metabolism in patients. Development of new tools as well as utilising existing tools to help understand the metabolism of tumours in patients in vivo is of interest to help move metabolically targeted drugs and drug-combinations into the clinic. I will discuss on going work on the development of such tools in preclinical models of cancer especially focussing on tools to measure cellular glucose uptake and glucose metabolism.
Saturday, November 11, 2017

Topic IV Systems Biology

Location: Rode Zaal / Red Room

08.30 Opening by chairs Tamara Tchkonia (Mayo Clinic) & Paul Robbins (Scripps Research Institute, Jupiter, Florida)

08.35 From the control of erythropoiesis to patient-specific anemia treatment

Ursula Klingmüller, PhD, Division Head, Division Systems Biology of Signal Transduction, German Cancer Research Center (DKFZ), Heidelberg, Germany

09.05 Systems modelling of cell signalling networks in ageing

Daryl Shanley, PhD, Senior Lecturer, Institute for Cell and Molecular Bioscience, Newcastle University, UK

09.35 Multilevel regulation of mitochondrial metabolism during muscle ageing

Barbara Bakker, PhD, Professor of Medical Systems Biology, Department of Pediatrics and Systems Biology Center for Energy Metabolism and Ageing, University Medical Center Groningen, Groningen, the Netherlands

10.05 Saccharomyces cerevisiae goes through distinct metabolic phases during its replicative life

Matthias Heinemann, PhD, Professor of Biochemistry & Molecular Biology, Microbiology, Faculty of Science and Engineering, University of Groningen, Groningen, the Netherlands

10.35 Summary by chairs

Location: Blauwe Patio / Blue Patio

10.40 Coffee break
Ursula Klingmüller, PhD

2004  Venia Legendi in Cell Biology, Heidelberg University
2000  Habilitation and Venia Legendi in Molecular Biology and Genetics, University of Freiburg
1992  Graduate Studies at Heidelberg University, Doctoral Thesis
1988  Diploma in Molecular Biology, Cell Biology and Virology, Heidelberg University
1985  Bachelor of Science, University of Bayreuth

Major previous appointments
Since 2011  W3 Professor, Heidelberg University, Germany
1996-2003  Group Leader of an Independent Junior Group (Hans-Spermann-Laboratories), Max-Planck-Institute of Immunobiology, Freiburg, Germany
1993-1996  Postdoctoral fellow, Whitehead Institute for Biomedical Research, Cambridge, USA
1992-1993  Postdoctoral fellow, Harvard Medical School, Boston, USA

Activities in the scientific community / Professional memberships (selection)
Since 2014  Member of SAB of BREAST-PREDICT, Dublin, Ireland
2007-2015  Member of Board of Trustees DKFZ
Since 2015  Coordinator of ERASysAPP “IMOMESIC – Integrative Modelling of Metabolism and Signal Transduction for the Application in Liver Cancer”
Since 2016  Coordinator of the MS_DILI network in the BMBF funding initiative e:bio
Since 2011  Co-Coordinator of the Disease Area Lung Cancer in the German Center for Lung Research (DZL and DZL2)
Since 2015  Associate Editor for Nature Systems Biology and Applications

Honors and awards (selection)
Since 2016  Election as Member of the German Ethics Council
2012-2017  Election as Member of the DFG “Hinterzartener Kreis of Cancer Research”

From the control of erythropoiesis to patient-specific anemia treatment
Erythropoiesis, the formation of red blood cells, is tightly controlled by the hormone erythropoietin (Epo). Binding of Epo to its cognate receptor on erythroid progenitor cells induces the activation of the AKT and ERK pathways, which control cell proliferation. Different hematopoietic cell types that share the molecular network topology for pro-proliferative Epo signaling exhibit distinct proliferative responses. Iterating quantitative experiments and mathematical modeling, we identify two molecular sources for cell type-specific proliferation. First, cell type-specific protein abundance patterns cause differential signal flow along the AKT and ERK pathways. Second, downstream regulators of both pathways have differential effects on proliferation. An integrated mathematical model of Epo-driven proliferation explains cell type-specific effects of targeted AKT and ERK inhibitors and predicts, based on the protein abundance, anti-proliferative effects of inhibitors in primary human erythroid progenitor cells. Anemia due to reduced
numbers of red blood cells is highly prevalent in cancer and reduces the response to chemotherapy and the quality of life. Epo and its derivatives, termed Erythropoiesis Stimulating Agents (ESAs), have been widely used to correct anemia in cancer. Unfortunately, 30-50% of the patients do not respond to ESA treatment and mortality risk is increased. We developed a new dosing approach in order to increase treatment efficacy and reduce associated risk of mortality. We established a predictive multiscale model by combination of a cell-scale model with pharmacokinetic and pharmacodynamic data on ESA treatment in human subjects. This model will be applied to predict the minimal efficacious ESA doses to optimize anemia treatment for individual cancer patients.
Daryl Shanley has over 20 years experience in developing computational models to study the ageing process and is the current director of the Newcastle University Centre for Integrated Systems Biology of Ageing and Nutrition (CISBAN).

His recent work has focused on: 1) nutrient signalling, e.g. although we know that mTOR signalling plays an important role in ageing, surprisingly little is known on the regulation of one of the main players mTORC2. We used a combined computational experimental approach to explore this regulation (Dalle Peze 2012). More recent work has extended this model to explore amino acid regulation of the network (Dalle Peze et al 2016); 2) Oxidative stress, e.g. we have recently shown that a cellular response to a H2O2 bolus is biphasic with a initial lag in response due to buffering by the protein thiol pool (Tomalin et al 2016); 3) DNA damage response, e.g. we developed a model that combined earlier work in DNA damage response together with P53 signalling to demonstrate that pulses of low level irradiation could be used as an alternative strategy to high single pulse therapy (Dolan et al 2015); 4) cellular senescence, e.g. we developed a model embodying the interaction of these mechanisms to simulate the process of cellular senescence. Our model highlighted the importance of mitochondrial dysfunction and revealed that potential preventative strategies were only effective if applied early in the process (Dalle Peze et al 2014).

**Systems modelling of cell signalling networks in ageing**

I will present some of our recent work using computational models to study nutrient signalling networks in ageing. I will show how the models are used to clarify network topology; to explore strategies for targeted intervention; and to investigate interaction with other important signalling networks such as that responsive to TGFβ. Our models are data-driven and I will describe our efforts to ensure close connection between data and model.

Barbara Bakker studied biochemistry at the University of Amsterdam and did her PhD in systems biology ‘avant la lettre’ at the VU University Amsterdam. During her PhD and postdoc period she also worked at the De Duve Institute in Brussels, the Biozentrum in Frankfurt, and the Delft University of Technology. Subsequently, she became Assistant (2000) and Associate Professor (2003) at the VU University Amsterdam. Since 2009 she is a group leader in Groningen.

The Bakker group applies systems biology approaches closely to the clinic, to inborn errors of metabolism and age-related metabolic diseases, focusing on the interplay between lipid and carbohydrate metabolism. The philosophy of the Bakker group is to build computational models of metabolism with diet and disease as perturbations, use these to understand the fundamental organization and regulation of metabolic networks, and then apply the new knowledge and models to questions related to health and disease. In short: one system, many diseases. The group develops ODE type of computational models for metabolic pathways, deeply rooted in biochemistry, biochemical kinetics and thermodynamics. Core experimental technology includes: enzyme kinetics, quantitative proteomics, metabolomics, and fluxomics based on stable isotopes.

Barbara Bakker was awarded the yearly prize of the Netherlands Society for Biochemistry and Molecular Biology (2003) and a Rosalind Franklin award from the University of Groningen (2009). She is a board member of the Dutch research school for Bioinformatics and Systems Biology (BioSB), the chair of the International Study Group for Systems Biology, and one of the founders of the Systems Biology Centre for Metabolism and Ageing in Groningen. Bakker has over 90 peer-reviewed publications (h-index 37 in Google Scholar).

Multilevel regulation of mitochondrial metabolism during muscle ageing

In vivo rates of metabolic enzymes can be regulated at multiple levels: by concentrations of metabolites (metabolic regulation), by covalent modification of enzymes (through signalling), or via the concentration of the enzyme (through the gene-expression cascade). Previously we developed the theoretical framework of Regulation Analysis to dissect these contributions quantitatively and we showed in microbes that regulation was distributed. Not only was a large part of the regulation metabolic, also the regulation within the gene-expression cascade was distributed between transcription and posttranscriptional processes, such as mRNA processing or translation. In mammalian biology, however, the question to which extent the proteome is dictated by the transcriptome is unresolved, and the issue of metabolic regulation has hardly been addressed. In the presentation I will address the distribution of regulation of mitochondrial metabolism in the context of mammalian ageing.

I will focus on loss of mitochondrial respiratory flux, which is a hallmark of skeletal muscle ageing and contributes to a progressive decline of muscle strength. We found that endurance exercise (voluntary running) protects mice from mitochondrial flux decline until 18 months of age, irrespective of their diet. Beyond this time point all experimental groups converged. Mitochondrial flux was related to transcriptome (RNASeq) and proteome (targeted LC-MS/MS analysis with $^{13}$C-labelled standards).
Regulation Analysis showed that the decline of flux was equally regulated at the proteomic and at the metabolic level, while regulation at the transcriptional level was marginal. Proteomic regulation was most prominent at the beginning and at the end of the mitochondrial pathway, namely at the pyruvate dehydrogenase complex and at the synthesis and transport of ATP. Further proteomic regulation was scattered across the entire pathway, revealing an effective multisite regulation. Finally, reactions regulated at the protein level were highly overlapping between mice with and without a running wheel, suggesting a common, posttranscriptional mechanism of muscle ageing, which was delayed by physical activity. I will discuss the results in the context of the debate about multi-level enzyme regulation in mammalian cells and tissues.
Matthias Heinemann, PhD

Matthias Heinemann received a PhD in engineering from the RWTH Aachen University, Germany, did a postdoc in the bioprocess lab of the ETH Zurich, from 2004 to 2009 he was group leader at the Institute of Molecular Systems Biology at ETH Zurich, and since 2009 he is professor for molecular systems biology at the University of Groningen. He leads a research program aiming at generating a system-level understanding of core metabolism, for which he combines experimental and computational approaches. Part of this endeavor is also to unravel the metabolic changes during aging. Matthias Heinemann received the DuPont Young Professorship award and was granted a prestigious VIDI-grant from the Netherlands Organisation for Scientific Research (NWO).

Saccharomyces cerevisiae goes through distinct metabolic phases during its replicative life

An integrated account of the molecular changes occurring during the process of cellular aging is crucial towards understanding the underlying mechanisms. Here, using novel culturing and computational methods as well as the latest analytical techniques, we mapped the proteome, transcriptome, metabolome and physiology during the replicative lifespan of budding yeast. With age, we found primarily proteins involved in protein biogenesis to increase relative to their transcript levels. Exploiting the dynamic nature of our data, we reconstructed high-level directional networks, where we found the same protein biogenesis-related genes to have the strongest ability to predict the behavior of other genes in the system, revealing that they are the drivers of the aging phenotype. Our physiological analyses showed that metabolism first shifts from fermentation to respiration and at a later stage to glycerol production. We identified these metabolic shifts and the loss of stoichiometry in protein complexes as being consequences of aging. We integrate these findings in a model aiming to generate a first system-level consideration of replicative aging in yeast.
Saturday, November 11, 2017

Topic V  Metabolism and stem cell ageing

11.10  Opening by chairs Laura Niedernhofer (Scripps Research Institute) & Gerald de Haan (UMCG)

11.15  Mitochondrial Metabolic Checkpoint, Stem Cell Aging and Rejuvenation  
       Danica Chen, PhD, Professor of Nutritional Sciences and Toxicology, Department of Nutritional Sciences & Toxicology, Berkeley University of California, USA

11.45  Epigenetic stress response and stem cell aging  
       K. Lenhard Rudolph, MD, Head of the research group on ‘Stem cell aging’ and Scientific Director Leibniz Institute on Aging – Fritz Lipmann Institute, Jena, Germany

12.15  Using stem cells to understand and model age related macular degeneration  
       Majlinda Lako, PhD, Professor of Stem Cell Science, Institute of Genetic Medicine, Newcastle University, UK

12.45  Mitochondrial and senescence mechanisms in lung disease: aging at birth?  
       Y.S. Prakash, MD, PhD, Chair of Physiology and Biomedical Engineering, Mayo Clinic Robert and Arlene Kogod Center on Aging, Rochester, Minnesota, USA

13.15  Summary by chairs

Location: Blauwe Patio / Blue Patio

13.20  Conference closing by conference and program directors followed by Closing lunch
Danica Chen, PhD

Education
2004-2008  Postdoctoral Fellow, MIT, Biology
1999-2003  Doctor of Philosophy, University of California, Berkeley, Molecular & Cell Biology
1992-1996  Bachelor of Science, Xiamen University, China, Cell Biology

Employment
2014-Present  Associate Professor, Program in Metabolic Biology, Nutritional Sciences and Toxicology, University of California, Berkeley
2004-2014  Assistant Professor, Program in Metabolic Biology, Nutritional Sciences and Toxicology, University of California, Berkeley
2008-Present  Principal Investigator, Berkeley Stem Cell Center
2013-Present  Principal Investigator, QB3 Consortium on Life Span Extension

Honors and awards
2012  Kavli Fellow, National Academy of Sciences
2012  The Glenn Award
2011-2015  Ellison Scholar
2010  Hellman Fellow
2009-2012  Searle Scholar
2009  Regents’ Junior Faculty Fellowship

Mitochondrial Metabolic Checkpoint, Stem Cell Aging and Rejuvenation
Cell cycle checkpoints are surveillance mechanisms in eukaryotic cells that monitor the condition of the cell, repair cellular damages, and allow the cell to progress through the various phases of the cell cycle when conditions become favorable. Recent advances in hematopoietic stem cell (HSC) biology highlight a mitochondrial metabolic checkpoint that is essential for HSCs to return to the quiescent state. As quiescent HSCs enter the cell cycle, mitochondrial biogenesis is induced and mitochondrial stress is increased. Mitochondrial unfolded protein response and mitochondrial oxidative stress response are activated to alleviate stresses and allow HSCs to exit the cell cycle and return to quiescence. Because loss of HSC quiescence results in the depletion of the HSC pool and compromised tissue regeneration, deciphering the molecular mechanisms that regulate the mitochondrial metabolic checkpoint in HSCs will increase our understanding of hematopoiesis and how it becomes dysregulated under pathological conditions and during aging. More broadly, this knowledge is instrumental for understanding the maintenance of cells that convert between quiescence and proliferation to support their physiological functions.
K. Lenhard Rudolph, MD

Lenhard Rudolph is heading the research group on “Stem cell aging” at the Leibniz Institute on Aging - Fritz Lipmann Institute in Jena (www.leibniz-fli.de) since 2012 and appointed professor for molecular age research at the faculty for medicine of the Friedrich Schiller University Jena. After completing medical studies in Göttingen and a residency in internal medicine with Michael P. Manns in Hannover, he engaged in postdoctoral studies with Ronald A. DePinho at the Albert Einstein College in New York and at the Dana Farber Cancer Institute in Boston. He headed an Emmy Noether Research Group in Hannover from 2001 to 2006 and the Max Planck Research Group at Ulm University from 2007 to 2012. From 2012 – 2017 he was the scientific director of the FLI in Jena. K. Lenhard Rudolph has received several research awards including the Gottfried-Wilhelm Leibniz Award of the DFG in 2009, the Wilhelm Vaillant Award in Molecular Medicine in 2011, the Science award “Society needs science” of the Stifterverband for the German science system 2012, and in 2015 the German Cancer Award of the German Cancer Society as well as the Seneca medal for Aging Research of the Industrial Club of Düsseldorf.

Epigenetic stress response and stem cell aging

Adult tissue stem cells contribute to the lifelong maintenance of organ homeostasis and regeneration. However, the functionality of stem cells declines during aging and there is emerging evidence for the clonal dominance of mutant stem cells. Both processes contribute to the evolution of aging associated dysfunctions and diseases but molecular mechanisms that impair the function of stem cells during aging remain incompletely understood. Our recent work revealed that alterations in epigenetic stress responses lead to an aberrant activation of developmental pathways that impair the self renewal and regenerative capacity of muscle stem cells. Recent studies from the laboratory of David Scadden indicate that heterogeneity of epigenetic memory in hematopoietic stem cell is linked to the number of cell divisions and determines the heterogeneity in the functionality of HSCs during aging. Interestingly, the vast majority of gene mutations leading to clonal dominance of HSCs during aging affect epigenetic regulators. Together, these data indicate that alteration in epigenetic memory and stress responses represent driving forces for the decline of stem cell function and the selection of stem cell mutation during aging. During my talk I will present new data on physiological conditions and molecular mechanisms that may contribute to alterations of the epigenome and gene regulation in aging stem cells and thus to disease development in aging.
Majlinda Lako, PhD

Dr. Lako is currently Prof. of Stem Cell Sciences at Newcastle University, Institute of Genetic Medicine. She has 25 years’ experience in human genetics and stem cell biology. Her group works on human pluripotent stem cells. One of the key themes of her group’s research is to understand and define the early events occurring in human embryogenesis with special focus on eye formation and developing new treatments for eye disease. Her group is involved in several large research programmes that aim to define good manufacturing protocols for deriving functional corneal and retinal cells that can be used for drug testing, disease modelling and cell based replacement therapies.

Using stem cells to understand and model age related macular degeneration

Age related macular degeneration (AMD) is the most common cause of blindness, accounting for 8.7% of all blindness globally. Vision loss is caused ultimately by apoptosis of the retinal pigment epithelium (RPE) and overlying photoreceptors. Treatments are evolving for the wet form of the disease, however these do not exist for the dry form. Complement factor H (CFH) polymorphism in exon 9 (Y402H) has shown a strong association with susceptibility to AMD resulting in complement activation, recruitment of phagocytes, retinal pigment epithelium (RPE) damage and visual decline. We have derived and characterised induced pluripotent stem cell (iPSCs) lines from two patients without AMD and low risk genotype and two patients with advanced AMD and high risk genotype and generated RPE cells that show local secretion of several proteins involved in the complement pathway including factor H (FH), factor I (FI) and factor H like 1 (FHL-1). The iPSC RPE cells derived from high risk patients mimic several key features of AMD including increased inflammation and cellular stress, accumulation of lipid droplets, impaired autophagy and deposition of “drüsen” like deposits. The low and high risk RPE cells respond differently to intermittent exposure to UV light which leads to an improvement in cellular and functional phenotype only in the high risk AMD-RPE cells. Taken together our data indicate that the patient specific iPSC model provides a robust platform for understanding the role of complement activation in AMD, evaluating new therapies based on complement modulation and drug testing.
Y.S. Prakash, MD, PhD

The research group of Y.S. Prakash, MD, PhD, studies human lung diseases such as asthma, chronic obstructive pulmonary disease (COPD), emphysema, pulmonary fibrosis and pulmonary hypertension. Using state-of-the-art tools applied to human and animal models, Dr. Prakash’s group is working toward developing novel therapies and approaches to treat such diseases in babies, children and adults, especially in women and older adults.

Dr. Prakash has a unique training background as an anesthesiologist, physiologist, and electrical and biomedical engineer, which allows him to bring unique perspectives to research on the “how and why” of these clinically relevant diseases.

Dr. Prakash works with an outstanding interdisciplinary team of young clinician-scientists, researchers, graduate students and technicians in his Pulmonary Cell Biology Laboratory, with the motto "you are only as good as the people you work with."

Areas of Research
- Pulmonary Cell Biology - Y. S. Prakash
- Physiology and Biomedical Engineering
- Center for Biomedical Discovery
- Anesthesiology and Perioperative Medicine Research

Focus areas
- Asthma and inflammation
- Asthma in women
- Lung diseases in premature babies
- Pulmonary hypertension

Dr. Prakash’s work has tremendous potential in identifying novel biomarkers and therapeutic targets for a range of human lung diseases across the life span. Ongoing work on the immature airways of newborns has the potential to significantly impact the lives of premature babies. His recent work on sex differences and hormones has the potential for individualized medicine approaches to asthma and pulmonary hypertension.

Academic Rank: Professor of Anesthesiology and Professor of Physiology.

Mitochondrial and senescence mechanisms in lung disease: aging at birth?

In spite of improved mechanistic understanding, and a number of therapies, chronic lung diseases such as asthma, COPD and pulmonary fibrosis represent a major healthcare and financial burden worldwide. Here it is increasingly recognized that early insults to the growing lung (indeed even in utero) can have lifelong, detrimental consequences. Accordingly, understanding perinatal mechanisms of lung insult/injury may be critical to early interventions. In this regard, premature birth and perinatal insults such as maternal or fetal infection/inflammation and even secondhand smoke detrimentally influence subsequent lung growth and,
importantly, increase the risk of childhood asthma and wheezing. Such effects are exacerbated by medically and physiologically necessary interventions such as supplemental oxygen (hyperoxia) or mechanical ventilation in the neonatal ICU. While a number of mechanisms can underlie hyperoxia effects, in other organs and conditions oxidative stress induces cellular senescence and the senescence associated secretory phenotype (SASP) acts on the microenvironment in an autocrine and paracrine fashion causing fibrosis and promoting inflammation. Emerging studies including our own implicate cellular senescence as a driver of airway inflammation and remodeling in adult asthma and chronic obstructive pulmonary disease. Ongoing studies by our group suggest that hyperoxia and perinatal infection can induce senescence in the developing airway with enhanced SASP leading to airway remodeling, altered cell proliferation and furthermore altered mitochondrial structure and function. To this latter point, with increasing appreciation in lung diseases that mitochondria serve non-canonical cellular functions, we find that mitochondria sense upstream processes such as inflammation, infection, tobacco smoke and environmental insults and respond to such stimuli via altered mitochondrial protein expression, increased fragmentation, and resultant dysfunction. Such dysfunction has downstream influences on cytosolic and mitochondrial calcium regulation, airway contractility, gene and protein housekeeping, responses to oxidative stress, proliferation, apoptosis, fibrosis, and certainly metabolism: all key aspects of airway disease pathophysiology. Such effects are seen particularly in the developing airway in response to insults such as hyperoxia and infection. Finally, senescence and mitochondrial dysfunction are being found to play a role even in normal processes such as lung aging. Yet, our ongoing studies suggest that important conditions such as asthma in the elderly may represent a “failure” of senescence that promotes airway inflammation, hyperreactivity and fibrosis. Overall, via this presentation, we hope to emphasize emerging relationships between insults to the airway, senescence and mitochondrial dysfunction that contribute to lung diseases across the lifespan, thus identifying areas of unmet research need, and opportunities for novel therapeutic strategies.
Abstracts
Oral and poster presentations
<table>
<thead>
<tr>
<th>Last</th>
<th>Title</th>
<th>Affiliation</th>
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<tbody>
<tr>
<td>Huerta Guevara, Ana</td>
<td>Inability to repair endogenous DNA damage in pancreatic beta cells causes impaired glucose homeostasis.</td>
<td>UMCG</td>
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<td>Osmanagic-Myers, Selma</td>
<td>Progerin expression in endothelial tissue causes aging-related endothelial dysfunction and cardiovascular pathology</td>
<td>BOKO University</td>
</tr>
<tr>
<td>Tarragó, Mariana</td>
<td>A potent and specific CD38 inhibitor ameliorates age-related metabolic and skeletal muscle dysfunction by reversing tissue NAD decline.</td>
<td>Mayo Clinic</td>
</tr>
<tr>
<td>Ackermann, Tobias</td>
<td>C/EBPβ-LIP regulates the let-7/Lin28 circuit to control cellular metabolism</td>
<td>UMCG</td>
</tr>
<tr>
<td>Chapman, James</td>
<td>MitDNA mutations and mitochondrial dysfunction accelerate telomere-induced senescence in vivo</td>
<td>Newcastle</td>
</tr>
<tr>
<td>Chini, Claudia</td>
<td>Understanding the role of the CD38 ecto-NADase activity on cellular NAD metabolism in aging</td>
<td>Mayo Clinic</td>
</tr>
<tr>
<td>Dommerholt, Marleen</td>
<td>Protein restriction; does it improve metabolic health even at old age?</td>
<td>Mayo Clinic</td>
</tr>
<tr>
<td>Farr, Joshua</td>
<td>Causal Role of Senescent Cells in Mediating Age-Related Bone Loss</td>
<td>Mayo Clinic</td>
</tr>
<tr>
<td>Granic, Antoneta</td>
<td>Immunosenescence profiles, muscle strength, physical performance and risk of sarcopenia in very old adults</td>
<td>Newcastle</td>
</tr>
<tr>
<td>Grelscheid, Sushma</td>
<td>Signatures of Senescence Progression in a Transcriptomic Landscape Analysis Across the Mouse Lifespan</td>
<td>Durham University</td>
</tr>
<tr>
<td>Heberle, Alexander</td>
<td>Regulation of the mammalian target of rapamycin (mTOR) by RNA-protein granules</td>
<td>UMCG</td>
</tr>
<tr>
<td>Honrath, Birgit</td>
<td>MiRNA-135a regulates the expression of small conductance calcium-activated potassium (SK3) channels in epilepsy-like conditions</td>
<td>UMCG</td>
</tr>
<tr>
<td>Hoogerland, Joanne</td>
<td>The hepatic glucose sensor ChREBP controls bile acid homeostasis</td>
<td>UMCG</td>
</tr>
<tr>
<td>Houghton, David</td>
<td>Impact of age-related mitochondrial dysfunction and exercise on intestinal microbiota composition.</td>
<td>Newcastle</td>
</tr>
<tr>
<td>Ishaq, Abbas</td>
<td>Dietary restriction ameliorates age-related increase in DNA damage, senescence and inflammation in mouse adipose tissue</td>
<td>Newcastle</td>
</tr>
<tr>
<td>Krabbendam, Inge</td>
<td>SK channel activation promotes neuronal survival by inducing metabolic reprogramming</td>
<td>UMCG</td>
</tr>
<tr>
<td>Lagnado, Anthony</td>
<td>Neutrophils accelerate telomere-dependent senescence in vitro and in vivo.</td>
<td>Newcastle</td>
</tr>
<tr>
<td>Nijholt, Kirsten</td>
<td>A Kinase Interacting Protein 1 (AKIP1) promotes physiological cardiac hypertrophy</td>
<td>UMCG</td>
</tr>
<tr>
<td>Okwose, Nduka</td>
<td>Inert Gas Rebreathing is a reproducible method to assess cardiac and metabolic function at rest and during cardiopulmonary exercise stress testing</td>
<td>Newcastle</td>
</tr>
<tr>
<td>Ong, Jennie</td>
<td>Age-related changes in miRNA expression in healthy airways</td>
<td>UMCG</td>
</tr>
<tr>
<td>Oosterveer, Maaike</td>
<td>The hepatic glucose sensor ChREBP is a key factor in the development of metabolic liver disease</td>
<td>UMCG</td>
</tr>
<tr>
<td>Ovsyannikova, Inna</td>
<td>Systems Biology-Derived Innate and Adaptive Transcriptional Signatures of Influenza Vaccine Responses in Elderly Individuals</td>
<td>Mayo Clinic</td>
</tr>
<tr>
<td>Palmer, Allyson</td>
<td>Senescent cell clearance in diet-induced obese mice decreases adipose tissue macrophage burden</td>
<td>Mayo Clinic</td>
</tr>
<tr>
<td>Razquin Navas, Patricia</td>
<td>A systems study reveals concurrent activation of AMPK and mTOR by amino acids</td>
<td>UMCG</td>
</tr>
<tr>
<td>Saretzki, Gabriele</td>
<td>Telomerase Activators Improve Balance, Gait and Mitochondrial Function in a Mouse Model of Parkinson's Disease</td>
<td>Newcastle</td>
</tr>
<tr>
<td>Sediackova, Lucy</td>
<td>Autophagy impairment plays a role in mitochondrial dysfunction and the pathology of NPC</td>
<td>Newcastle</td>
</tr>
<tr>
<td></td>
<td>Name</td>
<td>Title</td>
</tr>
<tr>
<td>---</td>
<td>-------------------</td>
<td>--------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>27</td>
<td>Strazhesko, Irina</td>
<td>GH/IGF-1 axis as determinant of vascular aging and cellular senescence in subjects free of cardiovascular diseases.</td>
</tr>
<tr>
<td>28</td>
<td>Trump, Saskia</td>
<td>Restricting genome scale metabolic models with expression data reveals novel enriched signatures in glioblastoma</td>
</tr>
<tr>
<td>29</td>
<td>Victorelli, Stella</td>
<td>The role of telomeres in melanocyte senescence and skin ageing</td>
</tr>
<tr>
<td>30</td>
<td>Woldhuis, Roy</td>
<td>Paraquat-induced senescence in human lung fibroblasts as a model to study ageing in fibroblasts of COPD patients</td>
</tr>
<tr>
<td>31</td>
<td>Wu, Xinhui</td>
<td>Role of Non-canonical WNT signaling pathway in ageing and lung repair</td>
</tr>
</tbody>
</table>
8TH ANNUAL ALLIANCE FOR HEALTHY AGING CONFERENCE

Metabolism and ageing

Oral Presentations
1. Inability to repair endogenous DNA damage in pancreatic beta cells causes impaired glucose homeostasis.

A.P. Huerta Guevara¹, M.J. Yousefzadeh², S.J. McGowan², T. Sano², N.L. Mulder¹, A. Jurdzinski¹, T. van Dijk¹, B.J. Eggen³, J.H.J. Hoeijmakers⁴, A.K. Groen¹, J.W. Jonker¹, L.J. Niedernhofer², J.K. Kruit¹

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**Background and objectives:** Beta cell mass loss and impaired function are key features of Type 2 Diabetes (T2D). Patients with hyperglycemia also show increased levels of DNA damage, suggesting a potential connection between these events. Our research aimed to elucidate the impact of DNA damage on beta cell mass and function using a mouse model with deficient DNA repair. **Methods:** Glucose metabolism, beta cell mass, proliferation and apoptosis were studied in Ercc1⁻/⁻ mice, in which ERCC1-XPF repair endonuclease is knocked-down systemically to increase the burden of endogenous DNA damage, and control littermates. Glucose metabolism, beta cell area and mitochondrial respiration were also measured in Ercc1⁻/⁻;Rip-Cre⁺/− mice, in which ERCC1-XPF is only deleted in pancreatic beta cells, and control littermates. **Results:** The beta cells of Ercc1⁻/⁻ mice showed signs of persistent DNA damage, indicated by increased γH2AX staining. Ercc1⁻/⁻ mice had a 62% reduction in beta cell area (control mice 0.60±0.14 vs. Ercc1⁻/⁻ mice 0.23±0.07; p<0.01) with increased apoptosis, whereas beta cell proliferation was unaffected. Isolated islets from Ercc1⁻/⁻ mice showed a 2-fold increased sensitivity to apoptosis induced by high glucose. Ercc1⁻/⁻ mice, however, showed lower blood glucose levels due to increased insulin sensitivity. Loss of Ercc1 specifically in beta cells resulted in a progressive disarrangement in glucose homeostasis. Glucose tolerance and glucose stimulated insulin secretion were impaired in Ercc1⁻/⁻;Rip-Cre⁺/− mice both in vivo and ex vivo, whereas insulin sensitivity was unaffected. Furthermore, Ercc1⁻/⁻;Rip-Cre⁺/− showed reduced beta cell area (control mice 0.65±0.16 vs. Ercc1⁻/⁻;Rip-Cre⁺/− mice 0.34±0.12; p<0.01) and impaired glucose stimulated mitochondrial respiration. **Conclusion:** Our data suggest that endogenous DNA damage when not repaired in beta cells induce apoptosis, which contributes to loss of beta cell mass. In addition, DNA damage impairs insulin secretion, possibly through impairment in mitochondrial function. Therefore, therapies aimed to decrease DNA damage may contribute to the preservation of beta cells during T2D.
2. Progerin expression in endothelial tissue causes aging-related endothelial dysfunction and cardiovascular pathology

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**Background:** Hutchinson-Gilford progeria syndrome (HGPS) is a premature aging disorder characterized by accelerated cardiovascular disease with extensive adventitial fibrosis and atherosclerosis development. It leads to death at an average age of 14.6 years due to myocardial infarction or stroke. HGPS is caused by a mutation in LMNA leading to expression of a truncated prelamin A (progerin) in the nucleus. How this mutated protein causes cardiovascular disease especially in the context of endothelial tissue is largely unknown.

**Objective:** To study the mechanisms of aging-related endothelial dysfunction, a known risk factor for cardiovascular disease development using HGPS model system.

**Methods:** We generated a novel endothelium-specific HGPS transgenic mouse model (Prog-Tg) and examined cardiac fibrosis and hypertrophy by immunohistochemistry and gene expression analysis. Shear stress response was assessed in aortic endothelial sheet preparations and in primary endothelial cells using flow channels, and expression and localization of proteins involved in mechano-signaling were monitored by immunoblotting, gene expression analysis and immunofluorescence microscopy in cells and aortic specimens.

**Results and conclusions:** We demonstrate that Prog-Tg mice expressing progerin selectively in endothelial tissue phenocopy major clinical cardiovascular defects in HGPS, such as perivascular and interstitial fibrosis, cardiac hypertrophy and premature death. Endothelial-specific progerin expression induced aging-related changes as evidenced by increased collagen expression in heart, unresponsiveness to shear stress and downregulation of shear stress responsive endothelial nitric oxide synthase (eNOS). On the molecular level we show that progerin expression perturbs nucleo-cytoskeletal coupling and F-/G-actin ratio presumably leading to mislocalization of mechano-responsive myocardin-related transcription factor-A (MRTF-A). Treatment of progerin expressing endothelial cells with selective MRTF-A inhibitor rescued atheroprotective eNOS levels. We conclude that cardiovascular defects associated with excessive fibrosis in children with progeria are largely caused by progerin-induced endothelial dysfunction. Progerin perturbs nucleo-cytoskeletal coupling in endothelial cells causing aging-related changes such as flow shear stress defects and deregulated mechanosensitive MRTF-A/eNOS signalling that presumably leads to increased fibrosis in surrounding tissue. These findings unveil novel targets for the treatment of progeric and possibly geriatric cardiovascular disease.

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Title: A potent and specific CD38 inhibitor ameliorates age-related metabolic and skeletal muscle dysfunction by reversing tissue NAD decline. Abstract: NAD is a molecule that provides an important link between signaling and metabolism, and serves as a cellular metabolic sensor. Importantly, it has now been clearly demonstrated that cellular NAD levels decline during chronological aging. This decline appears to play a crucial role in the development of metabolic dysfunction and age-related diseases. We recently demonstrated that expression and activity of the NADase CD38 increase with aging and that CD38 plays a central role in the age-related NAD decline. Thus, CD38 may be a viable pharmacological target for age-related metabolic decline by reversing the decrease in NAD associated with aging. Here we investigated a highly potent and specific CD38 inhibitor (CD38i), and its role in NAD metabolism during the aging process. We first performed kinetic studies with CD38i and demonstrated that it is a potent inhibitor with an uncompetitive inhibition pattern. To investigate the effect of this inhibitor during aging, chronologically aged C57BL/6 mice of 2 years old received CD38i or vehicle (control) by intraperitoneal injections bi-daily. CD38i reverses age-related NAD decline and improves several physiological and metabolic parameters of aging. Mice treated with CD38i showed an improvement of glucose tolerance and insulin sensitivity. We next evaluated the effect of the inhibitor on physical activity, exercise tolerance, and muscle architecture in aged mice. After administration of CD38i, mice demonstrated an increase in exercise capacity assessed by a motorized treadmill and in spontaneous locomotor activity assessed by Laboratory Animal Monitoring System (CLAMS). Moreover, treatment with CD38i also reverted several morphological features of aging in skeletal muscle including centrally positioned nuclei, inflammatory cell infiltration, number of necrotic fibers, and ATP/O2 coupling. Furthermore, CD38i increased NAD levels in vivo, resulting in activation of pro-longevity and healthspan-related factors including SIRTUINS, AMPK, and PARPs. On the other hand, in animals treated with CD38i we observed inhibition of pathways that negatively affect healthspan, such as the mTOR-S6K and ERK, and attenuation of telomere-associated DNA damage, a marker of cellular aging. Together, our results detail a novel strategy for prevention and/or reversal of age-related NAD-decline and subsequent metabolic dysfunction.

8th Annual Alliance for Healthy Aging Conference

Metabolism and Ageing

Poster Presentations
4. C/EBPβ-LIP regulates the let-7/Lin28 circuit to control cellular metabolism

Tobias Ackermann1,2, Götz Hartleben1,2, Britt A. Sterken1, Mohamad Amr Zaini1,2, Guido Mastrobuoni3, Marco Groth2, Zhao-Qi Wang2, Matthias Platzer2, Stefan Kempa3, Gerald de Haan1 and Cornelis F. Calkhoven1,2

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A high expression of C/EBPβ-LIP, the small protein isoform of the transcription factor C/EBPβ, is associated with breast cancer development. Experimental mouse models show that LIP-deficiency reduces, while transgenic LIP-overexpression increases general tumor incidence. Furthermore, various cancer types like breast cancer and anaplastic large cell lymphoma (ALCL) have increased levels of C/EBPβ-LIP. However, the molecular mechanisms underlying the oncogenic function of C/EBPβ-LIP are not fully understood.

Here we show that C/EBPβ-LIP enhances aerobic glycolysis and mitochondrial respiration (Seahorse XF analysis), resembling a shift to cancer/stem cell metabolism. By using an integrative analysis of genome wide transcriptome and whole cell proteome we show that although the induction of C/EBPβ-LIP does not significantly alter mRNA levels of glycolytic enzymes, the protein levels of these enzymes are elevated. Further analysis of the C/EBPβ-LIP transcriptome revealed that C/EBPβ-LIP stimulates the expression of Lin28b, which is an oncofetal RNA-binding protein that enhances the translation of glycolytic and mitochondrial enzymes in order to increase the cellular metabolism and energy production. Moreover, Lin28b knockout by CRISPR/Cas9 genomic editing ablates C/EBPβ-LIP induced metabolic reprogramming in cells. We show that C/EBPβ-LIP controls Lin28b expression through transcriptional repression of let-7. Let-7 and Lin28a/b have reciprocal functions in a regulatory circuitry where let-7 represses Lin28a/b-mRNAs, while Lin28a/b represses let-7 maturation. Finally, first analyses using a conditional C/EBPβ-LIP overexpressing mouse model show that let-7 levels are repressed and Lin28b levels are upregulated by C/EBPβ-LIP in vivo. Furthermore, increased LIP level enhance the cellular metabolism in bone marrow cells and results in hyperplasia in the examined tissues, skin and spleen.

Therefore, our data suggest a key role of C/EBPβ-LIP in controlling the Lin28/let-7 regulatory circuit and thereby regulating cellular metabolism in the context of stem cell function, tissue repair and tumour development.
5. MtDNA mutations and mitochondrial dysfunction accelerate telomere-induced senescence 

in vivo

James Chapman, Rhys Anderson, Derek Mann, Laura Greaves, João F. Passos

Affiliations: Newcastle University Institute for Ageing and Institute for Cell and Molecular Biosciences, Newcastle University, UK

Senescent cells has been implicated in the ageing process and in the development of various age-related disorders. Telomeres are specialised tandem DNA repeats found at chromosome ends which have been causally implicated in cellular senescence. It has been previously shown in fibroblasts grown in vitro that senescence can be induced by reactive oxygen species (ROS) produced by the mitochondria as a by-product of oxidative phosphorylation. Mechanistically, it has been shown that ROS can accelerate the rate of telomere shortening, resulting in the premature activation of a DNA damage response at telomere-ends. However, the impact of mitochondrial dysfunction in telomere-induced senescence in vivo has been poorly investigated.

In this study, we utilised the PolGAmut mouse model which is deficient for mtDNA polymerase and is characterised by high frequency of mtDNA mutations, mitochondrial dysfunction and accelerated ageing (Trifunovic et al. 2004). Our data show that various tissues from PolGAmut mice (liver, lung and heart) show evidence for increased Telomere-associated DNA damage Foci (TAF), measured by Immuno-FISH, when compared to age-matched controls. Interestingly, we found that exercise was able to counteract telomere-dysfunction in these mice.

Using super-resolution stimulation emission depletion microscopy (STED) which allowed a much more accurate detection of telomere length by FISH than conventional confocal microscopy, we found that telomere dysfunction could not be attributed to increased telomere shortening and occurred irrespective of telomere length.

Here, we propose that the accumulation of mtDNA mutations with age in vivo lead to mitochondrial dysfunction and exacerbated production of ROS which will drive telomere-induced senescence in vivo.
Understanding the role of the CD38 ecto-NADase activity on cellular NAD metabolism in aging

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Aging is characterized by the development of age-related metabolic diseases and frailty. Recent studies show that a decrease in levels of Nicotinamide adenine dinucleotide (NAD) is a key factor for the development of age-related metabolic decline. Administration of NAD precursors such as nicotinamide mononucleotide (NMN) or nicotinamide riboside (NR) is sufficient to improve healthspan and longevity in mice. To date, the mechanisms that lead to NAD decline during aging have not been completely elucidated, but we recently showed that CD38 is the main NADase responsible for the aging-related NAD decline. To understand the role of CD38 in NAD metabolism during aging we need to determine how CD38 regulates NAD levels in tissues. CD38 is mostly an ecto-enzyme that is highly expressed in inflammatory cells, but also in other tissues. Because the majority of the NADase catalytic activity of CD38 faces the outside of the cell, we explored 2 possibilities: 1) the relative role of the CD38 ecto versus endo-enzymatic activity in NAD homeostasis and 2) the possibility that extracellular NADase activity of CD38+ cells (such as immune cells) could influence NAD levels in nearby parenchymal cells via degradation of extracellular NAD precursors such as NMN. To test the role of the ectoenzyme in regulating NAD levels we used specific anti-CD38 antibodies. These antibodies inhibit the NADase activity of recombinant human CD38, and also CD38 activity from cells and mice tissue. After treatment with these antibodies, cells showed an increase in NAD levels. Importantly, when mice were treated with anti-CD38 antibodies for 2 days, there was an increase in NAD levels in multiple tissues. These results indicate that the ecto-enzymatic activity of CD38 is important for the regulation of intracellular NAD levels. To determine the role of ecto-NADase activity of CD38+ cells on NAD levels in adjacent or nearby CD38- cells, we performed co-culture experiments. Co-culture of CD38+ cells with CD38- cells shows that CD38+ cells can regulate NAD levels in CD38- cells by influencing the availability of NAD precursors. These results together demonstrate that the ecto-enzymatic activity of CD38 is important for regulation of NAD in neighboring cells and provide pre-clinical support for the use of CD38 inhibitory antibodies to improve NAD homeostasis in aging.
7. Protein restriction; does it improve metabolic health even at old age?

M.B. Dommerholt¹, M. Blankestijn¹*, R.P. van Os², F. Kuipers³, J.K. Kruit³, J.W. Jonker¹

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2. Mouse Clinic for Cancer and Aging, Central Animal Facility, University of Groningen, The Netherlands

* equal contribution

Caloric restriction and dietary macronutrient composition have been extensively studied in the context of increasing life expectancy. Recently it was reported that the ratio of macronutrients, not caloric intake, dictates cardiometabolic health and aging (Solon-Biet et al., Cell Metab., 2014). A protein restricted diet, where protein was replaced by carbohydrates, generated the metabolic benefits of caloric restriction without reducing total caloric intake (Solon-Biet et al., Cell Reports, 2015). The complex metabolic network underlying the positive effects involves signalling through AMPK, mTOR, FGF21, insulin and IGF1 in multiple tissues, which subsequently influences mitochondrial biogenesis, autophagy, glucose homeostasis and adipogenesis (Solon-Biet et al., Cell Metab., 2014). However, these experiments were all in mice receiving these diets throughout their lifespan.

Since the pathways involved in the beneficial effects of a protein restricted diet are influenced by aging, it is important to know whether dietary intervention at a later age is still beneficial on metabolic parameters and microbiome composition. Therefore, we designed the current study to investigate metabolic health after a short-term dietary intervention varying in protein, carbohydrate and fat ratio in the context of ageing. For this, we are using wildtype C57Bl6/J mice, either at the age of 3 months or 18 months, challenged with a semi-synthetic low fat diet for 2 months, varying in protein-carbohydrate ratio. We will conduct a thorough search looking at all facets of glucose metabolism, insulin secretion, lipid profile, microbiome composition, fecal excretion, energy expenditure, muscle strength and mitochondrial capacity. Metabolic parameters will be tested before and after the diet intervention to determine individual improvement of both young and old mice.

The present research will shed further light on the possible differences between old and young animals in maintaining energy expenditure by a dietary challenge. We hypothesize the protein restriction will disrupt muscle metabolism in old mice, resulting in body weight loss and decline in physical appearance. It will be interesting to see whether this will overshadow the beneficial effects in glucose and lipid metabolism seen in young animals. In conclusion, it need to be further determined whether increased age, and its side-effects, influences the beneficial dietary effects before translating the current understanding on metabolic health onto the human population.
Accumulation of DNA damage and other cellular stressors cause proliferating as well as terminally differentiated, non-dividing cells to undergo senescence, characterized by increased expression of the cell cycle inhibitor, p16\(^{Ink4a}\), along with profound morphological changes. In addition, senescent cells can produce the senescence-associated secretory phenotype (SASP), consisting of pro-inflammatory cytokines, chemokines, and extracellular matrix-degrading proteins, which have deleterious paracrine and systemic effects. Indeed, even a relatively low abundance of senescent cells (~10-15%) is sufficient to cause tissue dysfunction. Here, we investigate a role for senescent cells in age-related bone loss using 3 strategies: 1) reducing senescent cell burden using mice expressing the INK-ATTAC “suicide” transgene via drug (AP20187)-inducible caspase-8 driven by the senescence-associated p16\(^{Ink4a}\) promoter; 2) clearing senescent cells by administering previously validated “senolytic” compounds (dasatinib + quercetin) that specifically kill senescent cells without affecting proliferating or quiescent, differentiated cells; or 3) inhibiting the SASP production by senescent cells using a JAK inhibitor (JAKi). In old (20-22 month) mice with established bone loss, 2-4 month treatment with each of these interventions improved bone mass, microarchitecture, and strength. The beneficial effect of targeting senescent cells was due to suppression of bone resorption with either maintenance (trabecular bone) or an increase (cortical bone) in bone formation. In vitro studies demonstrated that senescent cell conditioned medium impaired osteoblast mineralization and enhanced osteoclast progenitor survival, leading to increased osteoclastogenesis; the latter effect was abrogated by pre-treatment of the senescent cells with the JAKi. The specificity of these interventions to aging was demonstrated by the absence of any skeletal effects in response to these interventions in young (7-12 month-old) mice. Collectively, these data establish a causal role for senescent cells in bone loss with aging. Because eliminating senescent cells and/or inhibiting their SASP also improves cardiovascular function, enhances insulin sensitivity, and reduces frailty, the efficacy of this approach to prevent age-related bone loss reveals a novel treatment strategy for osteoporosis via targeting a fundamental aging mechanism to thereby simultaneously treat multiple age-related co-morbidities.
Title: Immunosenescence profiles, muscle strength, physical performance and risk of sarcopenia in very old adults

Authors: Antoneta Granic, Carmen Martin-Ruiz, Karen Davies, Richard Dodds, Carol Jagger, Thomas BL Kirkwood, Thomas von Zglinicki, Avan A Sayer

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Abstract

Background: Loss of skeletal muscle mass and strength with ageing (sarcopenia) leads to impaired function in the form of reduced mobility, increased disability, and poor quality of life in older adults. Altered metabolic, hormonal, and immune factors have been suggested to play a role in skeletal motor unit remodelling, reduced muscle fibre regeneration upon injury, and increased muscle atrophy with ageing. However, little is known whether age-related immunosenescence in lymphocyte compartments associates with muscle strength, function and progression to sarcopenia in older adults.

Objective: Utilising data from the Newcastle 85+ Study we aimed to: (a) derive and characterise immunosenescence profiles by clustering 13 immunosenescence-related biomarkers; (b) explore the association between the profiles, muscle strength (grip strength, GS) and physical performance (Timed Up-and-Go test, TUG) decline over 5 years, and (c) determine the relationship between the profiles and prevalent and 3-year incident sarcopenia in very old adults (aged ≥85 years).

Methods: We used Two-Step clustering and the following biomarkers describing lymphocyte compartments to derive immunosenescence profiles in 657 participants: Memory and Naïve B cells; Natural Killer (NK) cells; NK T cells; total, Naïve and Memory CD4 and CD8 T cells; CD4 senescence-like effector memory cells (CD4\textsuperscript{TEMRA}); Senescent Naïve CD4; and CD8 senescent-like effector memory (CD8\textsuperscript{TEMRA}) cells. Mixed models were used to investigate the association between the profiles and GS and TUG at baseline and over time. Logistic regression was used to determine the risk of prevalent and incident sarcopenia across the profiles.

Results: We identified two distinct clusters (profiles): Cluster 1 (‘Senescent-like phenotype, n=421), and Cluster 2 (‘Less senescent-like phenotype’, n=236). Eight immunosenescence-related biomarkers contributed the most to cluster separation (in the order of importance): Memory CD4, NK, total CD8, CD8\textsuperscript{TEMRA}, CD4\textsuperscript{TEMRA}, Memory CD8, total CD4, and Naïve CD4 cells. Compared to participants in Cluster 2, those in Cluster 1 had higher frequency of Memory CD4, NK, total CD8, CD8\textsuperscript{TEMRA}, CD4\textsuperscript{TEMRA}, and Memory CD8 (all p<0.001), but lower frequency of total CD4 and Naïve CD4 cells (both p<0.001), and lower CD4/CD8 ratio. They were more likely to be positive for Cytomegalovirus (CMV +) (all p<0.001), and had higher basal IL-6 (p=0.02) and hsCRP (p=0.01) concentrations. Mixed models adjusted for sex, fat-free mass, and physical activity showed no association between Cluster 1 and baseline GS (β (SE) = -0.39 (0.41), p=0.34) and TUG (0.03 (0.02), p=0.08), and their change over time (0.008 (0.1), p=0.94; -0.001 (0.004), p=0.78, respectively) in all participants. Significant association between baseline GS and Cluster 1 in men (0.05 (0.03), p=0.05) was explained by CMV seropositivity. Although raised, odds ratios (OR, 95% CI) for prevalent and incident sarcopenia were not significantly associated with Cluster 1 (1.37, 0.86-2.19, p=0.19; 1.49 (0.81-2.76, p=0.21, respectively) after adjusting for education, social class, BMI, and cognitive status.

Conclusion: Two distinct immunosenescence profiles were derived using 13 biomarkers describing lymphocyte compartments in very old adults. ‘Senescent-like phenotype’ characterised by T cell senescence and elements of the immune risk profile (e.g. CMV+) was not associated with GS and TUG (initially and over time), and sarcopenia. Future studies will determine whether change in immunosenescence biomarkers predicts decline in muscle strength and physical performance, and transition to sarcopenia in the very old.
10. Signatures of Senescence Progression in a Transcriptomic Landscape Analysis Across the Mouse Lifespan

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Ageing is characterised by deterioration of health and increased mortality rate and the ageing process is affected by both genotype and environment. Dietary restriction has been shown to increase lifespan and healthspan across many organisms.

Here we present a landscape analysis of ageing in C57/BL6 mice across multiple time-points from 3 months till 30 months of age, and under normal or long term calorie restricted diets. Total RNA was extracted from livers of 3 biological replicates per time point, DNase treated and stranded libraries were prepared and sequenced on an Illumina platform to obtain paired end reads of 100 bases, with a minimum of 25 million reads per time point replicate. The resulting data was analysed to interrogate changes in gene expression regulation at multiple levels: transcriptional, post-transcriptional RNA processing such as alternative splicing, as well as long non-coding RNA.

We focus on illuminating the possible mechanisms affording improved healthspan and lifespan to dietary restricted organisms. Our data shows strong correlations between age and diet related gene expression changes and senescence markers. We also report tight regulation across the lifespan for specific biological processes, at multiple levels of gene expression regulation, with specific time-points showing major changes, potentially representing turning points.
Title: Regulation of the mammalian target of rapamycin (mTOR) by RNA-protein granules

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Abstract:
Mammalian target of rapamycin (mTOR) kinase is a central regulator of cellular growth and metabolism and plays an important role in ageing and age-related diseases. mTOR forms two distinct multiprotein complexes named mTOR complex 1 (mTORC1) and mTORC2. mTORC1 responds to insulin, amino acids and cellular energy to control cell growth, protein translation and autophagy. Next to these well-known inputs, also cellular stress has been shown to influence the mTOR pathway, including oxidative stress, hypoxia and endoplasmic reticulum stress. Upon stress cells activate protective mechanisms in order to prevent cellular death. One of these mechanisms is stress granule (SG) formation where protein and mRNA molecules aggregate into cytoplasmic, non-membranous cell organelles. Once formed they sort mRNAs for decay or maintenance. SGs can also trap signaling molecules and communicate a state of emergency to different pathways. Notably, SGs inhibit mTORC1 [1], but the underlying molecular mechanisms are only beginning to be elucidated [2]. We conducted mass-spectrometry enhanced interactomics and present here new evidence on the interconnection between mTOR and SGs.

References
12. MiRNA-135a regulates the expression of small conductance calcium-activated potassium (SK3) channels in epilepsy-like conditions

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Background
Excessive and hypersynchronous neuronal discharges are key characteristics in the pathophysiology of neurological disorders such as epilepsy. Owing to their ability of regulating neuronal excitability, small conductance calcium-activated potassium (SK) channels have been implicated in several diseases of the brain, and their activation provided neuroprotection in different paradigms of cell death, including oxidative stress and excitotoxicity.

Objectives
In our study, we investigated the function and regulation of SK channel expression in different models of epilepsy and excessive neuronal firing.

Methods
As a model for hypersynchronous neuronal firing in vitro, we used primary cortical neurons either challenged with glutamate or deprived of magnesium to increase neuronal firing. In addition, we used perforant pathway stimulation (PPS) to induce hippocampal seizures in vivo. We investigated neuronal firing using multielectrode array recordings, analyze SK channel expression by Western blot, and assess mitochondrial performance by evaluating mitochondrial complex activity. MicroRNA135a-dependent effects on SK3 channels were investigated using a dual-luciferase assay.

Results and Conclusions
In vitro, analysis of neuronal firing in magnesium deprived primary neuronal cultures revealed that SK channel activation fully blocked the increase in neuronal activity, and restored homeostatic signaling. We found reduced SK3 channel expression following glutamate-induced excitotoxicity in vitro, and following PPS in the rat hippocampus in vivo. Further, PPS in vivo impaired the performance of mitochondrial complex I. Interestingly, we identified miRNA-135a as a key regulator of SK3 channel expression in primary neurons. Thus, we provide strong evidence that SK3 channels are involved in epilepsy(-like) conditions which are characterized by enhanced neuronal firing and an impairment of mitochondrial function, and the miRNA135a-dependent regulation of SK3 channel expression was unraveled as a new regulatory mechanism.

Support
This project was funded by a grant from the Deutsche Forschungsgemeinschaft, DFG (DO 1525/3-1), and the European Union’s ‘Seventh Framework’ Programme (FP7) EpimiRNA.
The hepatic glucose sensor ChREBP controls bile acid homeostasis


Background: Besides promoting intestinal lipid uptake, bile acids act as signaling molecules that affect glucose and lipid homeostasis. Altered bile acid metabolism may contribute to the development of age-related metabolic diseases such as Type 2 Diabetes. Bile acid metabolism is fine-tuned by insulin-, sterol- and bile acid-sensitive transcription factors that control the expression of bile acid synthesis and transporter genes. Recent studies suggest that glucose may play a role herein, but underlying mechanisms have remained elusive.

Objectives: We aimed to characterize the regulatory role of the transcriptionally active glucose metabolite glucose-6-phosphate (G6P) on bile acid synthesis.

Methods: We quantified hepatic gene expression patterns and analyzed bile acid profiles in mice that accumulate G6P in the liver, i.e., liver-specific glucose-6-phosphatase knockout (L-G6pc−/−) mice and G6P-transporter-inhibited (S4048-treated) mice. In parallel, we performed in vivo ChIPs and cell reporter assays to investigate the transcriptional regulation of the Cyp8b1 gene by G6P.

Results: Hepatic G6P accumulation resulted in an induction of hepatic Cyp8b1 expression in L-G6pc−/− and S4048-treated mice, while Cyp7a1, Cyp27a1 and Cyp7b1 mRNA levels were reduced in L-G6pc−/− mice only. These gene expression changes were reflected in an altered biliary bile acid composition with more cholic acid-derived species and a more hydrophobic bile acid pool in L-G6pc−/− mice, while total plasma bile acid concentrations remained unaltered. The induction of Cyp8b1 expression and the consequent change in the hydrophobicity of the bile acid pool were mediated by the major glucose-sensitive transcription factor ChREBP.

Conclusions: Hepatic G6P accumulation activates ChREBP and subsequently alters the expression of bile acid synthesis genes in the liver, resulting in a corresponding qualitative change of the bile acid pool that may have long-lasting (patho)physiological impact. Increased G6P synthesis in the liver may contribute to perturbed bile acid metabolism in Type 2 Diabetes.

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Abstract

Background: Mitochondrial dysfunction is prevalent in the ageing gastrointestinal tract. The complex nature of the GIT means that any reduction in its function with ageing makes it more susceptible to GIT disorders and potentially pathogenic microorganisms, which are prevalent in the ageing population and primary mitochondrial disorders. Slower transit time of digesta is commonly reported, having a direct impact upon digestion, absorption of nutrients, fermentative processes, defecation, and bacterial excretion. This culminates in reduced diversity of the bacterial community, termed ‘gut microbiota’ and contributes to gut microbiota dysbiosis and been shown to have a profound impact upon human health and quality of life.

Objectives: We investigated whether changes in mitochondrial function in ageing colonic crypts influence the microbial gut communities in mice, and whether exercise modulates any such changes.

Methods: Twelve PolgAmut/mut mice and seven age matched wild type PolgA+/+ mice were used in the current study. The twelve PolgAmut/mut mice were randomly divided into a sedentary and exercise group at 4 months, and PolgA+/+ remained sedentary throughout. Stool samples were collected at 4, 7 and 11 months, and bacterial profiling was achieved through 16S rDNA sequencing profiling. Mitochondrial enzyme activity was assessed in colonic epithelial crypts at 11 months for PolgAmut/mut and PolgA+/+ mice.

Results: Sedentary and exercised PolgAmut/mut mice had significantly higher levels of mitochondrial dysfunction than PolgA+/+ mice (78\%, 77\% and 1\% of crypts, respectively). Bacterial profiles of sedentary PolgAmut/mut mice were significantly different from the sedentary PolgA+/+ mice, with increases in Lactobacillus and Mycoplasma, and decreases in Alistipes, Odoribacter, Anaeroplasma, Rikenella, Parabacteroides, Allobaculum in the PolgAmut/mut mice. Exercise did not have any impact upon gut mitochondrial dysfunction, however, exercise did increase gut microbiota diversity and significantly increasing bacterial genera Mucispirillum and Desulfovibrio. Conclusion: Mitochondrial dysfunction is associated with changes in the gut microbiota. Endurance exercise moderated some of these changes, establishing that environmental factors can influence gut microbiota despite mitochondrial dysfunction. However, environmental factors must be tailored to the individual’s phenotype to ensure optimal benefits of the patients.
Dietary restriction ameliorates age-related increase in DNA damage, senescence and inflammation in mouse adipose tissue

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Background:
Ageing is associated with redistribution of fat around the body and saturation of visceral adipose depots. Likewise, the presence of excess fat in obesity or during ageing places extra stress on visceral depots, resulting in chronic inflammation and increased senescence. This process can contribute to the establishment of the metabolic syndrome and accelerated ageing. Dietary restriction (DR) is known to alleviate physiological signs of inflammation, ageing and senescence in various tissues including adipose tissue.

Objectives:
Our two studies aimed to analyse senescence and inflammation parameters in mouse visceral fat tissue during ageing and by short term, late-onset dietary restriction as a nutritional intervention.

Methods:
In these studies we used visceral adipose tissue from mice and analysed markers of senescence (adipocyte size, \( \gamma H2A.X \) foci, \( p16 \), \( p21 \)) and inflammation (e.g. IL-6, TNF\( \alpha \), IL-1, macrophage infiltration) using immuno-staining, as well as qPCR for gene expression analysis.

Results and Conclusions:
The first study was a late-onset, short term DR study and we analysed mice aged between 5 and 30 months while the second study DR began at 3 months, where some mice were switched at 12 months of age from DR to AL and from AL to DR. We found that adipocyte size, number of \( \gamma H2A.X \) foci, as well as the expression of senescence and inflammation markers increased during ageing but decreased with short term DR. This was confirmed independently in the AL/DR and DR/AL crossover experiment, where the AL/DR crossover showed the same effects as the late-onset, short term DR in the first study while the DR/AL switched mice kept their beneficial parameters even after fed AL. We also found an increase in the amounts of single or aggregated macrophages in fat depots occurred at higher ages.

Our results demonstrate increased senescence and inflammation during ageing in mouse visceral fat while DR was able to ameliorate several of these parameters as well as increased adipocyte size. Importantly, the cross-over study showed that the beneficial effects dietary restrictions were maintained even when the DR mice were switched back to AL conditions. These two studies highlight the health benefits of late-onset decrease in caloric intake over a relatively short period of time which remain with subsequent increase in caloric intake.
16. SK channel activation promotes neuronal survival by inducing metabolic reprogramming

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Background
Mitochondria are essential for cell viability since they are responsible for energy production via oxidative phosphorylation (OXPHOS), regulation of calcium (Ca\textsuperscript{2+}) homeostasis, reactive oxygen species (ROS) generation and apoptosis. Oxidative stress induces mitochondrial Ca\textsuperscript{2+} ([Ca\textsuperscript{2+}]\textsubscript{m}) overload, causing changes in mitochondrial metabolism and in ROS formation. Increasing evidence suggests that cells can shift their energy metabolism to anaerobic glycolysis as an adaptive response to oxidative stress. Previous data showed that small-conductance Ca\textsuperscript{2+} - activated K\textsuperscript{+} (SK) channels contribute to the regulation of [Ca\textsuperscript{2+}]\textsubscript{m} buffering, mitochondrial ROS generation and metabolic functions of mitochondria, thereby conferring cellular protection in conditions of oxidative stress\textsuperscript{1,2}.

Objective
In this study, we address the question whether SK channel activation regulate mitochondrial complex activity and may induce a metabolic shift towards glycolytic activity, that could further enhance its neuroprotective capacity in oxidative stress situations.

Methods
Cell viability was assessed by xCELLigence real-time cell impedance measurements and MTT assays. Oxidative phosphorylation (OXPHOS) and glycolytic activity were measured using extracellular flux analyzer (Seahorse Bioscience) in hippocampal-derived HT22 cells. High-resolution respirometry was used to study the effects of SK channel activation (with positive pharmacological modulator CyPPA) on the activity of different mitochondrial complexes in isolated mitochondria. Expression of mitochondrial respiratory chain complexes following SK channel activation was studied by Western blot.

Results / Conclusions
Glutamate mediates mitochondrial dysfunction, oxidative stress and cell death in HT22 cells. Activation of SK channels prevented glutamate-induced oxidative stress and cell death when both glycolysis and OXPHOS were present. However, when glycolytic activity was inhibited by exchanging glucose as a sugar source with galactose, the neuroprotective effect of CyPPA was reduced, and CyPPA alone facilitated cell death following long-term treatment (24-48h), attributed to a lack of ATP generation from glycolysis. High-resolution respiratory measurements revealed that activation of SK channels reduced mitochondrial complex I and II activity. Activation of SK channels did not alter the expression of these mitochondrial complexes following short treatment with CyPPA, while long-term treatment (24h-48h) decreased the protein expression. In line with these findings, Seahorse real-time measurements showed that CyPPA induced a dose-dependent initial increase in glycolytic activity followed by a slight reduction in OXPHOS activity, which dropped even further when glycolysis was inhibited. As a result of decreased mitochondrial OXPHOS activity, SK channel opening was able to reduce mitochondrial superoxide formation in conditions of oxidative stress. These experiments demonstrated that SK channels are able to induce a metabolic shift towards glycolysis and attenuate mitochondrial superoxide production. This study further enhances our understanding of neuroprotective molecular pathways of SK channel opening in conditions of oxidative stress.

References:
Anthony Lagnado

17. Title: Neutrophils accelerate telomere-dependent senescence in vitro and in vivo.


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Background and Objectives: Neutrophils have been shown to be key players in the recognition and elimination of pathogens, however, recent data has revealed that they may play other roles in disease, notably the development of cancer.

Senescence, the state of irreversible arrest observed in somatic cells is characterised by a Senescent Associated Secretory Phenotype (SASP) which includes pro-inflammatory cytokines, chemokines and extracellular matrix proteases. The SASP is believed to play a role in the recruitment and activation of immune cells, including macrophages, CD4 T and NK cells which have been shown to play a role in clearance of senescent cells. However, the relationship between neutrophil recruitment and senescence has not been completely investigated.

Methods: culture of human fibroblasts, co-culture with neutrophils, analysis of telomere length by FISH, DNA damage response assays (Immunocytochemistry, COMET), Immuno-FISH. Wild-type and TLR2-/- were injected with CCl$_4$. Neutrophils infiltration was blocked by Ly6G neutralising antibody delivered using a mini-pump.

Results and Conclusions:

We show that co-culture between young human fibroblasts and young neutrophils for 3 days leads to a significant reduction in the replicative lifespan of fibroblasts. Human fibroblasts pre-cultured with neutrophils experienced accelerated telomere shortening and increased expression of a variety of senescent markers. Pre-treatment with the enzyme catalase or ectopic overexpression of telomerase prevented the effects of neutrophils on senescence of human fibroblasts, suggesting a role for oxidative stress-mediated telomere shortening in the process.

Consistent with a role for neutrophils in telomere dependent senescence, we found an association between neutrophil infiltrations and telomere dysfunction in ageing mice.

Furthermore, we showed that induction of liver injury induced by CCl$_4$ which resulted in increased neutrophil infiltrations contributed to telomere dysfunction in hepatocytes. Consistent with a role for neutrophils in the process, inhibition of neutrophil recruitment using the neutralising antibody Ly6G or in mice lacking TLR2 prevented CCl$_4$ induced telomere dysfunction.

Our results suggest that neutrophils as a consequence of their role in the immune system may inadvertently induce senescence in young cells via oxidative stress-mediated telomere dysfunction.
18. A Kinase Interacting Protein 1 (AKIP1) promotes physiological cardiac hypertrophy


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Background: Overexpression of a Kinase Interacting Protein 1 (AKIP1) promotes physiological hypertrophy in cultured cardiomyocytes by activating AKT-mediated growth pathways. Whether AKIP1 regulates physiological cardiac hypertrophy in vivo is unknown.

Objective: We tested the hypothesis that cardiomyocyte-specific overexpression of AKIP1 promotes physiological hypertrophy in response to exercise.

Methods: Mice with cardiomyocyte-specific overexpression of AKIP1 (AKIP1-TG) and their wild type (WT) littermates were subjected to 4 weeks of voluntary wheel running, whereas control mice remained sedentary. Exercise capacity, cardiac weight, hemodynamics, cardiac histology and AKT phosphorylation were analyzed.

Results and Conclusions: While running time and distance were comparable between AKIP-TG and WT mice, the induction of physiological hypertrophy after voluntary exercise was markedly increased in AKIP1-TG mice compared to wild type mice (Heart Weight/tibia length 9.5 ± 0.3 mg/mm in AKIP-TG vs 8.7 ± 0.2 mg/mm in WT mice, p<0.05). The augmentation of exercise-induced cardiac hypertrophy was associated with a 6-fold increase in AKT phosphorylation and the activation of its down-stream pathways. In conclusion, cardiomyocyte-specific overexpression of AKIP1 promotes physiological cardiac hypertrophy after voluntary exercise by activating AKT-mediated cardiac growth. These findings suggest that AKIP1 may serve as a nodal point to induce beneficial reprogramming of hypertrophic heart disease.

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19. Inert Gas Rebreathing is a reproducible method to assess cardiac and metabolic function at rest and during cardiopulmonary exercise stress testing

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Abstract

Background Inert gas rebreathing is a technique which measures cardio-metabolic and respiratory function by measuring the rate of clearance of a physiologically inert gas from the pulmonary capillary circulation. Previous reproducibility investigations have focused on measurement obtained at rest and/or peak exercise in different clinical groups, and this offers limited insight to the performance of this technique.

Objective The aim of the study was to evaluate the reproducibility of inert gas rebreathing at rest and during cardiopulmonary exercise testing.

Methods Thirteen healthy subjects (range 23-32 years) performed maximal graded cardiopulmonary exercise stress test using cycle ergometer on two occasions (Test 1 and Test 2). Participants cycled at 30-watts/3-min increments until peak exercise. Haemodynamic variables were assessed at rest and during different exercise intensities (i.e. 60, 120, 150, 180 watts) using inert gas rebreathing technique.

Results Cardiac output and stroke volume were not significantly different between the two tests at rest (7.4 (1.6) vs. 7.1 (1.2) litre min⁻¹, p=0.54; 114 (28) vs. 108 (15) ml beat⁻¹, p=0.63) and all stages of exercise. There was a significant positive relationship between Test 1 and Test 2 cardiac outputs when data obtained at rest and during exercise were combined (r=0.95, p<0.01 with coefficient of variation of 6.0%), at rest (r=0.90, p<0.01 with coefficient of variation (CV) of 5.1%), and during exercise (r=0.89, p<0.01 with coefficient of variation 3.3%). The mean difference and upper and lower limits of agreement between repeated measures of cardiac output at rest and peak exercise and were 0.4 (-1.1 to 1.8) litre min⁻¹ and 0.5 (-2.3 to 3.3) litre min⁻¹ respectively. Oxygen consumption at rest and increased metabolic demand also showed good reproducibility (CV of within 5-10% for higher intensity stress)

Conclusion Inert gas rebreathing method demonstrates acceptable level of test-retest reproducibility for estimating cardiac- metabolic function at rest and during cardiopulmonary exercise testing, particularly at higher metabolic demands.
20. 8th Annual Alliance for Healthy Aging Conference — 9-11 November 2017

Abstract

Age-related changes in miRNA expression in healthy airways

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\textbf{Background:} MicroRNAs (miRNAs) are regulators that have been proposed to be involved in lung diseases and ageing. As such, miRNA changes may affect normal and abnormal ageing of the lungs.

\textbf{Aim:} To identify age-related miRNA expression changes in bronchial biopsies of healthy subjects.

\textbf{Methods:} Bronchial biopsies were obtained from 42 never-smoking and 40 smoking healthy subjects, with an age range of 18-73 years. Small RNA sequencing libraries were prepared using NEXTflex Small RNA-Seq Kit v3 and sequenced on the Illumina HiSeq2500. Data analysis was performed using the DESeq\textsuperscript{2} package in R. For each miRNA, a generalized linear model was fit to assess the relation between miRNA expression and age, adjusted for gender, library preparation batch and smoking status. Sensitivity analysis was performed for never-smoking and smoking subjects separately adjusted for gender and library preparation batch.

\textbf{Results:} We identified 29 miRNAs (16 up- and 13 downregulated) with significant age-related expression changes (FDR<0.05). Nineteen out of 29 miRNAs (11 up- and 8 downregulated) remained significant in the sensitivity analysis in never-smokers, including the most significantly upregulated miR-4532 and downregulated miR-146b-5p. Two miRNAs, miR-4532 (upregulated) and miR-362-5p (downregulated), remained significant in the sensitivity analysis in smokers. Interestingly, p21 (CDKN1A), a well-known ageing marker, is a proven target of miR-146b-5p.

\textbf{Conclusion:} The observed age-related miRNA expression changes in bronchial biopsies strengthens the suggestion that miRNAs can regulate lung ageing. Further research on these miRNAs and their targets may provide a better understanding of their role in (abnormal) lung ageing.
21. The hepatic glucose sensor ChREBP is a key factor in the development of metabolic liver disease

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Background: Ageing is frequently associated with metabolic derangements that lead to development of chronic diseases. Insight into the underlying causes is still limited and research in inborn errors of metabolism may provide unexpected clues. Glycogen storage disease type 1a (GSD Ia), caused by a defect in glucose-6-phosphatase (G6PC) activity, is characterized by hepatomegaly due to massive accumulation of glycogen and triglycerides in the liver. We have previously reported that the activity of the glucose-sensitive transcription factor Carbohydrate Response Element Binding Protein (ChREBP) is increased in GSD Ia. Moreover we have shown that ChREBP mediates the induction of glycolytic and lipogenic genes, suggesting that its activation contributes to liver disease in GSD Ia.

Objectives: We determined the contribution of ChREBP to the development of metabolic liver disease in a mouse model for hepatic GSD Ia, i.e., liver-specific G6pc knockout (L-G6pc⁻/⁻) mice.

Methods: L-G6pc⁻/⁻ mice and their wildtype (L-G6pc⁺/⁺) littermates were treated with AAV8-shChREBP to reduce hepatic ChREBP expression in comparison to animals of both genotypes receiving AAV8-shScramble. We subsequently conducted histological analyses of the liver, determined hepatic gene and protein expression levels, performed targeted metabolomics of the liver, and quantified de novo lipogenesis and VLDL-triglyceride (TG) secretion in vivo.

Results: Hepatic ChREBP knockdown markedly increased liver weight and hepatocyte size in L-G6pc⁻/⁻ mice. This was associated with the accumulation of G6P, glycogen and lipids in the liver, while glycolysis and de novo lipogenesis were reduced. Lipogenic flux measurements, targeted lipidomics and VLDL-TG analysis revealed that hepatic lipid accumulation in response to ChREBP knockdown mainly resulted from the storage of ‘old’ fat secondary to a strong suppression of VLDL lipidation and -secretion.

Conclusions: Normalization of hepatic ChREBP activity in GSD Ia liver aggravates hepatomegaly due to further accumulation of glycogen and lipids. Increased activity of the hepatic glucose sensor ChREBP therefore likely protects against liver disease in conditions of excess glucose availability.
22. Systems Biology-Derived Innate and Adaptive Transcriptional Signatures of Influenza Vaccine Responses in Elderly Individuals

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**Background:** Influenza and influenza-related complications pose a major health risk for vulnerable populations, such as the elderly. Despite an increased annual influenza vaccine coverage rate in the US, influenza-related morbidity and mortality increase with age. This is primarily due to poor immune response to influenza vaccine (immunosenescence) and an increased susceptibility to influenza infection among older persons. A systems biology approach offers an understanding of transcriptomic signatures associated with immunological protection and provides an approach to evaluate vaccine-induced immune responses in the elderly. **Objectives:** The aim of this study was to identify innate and adaptive transcriptomic signatures associated with immune responses after influenza vaccination in older individuals. **Methods:** We used pre-vaccination (Day 0) and post-vaccination (Day 3 and Day 28) mRNA-Seq transcriptional profiling on blood samples from 159 subjects (50-74 years old) following the receipt of seasonal trivalent influenza vaccine containing the A/California/7/2009/H1N1 virus. Influenza-specific serum hemagglutination-inhibition (HAI), virus-neutralization antibody (VNA) titers, frequency of memory B cells (Elispot), and mRNA-sequencing on PBMCs were performed using samples obtained at days 0, 3, and 28 after vaccination. Penalized regression modelling was used to identify associations with influenza A/H1N1-specific immune responses outcomes. **Results and Conclusions:** The median (IQR) age of the study subjects was 59.5 (55.3, 66.3) years (98.7% Caucasians and 61.6% female). Day 0 (baseline) influenza-specific median HAI and VNA titers (1/80; IQR 1/40-1/320) revealed the presence of pre-existing antibodies. There was no change in HAI or VNA titers from Day 0 to Day 3; however, median HAI and VNA titers increased by Day 28 (1/320; IQR 1/160-1/640, p<0.001). The influenza A/H1N1-specific B cell Elispot responses were relatively low at Day 0 and Day 3 with 8 spot-forming units (SFUs) per 200,000 PBMCs (IQR 3, 20). We observed a significant increase (from 11 SFUs [IQR 5, 22] at Day 0 to 38 SFUs [IQR 18, 60] at Day 28 (p=1.1 x 10⁻²¹). The innate (Day 3-Day 0) genes/genesets associated with HAI response are the dystrophin-associated glycoproteins (SGCD); lipid-linked alpha-1,2-glucosyltransferases (ALG10); and ssRNA binding proteins (PABPC4). The innate genes/genesets associated with VNA response include genes that play a fundamental role in pathogen recognition and activation of innate immunity, such as TLR8, ADARB2, protoplasmic signalling and cell-to-cell interaction, ssRNA binding, and mRNA ZFP36 protein genes. The adaptive (Day 28-Day 0) genes/genesets associated with HAI response are RNA transcription factor (TTF2); chemokine/cytokine/receptors (CCR9, IFNG, IL10RA); cytochromes (CYB5R2,3, CYB561), and carbonic-anhydrases (CA2,6,8,11,14). The genes associated with VNA response include TNF ligand TNFSF11, cytokines/receptors (IFNG, IL7, IL27, IL12A), and interferon-inducible transcription factors (IRF7,9). Further, the adaptive (Day 28-Day 3) genes/genesets associated with HAI response are genes that are involved in the IFN-g production pathway (FOXP3, TLRs, CEBPG, EB13, and IL12A). The genes associated with VNA are TLR3,7,9; cytokines (IL1, TGFβ2, IL12A); STAT and tyrosine kinases (STAT1, STAT3, TYK2). Lastly, the Day 28-Day 0 genes/genesets associated with memory B cell Elispot responses are genes involved in cholesterol and lipid/carbohydrate metabolism (MDV, PMVK, PI4KA, DHRS13), cell migration/adhesion, and cell signalling (NF-kB). In conclusion, using a systems biology approach, we identified innate and adaptive gene signatures associated with inter-individual variations in humoral responses to influenza vaccine in older individuals. The identification of these gene signatures associated with HAI, VNA, and B cell Elispot responses may provide a better understanding of genetic markers of immunity in the elderly, and may assist with the design of better vaccines and adjuvants. **Support:** This work was supported by the NIH (grant number U01AI089859).
Senescent cell clearance in diet-induced obese mice decreases adipose tissue macrophage burden

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Background. Senescent cells accumulate in adipose tissue of obese mice and humans and may contribute to the development of insulin resistance. Obesity is also associated with accumulation of immune cells, including macrophages and activated CD4+ lymphocytes, in adipose tissue, however the priming stimulus for this immune cell infiltration remains elusive. It remains unclear what effect senescent cells have on macrophage burden in adipose tissue, or what impact strategies to target senescent cells have on adipose tissue macrophage infiltration in obesity.

Objectives. We aimed to: 1) investigate the relationship between senescent cell burden and adipose tissue macrophages, 2) determine the impact of senescent cell clearance on adipose tissue macrophage burden, and 3) elucidate the role of senescent cells in macrophage infiltration into adipose tissue.

Methods. For these studies, we used two genetic mouse models in which p16-positive senescent cells can be eliminated: p16-3MR mice, in which a p16ink4a-promoter sequence drives expression of a trimodal reporter-killer fusion protein, allowing senescent cell killing by ganciclovir, and INK-ATTAC mice, in which a p16ink4a-promoter sequence drives expression of a vFKBP-caspase-8-FLAG fusion protein that can be activated by AP20187, a vFKBP dimerizer, to cause senescent cell apoptosis. Obesity was induced either by diet or genetically using leptin receptor knockout (db/db) mice.

Results and Conclusions. F4/80+ macrophage abundance positively correlated with senescent cell burden as measured by transgene expression in diet-induced obese mice. Following senescent cell clearance with ganciclovir from obese p16-3MR mice, expression of the macrophage marker F4/80 in intra-abdominal adipose tissue (IAT) was reduced and crown-like structures were decreased. Eliminating senescent cells also reduced plasma levels of the macrophage-attracting chemokines MCP-1 and MIP-1β as well as macrophage colony stimulating factor (M-CSF). By CyTOF, p16ink4a+ preadipocytes were decreased in DIO-INK-ATTAC mice 4 days after AP20187 treatment, while macrophages had not yet decreased. In addition, monocytes from donor mice injected into obese INK-ATTAC;db/db mice 4 days after AP20187 treatment exhibited decreased migration into IAT compared to vehicle-treated INK-ATTAC;db/db mice. Taken together, our results indicate that senescent cells can cause macrophage migration into adipose tissue in obesity, and targeting senescent cells prevents and reduces the adipose tissue macrophage infiltration characteristic of obesity.

Support: This work was supported by NIH grants AG13925 (J.L.K.), AG041122 (J.L.K.), AG31736 (Project 4: J.L.K.), AG044396 (J.L.K.), AG46061 (A.K.P.), the Connor Group (J.L.K.), the Glenn (J.L.K.), Ted Nash Long Life (J.L.K.), and Noaber Foundations (J.L.K.).
Amino acids (aa) are not only building blocks for proteins, but also signalling molecules, with the mammalian target of rapamycin complex 1 (mTORC1) acting as a key mediator. Data about whether aa, independently of mTORC1, activate other kinases of the mTOR signalling network are limited. To delineate the mTOR network dynamics upon aa stimulation, we combine a computational-experimental approach with text-mining-enhanced quantitative proteomics. We report that AMP-activated protein kinase (AMPK), phosphatidylinositide 3-kinase (PI3K) and mTOR complex 2 (mTORC2) are acutely activated by aa-readdition in an mTORC1-independent manner. AMPK activation by aa is mediated by Ca$^{2+}$/calmodulin-dependent protein kinase β (CaMKKβ). In response, AMPK regulates autophagy by impinging on Unc-51-like kinase-1 (ULK1) and c-Jun. AMPK is widely recognized as an mTORC1 antagonist that is activated by starvation. Surprisingly, we find that aa can acutely activate AMPK concurrently with mTOR and that AMPK under aa sufficiency acts to sustain autophagy. This may be required to maintain protein homeostasis and deliver metabolite intermediates for biosynthetic processes.
While telomerase maintains telomeres in dividing cells, its protein component TERT has various non-canonical functions such as localisation to mitochondria resulting in decreased oxidative stress, apoptosis and DNA damage. TERT protein is maintained in adult human and rodent brain while telomerase activity is downregulated early during development. We recently demonstrated increased mitochondrial TERT in hippocampal neurons from Alzheimer’s disease brains and mutual exclusion of pathological tau and TERT in situ. Transducing mutated tau (P301L) into neurons confirmed that TERT presence decreases mitochondrial oxidative stress and lipid oxidation (Spilsbury et al., Journal of Neuroscience, 2015). Mitochondrial dysfunction is also involved in the development of PD.

Our aim was to analyse the beneficial effects of 2 telomerase activators on mitochondrial and motor function such as balance and gait as well as on brain pathology in a transgenic mouse model of PD over-expressing human alpha-synuclein (line D, Masliah et al., 2000).

Transgenic mice were treated orally with both activators for 1 year and examined with a test battery for balance and motor function such as rota-rod, stride lengths test, novel object recognition and open field test. We also analysed TERT expression and mitochondrial ROS release in brain tissue and characterised brain pathology as well as markers of DNA damage, cellular senescence and inflammation.

Telomerase activator treatment increased TERT and BDNF levels in brain, improved motor performance, decreased mitochondrial ROS and ameliorated PD symptoms such as loss of gait and bradykinesia. We currently analyse brain pathology and will present data on DNA damage, telomere-associated foci (TAFs), BDNF, MnSOD, mitochondrial proteins, phosphorylated and total alpha synuclein and other markers in different brain regions.

Thus, telomerase activators might form novel treatment options for neurodegenerative diseases such as PD.
26. Autophagy impairment plays a role in mitochondrial dysfunction and the pathology of NPC

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Autophagy is a catabolic cellular pathway responsible for recycling superfluous or damaged proteins and organelles in the lysosomes, followed by liberation of nutrients. Autophagy impairment leads to loss of cellular quality control processes, resulting in accumulation of damaged intracellular components and toxicity linked to age-related neurodegeneration. Impaired autophagy is involved in the molecular pathology of type C Niemann Pick disease (NPC), a fatal neurodegenerative lysosomal storage disorder. In addition, recent reports suggest that mitochondrial dysfunction, the resulting energy crisis and increased levels of reactive oxygen species (ROS), contribute to the severity of NPC. However, the mechanisms underlying mitochondrial dysfunction, increased ROS production, ineffective autophagy and their interdependence in NPC have yet to be established.

Here we report a link between autophagy impairment and mitochondrial dysfunction in Npc1-deficient mouse embryonic fibroblasts (Npc1⁻/⁻ MEFs). Npc1⁻/⁻ MEFs display autophagy impairment, higher levels of glycolysis and alterations in mitochondrial morphology when grown in glucose-containing media. In addition, cell culture in a physiologically relevant galactose medium, which forces cells to respire via OXPHOS, leads to an increase in ROS levels, a higher proportion of mitochondria with abnormal cristae morphology and ultimately in apoptotic cell death. Supplementation of galactose medium with oleic acid, a medium length fatty acid with antioxidant properties, decreases ROS levels and prevents cell death of Npc1⁻/⁻ MEFs. Ketogenic diet is often recommended to patients with mitochondrial dysfunction and the success of fatty acid based cell death rescue of Npc1⁻/⁻ MEFs provides a possible basis for future therapies for NPC. If confirmed in animal models, the success of feeding interventions would demonstrate the involvement of dysfunctional mitochondria in the pathology of NPC and potentially other neurodegenerative diseases presenting with stalled autophagy.
27. **GH /IGF-1 axis as determinant of vascular aging and cellular senescence in subjects free of cardiovascular diseases.**

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Lomonosov Moscow State University, department of Age-Associated Diseases, 119991, Leninsky Gori 1, Moscow, Russia

**Background:**

Arterial aging is the key factor influencing risk of cardiovascular disease (CVD). The core feature of arterial aging is arterial stiffness, measured as increased carotid-femoral pulse wave velocity (c-f PWV) in relation to a subject’s chronological age and sex. It is well documented that cardiovascular system is an important target organ for growth hormone (GH) and insulin-like growth factor (IGF)-1 in humans, and GH /IGF-1 deficiency significantly increases the risk for CVD. Peripheral blood leukocytes telomeres length (TL) is cellular senescence and vascular aging biomarker, which has been proposed as an independent predictor of CVD. But presently there is no detailed information regarding the relationship between TL and blood GH/IGF-1 either the interactions of these hormones and conventional cardiovascular risk factors (CVRF) in vascular aging and cellular senescence.

The aim of this study was to determine the role of GH /IGF-1 in their interaction with CVRF in vascular aging and cellular senescence.

**Objectives:**

The study group included 303 ambulatory participants (104 males and 199 females) mean age 51.8 ±13.3 years, free of known cardiovascular diseases, diabetes mellitus, antihypertensive and lipid lowering medications, but with one or more CVRF (age, smoking, arterial hypertension, obesity, dyslipidemia, fasting hyperglycemia, insulin resistance – HOMA IR>2.5, high glycated hemoglobin). The study sample was divided into the two groups according to the age of participants: “younger” (m≤45 years, f≤55years) and “older” (m>45 years, f >55years).

**Methods:**

Arterial stiffness was appreciated by c-f PWV measuring with the help of SphygmoCor (AtCor Medical). TL was determined by quantitative polymerase chain reaction. Serum IGF-1 and GH concentrations were measured using immunochemiluminescent analysis

**Results:**

The results of multiple linear regression analysis (with adjustment for CVRF) in “younger” group (mean age 40.9 ±8.7 years, n=144) are represented in the table.

<table>
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<tr>
<th>Predictor</th>
<th>β ± S.E.</th>
<th>Type II SS</th>
<th>P</th>
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<td>Intercept</td>
<td>22,871±4,678</td>
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</table>

The linear regression analysis with TL as dependent variable did not identify the association of GH /IGF-1 and TL. But multiple logistic regression analysis demonstrated that GH level > Me reduced the likelihood of «short» (< 9,75) TL (OR =0.44, CI:0.20-0.98; p=0.044), There were no independent significant associations of GH /IGF-1 and c-f PWV, TL obtained in “older” group.

**Conclusions:** In healthy participants: 1)GH along with insulin resistance and TL determine arterial stiffness; 2)GH demonstrates protection of arterial wall and TL.
28. Restricting genome scale metabolic models with expression data reveals novel enriched signatures in glioblastoma

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\textsuperscript{6} Neurology Clinic and National Center for Tumor Diseases, University Hospital of Heidelberg, Heidelberg, Germany.

Glioblastoma (GBM) remains the most feared form of malignant gliomas, owed to its poor prognosis with a median survival of less than 15 months and consequences on cognitive functions. Currently, all GBM patients receive the same course of treatment when first diagnosed (resection, radio- and chemotherapy). The low success rates of glioblastoma therapies can be attributed to the complexity of the interactions of targeted pathways, and the success of the tumors to adopt compensatory mechanisms that allow resistance and recurrence. In light of the lower likelihood of compensation for disruptions in tumor metabolic pathways, an intervention at the level of cellular metabolism may provide benefits.

We have adopted a data driven approach to identify possible metabolic signatures that could lead to additional distinction between clustered GBM subtypes. It is important to highlight, that recent studies have shown that classifications based on bulk datasets of high throughput data reflect to a great extent the differences between tumor subtypes based mainly on tumor micro-environment (TME).

Using TCGA data, we identified infiltrating signatures of different cell populations that prevented clear identification of metabolic differences between GBM subtypes. We further applied a genetic algorithm to identify interactions between the different TME cell populations to develop a proper model to correct for their confounding effect. Genome scale metabolic models identified several signatures that differentiate between the classified GBM subtypes after accounting for TME. Our results were consistent using different thresholds of selected features applied for model restriction, and in combination with PCA, GSEA and DGE analysis outperformed the single use of any of the three methods. Our findings highlight the importance of combining genome scale modeling and TME signature corrections in identifying potential metabolic differences between GBM subtypes.
Cellular senescence is an irreversible cell cycle arrest, associated with the secretion of pro-inflammatory molecules, also known as the senescence-associated secretory phenotype (SASP), which can act in a paracrine manner, inducing senescence in neighbouring cells. It is thought that accumulation of senescent cells contributes to loss of tissue function during ageing. Melanocytes positive for senescence markers have been shown in the skin of middle-aged human donors, however, very little is actually known about the mechanisms underlying melanocyte senescence during skin ageing. In this study, I aimed to investigate whether telomere dysfunction is a driver of melanocyte senescence, and whether senescent melanocytes contribute to skin ageing phenotypes by acting in a paracrine manner.

I performed immunofluorescence combining immunofluorescence against γH2AX (a marker of DNA damage) and in situ hybridisation for telomere specific PNA probe in skin biopsies from young and older human donors, and found a significant increase in telomere-associated foci (TAF) in melanocytes in skin of older donors. However, by conducting quantitative-FISH I did not find evidence for telomere shortening in melanocytes. In fact, damaged telomeres were significantly longer than telomeres that did not signal a DNA damage response, suggesting that long telomeres may be more susceptible to damage in melanocytes in vivo. Furthermore, telomeric damage was significantly higher in keratinocytes surrounding melanocytes with a higher number of dysfunctional telomeres in skin of young and older donors. These results indicate that melanocytes may exert a bystander effect, and contribute to telomere-associated damage in neighbouring cells.

In order to further explore the bystander effect, I co-cultured young and senescent melanocytes with dermal fibroblasts in vitro, and found that senescent melanocytes induce higher frequencies of TAF in these cells. Interestingly, conditioned media from senescent melanocytes was sufficient to induce TAF in fibroblasts, suggesting that soluble factors can mediate paracrine damage induction. This corroborates the observations made in vivo, supporting the idea that factors secreted by senescent melanocytes can contribute to paracrine telomeric damage induction.

This study provides novel evidence showing that telomere dysfunction is a feature of human melanocyte ageing, and that melanocytes contribute to telomeric damage formation in neighbouring cells.

(This project is funded by a BBSRC/Unilever CASE studentship)
30. Paraquat-induced senescence in human lung fibroblasts as a model to study ageing in fibroblasts of COPD patients

Roy Woldhuis1,4, Maaike de Vries2,4, Wim Timens1,4, Maarten van den Berge3,4, Brian Oliver5, Irene Heijink1,4 and Corry-Anke Brandsma1,4

Abnormal lung ageing has been proposed to contribute to the pathology of COPD, including aberrant lung tissue repair and remodeling. Lung fibroblasts are important regulators of extracellular matrix homeostasis and lung tissue repair and remodeling. We hypothesize that abnormal ageing in fibroblasts, including increased susceptibility to undergo senescence, contributes to the pathology of COPD.

Therefore, the aim of this study was to develop a model to induce senescence in primary lung fibroblasts using Paraquat, an herbicide that induces oxidative stress. Fibroblasts isolated from lung tissue of two control donors were stimulated with 250 μM Paraquat for 24 hours, and allowed to recover for 6, 24, 48 and 72 hours and 4, 5 and 6 days. To measure reactive oxygen species (ROS) levels, fibroblasts were stained with the probe CM-H2DCFDA (or briefly DCF) and analyzed by flow cytometry. Read-out parameters to analyze cellular senescence were SA-β-gal activity, p16, p21, IL-6 and IL-8 mRNA expression and IL-6 and IL-8 protein secretion.

After 24 hours of Paraquat treatment, ROS levels were increased 1.6-fold compared to untreated fibroblasts. Furthermore, Paraquat induced a strong, 10-fold induction in p21 mRNA expression after 24 hours of recovery, which declined again after 72 hours and longer. However, p16 mRNA expression was not significantly affected. The percentage of SA-β-gal positive cells was increased upon Paraquat treatment compared to untreated cells, with the strongest induction after 4 days (50% vs. 11% positive cells in the untreated cells). IL-6 and IL-8 mRNA expression was also increased after 4 days of treatment (3.6-fold and 6.4-fold compared to untreated, respectively), while the strongest increase in protein secretion was observed after 5 days (2.4-fold and 3.3-fold compared to untreated).

In conclusion, Paraquat treatment induces senescence in vitro in human lung fibroblasts, likely via p21 up-regulation. Therefore, Paraquat-induced senescence can be used as a model to study differences in senescence induction between COPD and control-derived fibroblasts in future experiments. This may give new insights in the role of ageing in lung remodeling and repair in COPD.
31. Role of Non-canonical WNT signaling pathway in ageing and lung repair

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Background: Chronic obstructive pulmonary disease (COPD) is a disease believed to be driven by accelerated ageing of the lung and a worldwide concern with high morbidity and mortality. Although several studies indicate a role of non-canonical WNT signaling in ageing and COPD, the precise role and the interaction between non-canonical WNTs, ageing and COPD remains poorly understood. We hypothesized that non-canonical WNT signaling might impact on alveolar epithelial repair.

Methods: Animals were divided in two age groups: young WT (average age 24 weeks, body weight 23-41 g, n=20) and aged WT (average age 50 weeks, body weight 30-54 g, n=13). Lungs were harvested for precision-cut lung slices (PCLS) or the generation of lung organoids. Lung organoids recapitulate various features of the lung, which provide an in vitro model system for studying regenerative mechanisms of epithelial stem and progenitor cells proposed from in vivo studies. Lung organoids were established by growing EpCam+/CD45-/CD31- epithelial cells in co-culture with CCL206 fibroblasts.

Results: The gene expression levels of the non-canonical ligands WNT-5A and WNT-5B, increased in aged WT mice and their expression correlated with the senescence marker p16. Interestingly, in young WT mice, WNT-5B stimulation decreased gene expression levels of the type I, type I associated and type II epithelial cell markers Aqp5; Rage, Con43 and Sftpc; whereas T1α were increased. Lung organoids showed similar behavior as the number of organoids visible 7 days after culture was significantly repressed by WNT-5A and WNT-5B stimulation. WNT-5B stimulation selectively repressed alveolar organoid formation, whereas WNT-5A stimulation significantly repressed the number of airway organoids. Both WNT-5A and WNT-5B stimulation has no effects on the size of lung organoids measured after culturing for 14 days.

Conclusions: Non-canonical WNT signaling is correlated with ageing, and represses marker gene expression for alveolar epithelial cells in lung slices as well as lung organoid formation. We speculate that such a mechanism may contribute to defective alveolar repair in ageing and COPD.
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