ICSA
International Cell Senescence Association

7th INTERNATIONAL CELL SENESCENCE ASSOCIATION (ICSA) CONFERENCE

Groningen (UMCG), The Netherlands

29 September - 1 October 2022

ERIBA

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7th International Cell Senescence Association (ICSA) Conference

University Medical Center Groningen (UMCG), The Netherlands
29th September - 1st October 2022

www.icsa2022groningen.nl

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Welcome Note

We are extremely excited to welcome you all to the 7th ICSA conference, the first organized in the Netherlands. We have a spectacular line-up of speakers that will share with us the latest developments in our quest to understand cellular senescence. The agenda includes talks covering fundamental biology, development of interventions and clinical studies. This mixture reflects the latest trends in a field which is steadily moving towards human applications. We are looking forward to a constructive 3-day of discussions in the lovely city of Groningen!

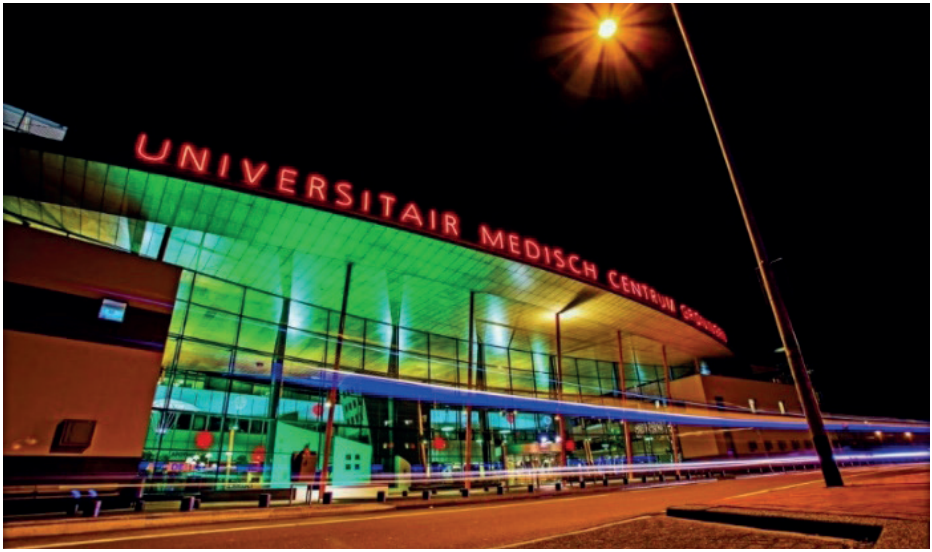
Warm Regards,

Marco Demaria

Andrea Maier

Peter de Keizer

Practical Information



Conference venue

University Medical Center Groningen
Blauwe Zaal (near fonteinstraat)
Hanzeplein 1
9713 GZ Groningen

Conference dinner & party

Date: September 30 2022

Time: 18:30

Location: DOT

Vrydemalaan 2

9713 WS Groningen

Closure dinner

Date: October 1 2022

Time: 18:00

Location: NOK

Nieuwe Markt 1

9712 KJ Groningen

Public transport

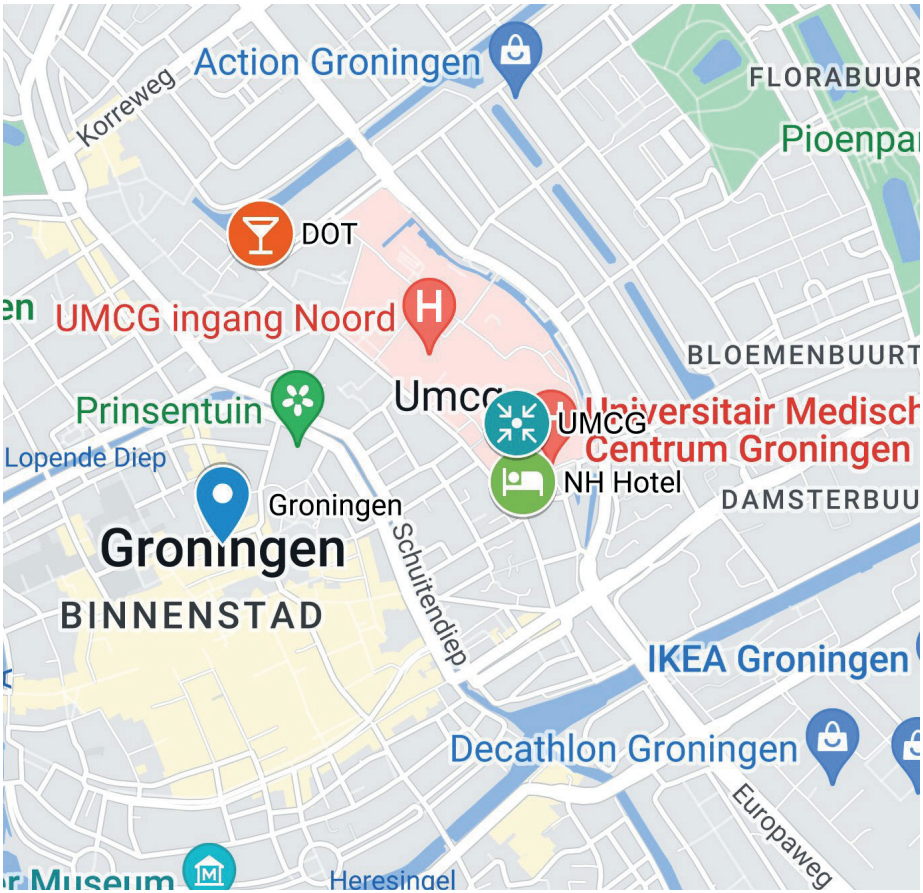
The website www.9292.nl very useful for planning your journey in the Netherlands. The planner combines all available public transportation – trains, buses, trams, metro, and boats – to provide an optimal route. Train schedules: Information on travelling by train is available on the NS website (www.ns.nl)

Taxis in Groningen

Taxi Groningen: +31 (0)50 – 549 7676, www.taxicentralegroningen.nl
Taxi Noord: +31 (0)50 – 549 4940, www.taxinoord.nl
Schiphol taxi Groningen: +31 (0)50 – 850 7519, www.schipholtaxigroningen.nl

Free Wifi: UMCG-guest network

Map of the City



Scientific Programme

Thursday, September 29

8:30-9:00	Registration and opening words
9:00-10:30	**Session 1**
	Speakers
9:00-9:30	**David Ferenbach**, University of Edinburgh, UK
9:30-10:00	**Andrea Maier**, National University of Singapore, Singapore
10:00-10:15	**Paula Carpintero-Fernandez**, Instituto de Investigación Biomédica de A Coruña, Spain
10:15-10:30	**Daniel Munoz-Espin,** University of Cambridge, UK
10:30-11:00	**Coffee break**
11:00-12:30	**Session 2**
	Speakers
11:00-11:30	**Ana O'Loghlen**, Blizard Institute, QMUL, UK
11:30-12:00	**Marco Demaria**, European Research Institute for the Biology of Ageing, The Netherlands
12:00-12:15	**Tomaz Rozmaric**, Ludwig Boltzmann Research Group Senescence and Healing of Wounds, Austria
12:15-12:30	**Marco Malavolta**, IRCCS INRCA, Italy

12:30-14:00	**Lunch and Poster session 1**
14:00-16:00	**City tour**
16:00-17:30	**Session 3**
	Speakers
16:00-16:30	**Francis Rodier**, CHUM Research Institute, Montreal, Canada
16:30-17:00	**Joao Passos**, Mayo Clinic, USA
17:00-17:15	**Laureline Urli**, Sorbonne Université, France
17:15-17:30	**Karen Crasta**, National University of Singapore, Singapore
17:30-18:30	**Keynote: Pura Munoz-Canoves,** Universitat Pompeu Fabra, Spain
18:30-20:00	Reception

Friday, September 30

9:00-10:30	**Session 4**
	Speakers
9:00-9:30	**Bill Keyes**, Institut de génétique, biologie moléculaire et cellulaire, France
9:30-10:00	**Cleo Bishop**, Blizard Institute, QMUL, UK
10:00-10:15	**Mohamed ElGhazaly**, University of Sheffield, UK
10:15-10:30	**Francesca Faggioli**, Institute for Genetic and Biomedical Research, Italy

10:30-11:00	**Coffee break**
11:00-12:30	**Session 5**
	Speakers
11:00-11:30	**Han Li**, Institut Pasteur, France
11:30-12:00	**Gerardo Ferbeyre**, University of Montreal, Canada
12:00-12:15	**Amit Sharma,** SENS Research Foundation, USA
12:15-12:30	**Staffan Strömblad**, Karolinska Institute, Sweden
12:30-14:30	**Lunch with the speakers**
14:30-16:00	**Session 6**
	Speakers
14:30-15:00	**Paul Robbins**, University of Minnesota, USA
15:00-15:30	**Miranda Orr**, Wake Forest University School of Medicine, USA
15:30-15:45	**Scott Haston**, University College London, UK
15:45-16:00	**Tamir Chandra**, University of Edinburgh, UK
16:00-17:00	**Keynote: Valery Krizhanovsky**, Weizmann Institute of Science, Israel
18:30-	Dinner/Party at DOT

Saturday, October 1

10:00-11:00	**Keynote: Kristina Kirschner**, Beatson Institute, University of Glasgow, UK
11:00-12:30	**Session 7** Speakers
11:00-11:30	**Peter de Keizer**, University Medical Center Utrecht, The Netherlands
11:30-12:00	**Diana Jurk**, Mayo Clinic, USA
12:00-12:15	**Ines Marin**, Institute for Research in Biomedicine, Spain
12:15-12:30	**Sarah Pringle**, University Medical Center, The Netherlands
12:30-14:00	**Lunch and Poster session 2**
14:00-15:00	**Keynote: Judith Campisi**, Buck Institute, USA
15:00-16:00	General assembly and closure, Poster Prize Ceremony
18:00-22:00	**Closure Dinner at NOK**

Keynote Speakers

Pura Munoz-Canoves, Universitat Pompeu Fabra, Spain

Valery Krizhanovsky, Weizmann Institute of Science, Israel

Kristina Kirschner, Beatson Institute, University of Glasgow, UK

Judith Campisi, Buck Institute, USA

Invited Speakers

Ana O'loghlen, UK
Andrea Maier, Singapore
Bill Keyes, France
Cleo Bishop, UK
David Ferenbach, UK
Diana Jurk, USA
Francis Rodier, Canada
Gerardo Ferbeyre, Canada
Han Li, France
Joao Passos, USA
Marco Demaria, The Netherlands
Miranda E Orr, USA
Paul Robbins, USA
Peter de Keizer, The Netherlands

Pura Munoz-Canoves

Valery Krizhanovsky

Molecular mechanisms of senescence on the crossroads of cancer and aging

Cellular senescence in ageing, tissue damage, cancer and embryonic development

Web: http://www.weizmann.ac.il/mcb/valery/

Prof. Krizhanovsky received his PhD in Biology at the Hebrew University of Jerusalem in 2006. He then did his postdoctoral training at Cold Spring Harbor Laboratory, USA with Scott Lowe. In 2010 Dr. Krizhanovsky joined Weizmann Institute of Science where he is now Associate Professor at the Department of Molecular Cell Biology. During his career, he discovered the role of cellular senescence in tissue damage, established the role of NK cells in the immune surveillance of senescent cells, presence of senescence in the placenta and discovered senolytic pathways allowing specific elimination of senescent cells *in vivo*. His laboratory studies the role of senescent cells in aging, age-related diseases and cancer.

Kristina Kirschner

Effects of senescence and other ageing-related changes on the hematopoietic stem cell compartment

Kristina is a Senior Lecturer/Associate Professor at the University of Glasgow/CRUK Beatson Institute, with an interest in age-related changes in carcinogenesis. She investigates stem cell aging, senescence and age-associated clonal haemopoiesis.

Kristina obtained her Ph.D. from the University of Edinburgh, characterising an early DNA damage-dependent premature ageing mouse model. During her post-doc in Masashi Narita's lab in Cambridge, she revealed unanticipated levels of complexity in p53's response to stress. Combining her expertise in ageing and cancer, Kristina joined Anthony Green's lab at the University of Cambridge, leading the way in identifying transcriptional clonal haemopoiesis by single cell RNA-seq.

Abstract

Clonal Haematopoiesis of Indeterminate Potential (CHIP) is defined as the expansion of HSCs in healthy aged individuals that results from genetic alterations. CHIP is driven by somatic mutations in leukaemia driver genes such as DNMT3A, TET2, and JAK2. We previously identified clonal hemopoiesis of hematopoietic stem and progenitor cells (HSPCSs) on a transcriptional level in aged mice, where we identified a p53 dependent senescence signature in a subset of HSPCs (Kirschner et al 2017)

In this talk, I will discuss the effects of CHIP on epigenetic age acceleration and implications for clinical management. Moreover, I will present a mathematical modelling framework to quantify stem cell fitness resulting from these CHIP mutations in longitudinal data. Lastly, I will discuss the effects of senescent cells in the tumour microenvironment in adult vs childhood acute lymphoblastic leukaemia and provide some mechanistic insights into senescence- related chemotherapy resistance.

Judith Campisi

Ana O'Loghlen

Extracellular vesicles and cytokines in senescent and healthy cells, how do they communicate?

My lab is based in London at the Blizard Institute which is part of Queen Mary University of London (UK). We are interested in understanding the molecular mechanisms regulating a cellular phenotype called "cellular senescence". Cells that become senescent stop growing and present a distinctive inflammatory response that has been termed senescence-associated secretory phenotype or SASP. The SASP induces a variety of cellular processes including immune cell recruitment, autocrine/paracrine senescence, differentiation and reprogramming. As senescent cells and the SASP are present during ageing and benign tumour lesions, we are interested in identifying new component of the SASP and investigating their role with the microenvironment in the context of ageing and cancer.

Abstract

The influence of the activation of the cellular phenotype termed senescence and its importance in ageing and age-related diseases is becoming more and more evident. In fact, there is a huge effort to tackle these diseases via therapeutic drugs targeting senescent cells named senolytics. However, a clearer understanding of how senescence is activated and the influence it has on its surrounding, on other cellular types and other tissues is needed. Here, we will describe the influence of senescent cells on its microenvironment in ageing and other age-related diseases.

Cellular senescence and its microenvironment

AnaO'Loghlen[1,2]

[1]Epigenetics & Cellular Senescence Group; Spanish National Research Centre (CSIC - CIB); Ramiro de Maeztu 9, 28040 Madrid (Spain)

[2]Queen Mary University of London; Blizard Institute, Whitechapel, London E1 2AT, UK

Andrea Maier

Senescence in the context of Longevity Medicine

Prof Andrea Britta Maier is a Bio-gerontologist, internal medicine specialist and international health policy specialist. Prof Maier was previously appointed as full Professor of Medicine at the VU University, Amsterdam, The Netherlands, and Professor of Medicine and Aged Care at the University of Melbourne, Australia.

In 2021, she continued her career with National University of Singapore as an Oon Chiew Seng Professor in Medicine, Healthy Ageing and Dementia Research. She is also Co-Director of the Centre for Healthy Longevity, of which its goal is to increase visibility, quality, and quantity of (ageing) research and its translation into clinical practice.

Abstract

Medical research has traditionally focused on disease mechanisms and therapies to restore health. This approach has been highly effective, but because of its effectiveness, demographics of countries are changing. Chronologic age is the largest risk factor for decline in organ function and for age-related diseases, which are now highly prevalent. Therewith, healthcare costs are steadily increasing and the gap between healthspan, the duration an individual maintains good health, and lifespan is escalating. Cellular senescence is one of the mechanisms driving ageing. Understanding the epidemiology of cellular senescence and the possible effect of senolytic interventions is crucial for its implementation in Longevity Medicine. Longevity Medicine is optimizing healthspan by targeting ageing processes across the lifespan. Therefore cutting edge evidence-based diagnostics and interventions are needed to be implemented into healthcare, to address the challenges of an ageing society.

Bill Keyes

Investigating new features and markers of senescent cells

Bill Keyes is a Group Leader and Head of the Department of Developmental Biology and Stem Cells at the IGBMC, Strasbourg France. His lab focuses on the investigation of cellular senescence, in particular investigating its role during normal development and in developmental birth defects. In addition, they study the impact of senescence on tissue regeneration, and how senescence contributes to disease pathogenesis and the aging process.

Cleo Bishop

The “outs and ins” of senescence

Cleo received her PhD in Biological Sciences from University College London in 2001. After a MRC Career Development Fellowship at Imperial College London, she spent four years working in the laboratory of Prof. David Beach, after which she established her group at Barts and The London Medical School, Queen Mary University of London.

Today, Cleo’s group is interested in illuminating novel senescence mechanisms and understanding how cells age. Through this work her team are exploring the interplay between healthy ageing and cellular rejuvenation, and how senescence can be targeted for ageing and cancer therapy.

David Ferenbach

The physiological and pathological roles of senescence in the kidney

David Ferenbach graduated in Medicine from the University of Edinburgh and after training in Edinburgh and Glasgow completed his PhD in the MRC Centre for Inflammation Research in Edinburgh. Here he developed a research interest in the mechanisms driving accelerated fibrosis in injured and aged kidneys. He pursued this research question during a Wellcome Trust Intermediate Fellowship in the Bonventre Laboratory at Harvard Medical School focusing on the role of senescent epithelia in ageing and disease. Today he works as an academic consultant nephrologist, whilst his laboratory continues to dissect the role played by senescent epithelia in driving kidney scarring. His group aims to develop new methods to study and manipulate senescent cells in order to generate treatments for human fibrotic disease.

Diana Jurk

Cellular senescence as a driver of cognitive decline

Dr. Diana Jurk, Ph.D. is an Associated Professor at Mayo Clinic Rochester and directs the Biology of Aging and Age-related Diseases laboratory.

Dr Jurk is originally from Germany where she graduated with a degree in Natural Sciences from the University of Freiberg in 2004. Following her degree, she conducted biomedical research at Bayer, first in Wuppertal and then in Leverkusen (where she was awarded a master's degree). Having decided to move to academia, Dr. Jurk was first a research assistant at the Uniklinik in Freiburg, Germany (2005-2007) and then conducted her PhD studies at Newcastle University in the UK (2007-2012), in the area of liver senescence and inflammation.

In 2015, Dr. Jurk was awarded the Newcastle University Faculty fellowship and in 2018 the prestigious Springboard Award from The Academy of Medical Sciences which allowed her to direct an independent research program. In 2018 she moved her research team to Mayo Clinic, Rochester.

Diana's work has led to new insights into the mechanisms driving the process of cellular senescence in the context of liver disease and neurodegeneration. Her work, published in Nature Communications, has demonstrated a key role for senescence in Non-alcoholic fatty liver disease. More recently, her team published in Cell Metabolism the first evidence for the involvement of senescence in neuropsychiatric diseases and in cognitive decline during aging (Aging Cell, 2021).

Abstract

Cellular senescence is characterized by an irreversible cell cycle arrest and a pro-inflammatory senescence-associated secretory phenotype (SASP), which is a major contributor to aging and age-related diseases. Clearance of senescent cells has been shown to improve brain function in mouse models of neurodegenerative diseases as well as obesity. However, it is still unknown whether senescent cell clearance alleviates cognitive dysfunction during the aging process. To investigate this, we first conducted single-nuclei and single-cell RNA-seq in the hippocampus from young and aged mice. We observed an age-dependent increase in $p16^{Ink4a}$ senescent cells, which was more pronounced in microglia and oligodendrocyte progenitor cells and characterized by a SASP. We then aged *INK-ATTAC* mice, in which $p16^{Ink4a}$-positive senescent cells can be genetically eliminated upon treatment with the drug AP20187 and treated them either with AP20187 or with the senolytic cocktail Dasatinib and Quercetin. We observed that both strategies resulted in a decrease in $p16^{Ink4a}$ exclusively in the microglial population, resulting in reduced microglial activation and reduced expression of SASP factors. Importantly, both approaches significantly improved cognitive function in aged mice. Our data provide proof-of-concept for senolytic interventions' being a potential therapeutic avenue for alleviating age-associated cognitive impairment.

Francis Rodier

Double knotting DNA damage and cell senescence

Rodier F. et al [1,2]

[1] Centre de recherche du CHUM (CRCHUM) et Institut du cancer de Montréal, Montreal, QC, Canada
[2] Département de Radiologie, Radio-Oncologie et Médicine Nucléaire, Université de Montréal, Montreal, QC, Canada

Abstract

Senescence is a tumor suppressor mechanism with links to genome stability. It is proposed that the engagement of the senescence program following DNA damage prevents further genome instability. However, we have recently shown that dysfunctional telomeres, which are recognized as DNA double-strand breaks, are insufficient to activate senescence because they generate a weak DNA damage response (DDR). Telomeric senescence is rather triggered via genomic instability following an ultimate mitosis involving telomeric sister chromatid fusions. I will discuss new data showing that a similar phenotype is required for irradiation-induced senescence including for the senescence-associated secretory phenotype (SASP, reinforcing the idea that genomic instability, and not DNA double-strand breaks, is the prerequisite for DNA damage-induced senescence. This is consistent with a well-established connection between genomic instability and the cGAS–STING signaling underlying the SASP. We propose that canonical DDR reduce the probability of further genomic instability via cell cycle control but cannot trigger senescence, which explains a gradual accumulation of DNA damage and chronic low DDR in the absence of overt senescence in many contexts. Eventually, genomic instability occurs after a mitosis with unrepaired DNA damage, triggering a full senescence response via yet undefined non-canonical DDR signaling and cGAS–STING damage sensing. This model has interesting implications for the accumulation of senescent cells in tissues as well as for senescent cell populations heterogeneity including single cell senolytic sensitivity.

Gerardo Ferbeyre

Ribosome biogenesis, nucleolar stress and cellular senescence in pancreatic cancer

Dr Gerardo Ferbeyre graduated from Medical School in Havana, Cuba in 1987 and has a PhD in biochemistry from the University of Montreal, Canada where he studied ribozymes. He did postdoctoral training at Cold Spring Harbor Laboratory with Dr. Scott Lowe. There he established a link between PML and oncogene-induced senescence and studied the role of p53 and p19ARF as mediators of senescence. In 2001, Dr Ferbeyre joined the Department of Biochemistry of the University of Montreal. Major contributions from his laboratory include the discovery that DNA damage signaling mediates senescence (Genes & Dev. 2007), the role of SOCS1 linking inflammation to p53 (Mol Cell 2009, Aging 2017, Cancer Res 2019), the role of ERK in senescence (Genes & Dev 2013), the discovery of ribosome biogenesis defects associated to senescence (Nature Cell Biol 2018) and a new metabolic cycle that inhibits senescence by reprogramming NAD metabolism (Mol Cell 2021).

Abstract

Pancreatic adenocarcinomas (PDAC) often possess mutations in K-Ras that stimulate the ERK pathway. Aberrantly high ERK activation triggers oncogene-induced senescence, which halts tumor progression. We report that low-grade pancreatic intraepithelial neoplasia display very high levels of phospho-ERK consistent with a senescence response. However, advanced lesions that have circumvented the senescence barrier exhibit lower phospho-ERK levels. Restoring ERK hyperactivation in PDAC using activated RAF leads to ERK-dependent growth arrest with senescence biomarkers. ERK-dependent senescence in PDAC was characterized by a nucleolar stress response including a selective depletion of nucleolar phosphoproteins and intranucleolar foci containing RNA polymerase I. Notably, comparable mechanisms were observed upon treatment with the platinum-based chemotherapy regimen FOLFIRINOX, currently a first-line treatment option for PDAC. Triggering senescence by hyperactive ERK signaling or FOLFIRINOX in pancreatic cancer cells exposed vulnerabilities to CRSPR-Cas9 mediated inactivation of genes in ribosome biogenesis inhibitors and ferroptosis. Together, our results provide insights to develop senescence-based therapeutics for pancreatic cancer.

Ribosome biogenesis, nucleolar stress and cellular senescence in pancreatic cancer

Rowell MC[1], Deschênes-Simard X[2], Lopes-Paciencia S[1], Le Calvé B[3], Kalegari P[1], Mignacca L[3], Fernandez-Ruiz A[1], Guillon J[1], Lessard F[3,4], Bourdeau V[3], Igelmann S[1,3], Stanom Y[3], Kottakis F[5], Deshpande V[5], Krizhanovsky V[6], Bardeesy N[5], Ferbeyre G[1,3].

[1]Centre de recherche du Centre Hospitalier de l'Université de Montréal (CRCHUM), Montréal, QC H2X 0A9, Canada, [2]Maisonneuve-Rosemont Hospital, Université de Montréal, Montréal, QC H1T 2M4, Canada, [3]Département de Biochimie et Médecine Moléculaire, Université de Montréal, Montréal, QC H3C 3J7, Canada, [4]Present: Laboratory of Growth and Development, St-Patrick Research Group in Basic Oncology, Cancer Division of the Quebec University Research Centre, Québec, Canada, [5]Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA 02114, USA, [6]Department of Molecular Cell Biology, The Weizmann Institute of Science, Rehovot 7610001, Israel

Han Li

New tricks of an old player: senescence induced-cellular plasticity in health and disease

Han Li is a principal investigator at the Institut Pasteur (IP). She leads the cellular plasticity in age-related pathologies group in the developmental and stem cell biology department. Han obtained her Ph.D. under Dr. Paul Hasty's supervision at the University of Texas, health science center at San Antonio in 2007. She carried out her postdoc training in Dr. Manuel Serrano's lab at the Spanish National Cancer Research Centre (CNIO) from 2008 to 2014 and established her group in IP in 2015. Han has made relevant contributions to the role of tumor suppressors and senescence in cellular plasticity in the context of reprogramming, cancer, and tissue regeneration. Currently, her group focuses on understanding the physiological relevance of senescence-modulated cellular plasticity in tissue regeneration and cancer.

Joao Passos

Targeting cell senescence for healthier aging: all roads lead to mitochondria

Dr. Joao Passos, Ph.D. is a cell and molecular biologist and directs the Cell and Molecular Aging laboratory at Mayo Clinic.

He is a Professor of Physiology at Mayo Clinic and director of the T32 Postdoctoral Training Program for Research on Aging

He has led an independent research program focused on cellular senescence and mechanisms of aging since 2010, firstly at the Newcastle University Institute for Ageing in the UK and since 2018 at Mayo Clinic. His laboratory has been continuously funded by several UK, European and US funding bodies since its inception. He has published >90 papers about biology of aging.

He has received several awards for his research including the 2019 FEBS Anniversary Prize for outstanding achievements in the field of Biochemistry and Molecular Biology and the 2022 Robert & Arlene Kogod Center on Aging Director's award. He is part of the editorial board of several journals in the aging field: Aging Cell, Mechanisms of Ageing and Development, Biogerontology and others. His research is focused on investigating the role of senescent cells in aging and age-related disease, with a focus on mitochondria and telomeres.

Marco Demaria

Purinergic signaling promotes the SASP and senescence-associated dysfunctions

Marco Demaria is an Associate Professor of Cellular Aging at the Medical Faculty of the University of Groningen, Netherlands. He obtained his PhD in Molecular Medicine at the University of Torino, Italy, under the supervision of Prof. Valeria Poli. He joined the laboratory of prof. Judith Campisi at the Buck Institute for Research on Aging, California USA, in the summer of 2010 to navigate through the complex phenotypes of senescent cells. He also started to be interested in therapeutic approaches to target the negative aspect of senescent cells. He moved to the University of Groningen and the European Research Institute for the Biology of Aging (ERIBA) in September 2015 as Group leader of the laboratory "Cellular Senescence and Age-related Pathologies". His research is focused towards understanding the cell non-autonomous functions of senescent cells, including their roles in tissue repair, cancer and aging. The goal of his group is to dissect positive and negative roles of cellular senescence in different physiological and pathological context. His laboratory is funded by several intramural and extramural agencies. In 2018 he co-founded a start-up company, Cleara Biotech. Dr Demaria also serves as Editor in Chief for *npj* Aging and from 2022 he is the President of the International Cell Senescence Association.

Abstract

Cellular senescence is characterized by a stable cell-cycle arrest, macromolecular alterations and a proinflammatory secretory phenotype (SASP). Senescent cells play a pivotal role in ageing, and preclinical studies have demonstrated that senotherapeutics can alleviate multiple age-related diseases (ARD). Because most of the detrimental senescence-associated functions are mediated by their secretory phenotype, the identification and targeting of the mechanisms underlying the SASP hold the potential to extend health. We show here that the gap junction component connexin43 (Cx43) is overexpressed in mouse and human senescent cells. Connexin-hemichannel activity results upregulated in senescence, leading to the accumulation of extracellular ATP (eATP). Importantly, genetic interfering with Cx43 was correlated with lower eATP levels and reduced expression of several SASP factors and NF-kB activation. As ATP mediates extracellular communication through purinergic signaling, we evaluated the effect of different purinergic blockers on the SASP *in vitro* and *in vivo.* Our data show that purinergic blockers efficiently halts SASP expression and results in reduced paracrine senescence without compromising natural clearance of senescent cells from tissues. Using mouse models of osteoarthritis and chemotoxicity, we observed a significant reduction of senescence-promoted dysfunctions and improvement of healthspan. These results indicate that Cx43 and

purinergic signaling may be involved in the inflammatory loop in senescent cells, therefore representing new targets for the treatment of ARD.

Purinergic signaling promotes the SASP and senescence-associated dysfunctions

Marta Varela-Eirín[1,2], Jamil Nehme[1], María D. Mayán[2], Marco Demaria[1]

[1]European Research Institute for the Biology of Ageing (ERIBA), University Medical Center Groningen (UMCG), University of Groningen (RUG), Groningen, The Netherlands.

[2]Instituto de Investigación Biomédica de A Coruña (INIBIC). Servizo Galego de Saúde (SERGAS). Universidade da Coruña (UDC). A Coruña, Spain

Miranda Orr

Spatial Profiling of Senescent Cells in Alzheimer's Disease

Dr. Miranda Orr is a Jarrahi Family Geroscience Scholar and Assistant Professor at Wake Forest School of Medicine, Internal Medicine Section on Geriatrics and Gerontology, Winston-Salem, NC. Her translational neurobiology program focuses on the intersection between advanced chronological age and increased risk of neurodegenerative diseases, like Alzheimer's disease. She is best known for discovering a link between Alzheimer's disease tau neuropathology and cellular senescence, and leading the first senolytic trial in older adults with cognitive impairment. Other notable work includes method development to identify, track and profile senescent brain cells throughout the lifespan and in neurological diseases.

Abstract

Neurons with tau-containing neurofibrillary tangles (NFTs) closely correlate with Alzheimer's disease (AD) progression and severity, but do not undergo immediate cell death. Our prior work determined that NFT-bearing neurons undergo a change in cell fate consistent with cellular senescence. CDKN2D/p19 was identified as a key biomarker for identifying senescent neurons in postmortem human AD brain tissue. Studying the interaction between senescent (e.g., p19+/NFT+) neurons and their environments is a necessary next step to understanding how these cells may be impacting their local and synaptically-connected neighboring cells. The goal of this project was to evaluate the expression and subcellular localization of multiple analytes in normal and senescent cells in postmortem mouse and human brains using non-destructive, multi-plex, spatially-resolved profiling methods. Postmortem mouse and human brains were analyzed using NanoString, Inc GeoMx digital spatial profiling (DSP) and CosMx spatial molecular imaging (SMI). Region of interest (ROI) selection included the presence or absence of neuronally expressed AT8 (phosphorylated tau, NFTs) and/or p19 (senescence). NFTs with or without p19 expression were compared to healthy neurons from the same cases. The expression of 86 proteins associated with neuropathology, inflammation, autophagy and cell typing was determined for each ROI and immediate environment using GeoMx. CosMx SMI was used to develop a subcellular expression map of ~900 genes and spatially-resolved cell type map of mouse and human entorhinal cortex and hippocampus. The complete dataset consisted of over 160,000 single cells and ~170 million transcripts, and a spatially-resolved cell type map of mouse brain tissue. Significant differences across biological aging pathways between disease and healthy conditions in both species were identified. Additionally, the results provide insights into which cells are susceptible to senolytic clearing interventions currently underway (NCT04685590).

Paul Robbins

Dr. Robbins received his B.A. from Haverford College, his Ph.D. from the University of California at Berkeley and then worked as a post-doctoral fellow in the laboratory of Dr. Richard Mulligan at the Whitehead Institute at MIT. He was an Assistant, Associate and then full Professor of Microbiology and Molecular Genetics at the University of Pittsburgh School of Medicine as well as Director of Basic Research for the Molecular Medicine Institute and Co-Director of the Paul Wellstone Cooperative Muscular Research Center. He then was a Professor of Molecular Medicine at Scripps Research in Jupiter, Florida and Director of the Center on Aging. He currently is a Professor of Biochemistry, Molecular Biology and Biophysics and Associate Director of the Institute on the Biology of Aging and Metabolism at the University of Minnesota. His current research is focused on developing therapeutic approaches to extend healthspan. He has co-authored more than 385 peer-reviewed manuscripts and 205 book chapters and reviews with an H-index of 131, i10-index of 477 and ~66,000 citations and has edited four books.

Peter de Keizer

Understanding senescence heterogeneity and preclinical development of FOXO4-DRI peptides against a “scarred” subtype

Abstract

Senescent cells are a cause for some aspects of aging and pose exciting candidates for therapeutic removal. There have been many attempts towards therapeutic removal of senescent cells, but with varying success. This is, at least in part, because senescence is often considered as one phenotype.

Today, I will discuss how we identified that what we call senescence, is in fact a range of phenotypes. Through multiplex characterization, involving Imaging Mass-Cytometry, we identified there is considerable heterogeneity even within the same population of senescent cells. I will provide examples and zoom a damaged type of senescence, which we call now call “scarred” senescence, a subtype characterized both by FOXO4/PML and a modified form of p53, i.e. phosphorylated on Ser46.

I will show that at least for this type of senescence, we have been able to progressivel develop potent therapeutics. We have shown before that interference with FOXO4-p53 through cell penetrating peptides could selectively eliminate senescent cells in mouse models where senescence is enhanced through defective DNA-damage repair (Baar .. de Keizer, Cell, 2017). Doing so could restore some signs of homeostasis. I will now show in more detail how this may be particularly true for scarred senescent and cancer cells.

From a translational point of view, I will show how human cancer cells in patients, in vitro, in 3D organoids and in vivo can present a state of scarring and thereby provide in ideal target disease for testing the efficacy of scarring-targeting FOXO4 peptides. Together, this argues we should better define senescence subtypes and focus on specific therapeutics. Scarred senescence can especially be targeted by FOXO4-based peptides, with a translational potential to the clinic.

Understanding senescence heterogeneity and preclinical development of FOXO4-DRI peptides against a “scarred” subtype

M.P. Baar[1,2]; D.A. Putavet[1,2] ; D. Hofmann[1], T. Leyten[1], E. Bouma[2], Timo Eijkman[2], J. Lehmann[1], and P.L.J. de keizer[1,2]

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Selected Speakers

Amit Sharma

Eliminating senescence: more ways to kill death resistant cells from novel senolytics to immune based therapeutics

I received my PhD from the University of Pune for demonstrating microRNA regulation of cytokines and regulation of allergic inflammation. During my postdoctoral research at Stanford University, I demonstrated age-related resistance in the reprogramming of fibroblasts with classical Yamanaka factors. To peruse my interest in aging, I did a second postdoc at the Buck Institute in investigating molecular regulatory pathways involved in genotoxic stress and cellular senescence in various models.

I joined SENS Research Foundation as Group Lead in 2019 and my laboratory focuses on developing strategies to harness the immune system in mitigating the deleterious effects of senescent cells

Abstract

We have recently developed human primary endothelial cell-derived paracrine senescence model. As several previous efforts to characterize secondary SCs have mostly been unreliable as their analysis is based on mixed populations of senescent and non-senescent cells. We have used previously characterized surface receptors to isolate and enrich paracrine senescent cells. Our RNA sequencing analysis demonstrated significant differences between paracrine and primary senescent cells. Intriguingly, paracrine senescent cells engage distinct pro-survival mechanisms compared to primary senescent cells. We further data demonstrate that these cells are resistant to several senolytic drugs.

Several lines of evidence show that Natural Killer (NK) cells play a vital role in the immune surveillance of these cells. However, therapeutic strategies to exploit NK cells to reduce the senescence burden have not yet emerged. We are investigating mechanisms involving NK cell-mediated targeting of senescent cells to improve NK cell-mediated senotherapeutics for the treatment of aging and inflammatory disorders.

Daniel Munoz-Espin

A tumour-promoting senescent secretome triggered by platinum chemotherapy exploits a targetable TGFbR1/Akt-mTOR axis in lung cancer

Daniel Muñoz-Espin is Assistant Professor and Principal Investigator in the Department of Oncology at University of Cambridge, and core member of the CRUK Cambridge Centre Early Detection Programme. Daniel is also Co-director of the CRUK Cambridge Centre Thoracic Cancer Programme, and member of the Cambridge Philosophical Society and the ICSA steering committee. Muñoz-Espin's laboratory works in the fundamental processes and mechanisms triggering cancer initiation and progression, with a particular focus on lung cancer and cellular senescence. Daniel´s group is interested in the tumour microenvironment and ageing, and how they can crucially contribute to cancer development.

Abstract

Platinum-based chemotherapy is commonly used for non-small cell lung cancer (NSCLC) treatment, yet clinical outcomes remain poor. Cellular senescence and its associated secretory phenotype (SASP) can have multiple tumour-promoting activities, although these are largely unexplored in lung cancer. Here we show that cisplatin-derived SASP enhances the malignant phenotype of lung cancer. Using xenograft, orthotopic and KrasG12V-driven murine NSCLC models, we demonstrate that cisplatin-induced senescent cells strongly promote tumour progression. Mechanistically, we find that a TGF-β-enriched SASP drives pro-proliferative effects through TGFβR1 and Akt/mTOR pathway activation. We validate the translational relevance of chemotherapy-induced SASP using clinical NSCLC samples from patients who received neoadjuvant platinum-based chemotherapy. Importantly, TGFβR1 inhibition with galunisertib/senolytic treatment significantly reduces tumour promotion driven by cisplatin-induced senescence. Finally, we demonstrate, using distinct murine NSCLC models, that addition of TGFBR1 inhibitors to platinum-based chemotherapy reduces tumour burden and improves survival, providing pre-clinical proof-of-concept for future trial designs.

Francesca Faggioli

Spatial resolution of cellular senescence dynamics in colorectal liver metastasis

I graduated cum laude in Chemical and Pharmaceutical Technologies at the University of Bologna in 2002 and obtained Ph.D. in Molecular Medicine at the University of Milan. During my education, I moved at the Albert Einstein College of Medicine (NY) where I investigated the role of genetic instability in aging and diseases. After, I moved back to Italy at Institute of Genetic and Biomedical Research (IRGB) of CNR, where I obtained the position of Tenured scientist in Physiopathology in 2016. My research is focused on cellular senescence and DNA damage response in gastric cancers and age-related diseases.

Abstract

Hepatic metastasis is a clinical challenge for colorectal cancer. Cellular senescence, a state of persistent cell-cycle arrest, could be targeted therapeutically for this disease. Here, we integrated spatial transcriptomics, 3D-microscopy and multicellular transcriptomics to study the role of cellular senescence in patients with colorectal liver metastasis (CRLM). We show that senescent metastatic cancer cells (SMCCs) are heterogeneous but spatially define two distinct cancer ecosystems with opposing biological and prognostic roles: epithelial (e)SMCC initiation relies on nucleolar stress, a chemotherapy-independent cell-autonomous process; mesenchymal (m)SMCCs undergo non-cell-autonomous regulation tightly connected with TGFb secretion in the microenvironment and chemotherapy. Cellular neighborhoods reflected opposing forces in immune regulation and predicted the prognostic values of eSMCCs and mSMCCs, a finding validated in primary colorectal tumor. Altogether, we provide comprehensive new understanding of the role of SMCCs in CRLM, and highlight their relevance as new therapeutic targets to limit CRLM progression.

Ines Marin

Induction of senescence renders cancer cells highly immunogenic

Studied Biomedicine in the University of Seville (Spain), where I started to work in the laboratory of Pablo Huertas at CABIMER (Seville, Spain), studying factors with a role in DNA repair. Later, I obtained a master's degree in Multidisciplinary Research (BIST, Barcelona) where I developed a project in the laboratory of Salvador Aznar-Benitah at IRB Barcelona, related with circadian rhythms and aging. Currently, I am a 4th year PhD student in the laboratory of Manuel Serrano at the IRB Barcelona (Spain), where I investigate how senescence cells interact with the immune system to promote adaptive immune responses.

Abstract

Cellular senescence is a stress response that activates innate immunity. However, the interplay between senescent cells and the adaptive immune system remains largely unexplored. Here, we show that senescent cells display enhanced MHC class I (MHC-I) antigen processing and presentation. Immunization of mice with senescent syngeneic fibroblasts generates CD8 T cells reactive against both normal and senescent fibroblasts, some of them targeting senescence-associated MHC-I-peptides. In the context of cancer, we demonstrate that senescent cancer cells trigger strong anti-tumor protection mediated by antigen-presenting cells and CD8 T cells. This response is superior to the protection elicited by cells undergoing immunogenic cell death. Finally, induction of senescence in patient-derived cancer cells exacerbates the activation of autologous tumor-reactive CD8 tumor-infiltrating lymphocytes (TILs) with no effect on non-reactive TILs. Our study indicates that immunization with senescent cancer cells strongly activates anti-tumor immunity, and this can be exploited for cancer therapy.

Karen Crasta

Small extracellular vesicles from therapy-induced senescent breast cancer cells elicit STING-dependent anti-tumour activity

Karen Crasta is Assistant Professor at the National University of Singapore, Centre for Healthy Longevity and Dept of Physiology, and Joint Principal Investigator at A*STAR Singapore. She is a recipient of the Singapore National Research Foundation (NRF) Fellowship, the A*STAR International Fellowship and the HHMI Research Associate Fellowship. Her postdoctoral work at Dana-Farber Cancer Institute elucidated a mechanistic link between mitotic errors and chromosomal breaks via micronuclei. Together with her team, Karen currently seeks to understand the impact of chromosomal instability-imposed senescence in cancer progression and therapeutic resistance, with a recent venture connecting to biological mechanisms of aging.

Abstract

TNBC, associated with poor prognosis and high tumour recurrence, are often-treated with anti-mitotic drugs. However, cells may bypass treatment-induced cell death via mitotic slippage, resulting in multinucleated polyploid cells and senescence activation. Senescent cancer cells represent a population of residual disease and are highly secretory. The SASP elicited is enriched in soluble cytokines linked to tumor recurrence and distant metastasis. In contrast, sEVs derived from senescent cancer cells represent an underappreciated aspect of SASP and its mechanistic role in mediating paracrine effects remains poorly-understood. Here, we show sEVs elicit anti-tumor activity. Mechanistically, DKK1, a negative regulator of WNT signalling, enriched in sEVs cause WNT inhibitory effects in sEV-co-cultured recipient cancer cells. Further investigation into inflammatory pathways with animal models and chemotherapy-treated patient samples revealed STING-dependent macrophage killing. Overall, this talk will shed light on implications of sEVs inherent in senescence secretome for treatment outcomes, as well as the aging process

Laureline Urli

Effect of intermittent hypoxia on cognition and senescence in brain of wild-type mice and transgenic Alzheimer's disease mice model

I studied physiology as well as cellular and molecular biology at the University of Rouen (France) from 2014 to 2018. I then specialized in neuroscience at the University of Paris Saclay from 2019 to 2020. I am currently doing PhD at the Institute of Biology Paris-Seine (Sorbonne University, France) under the supervision of Professor K. Kinugawa and Professor I. Petropoulos. I am studying the role of intermittent hypoxia, an experimental model of sleep apnea syndrome, in the development of aging and in the aggravation of Alzheimer's disease pathophysiology, using RT-qPCR, immunohistochemistry, western blot and behavioral testing.

Abstract

Aging is the major risk factor for Alzheimer's disease. Hallmarks of cellular senescence have been detected in aged brain and recently in brain from patients and from mice models. In the absence of effective treatment, identifying and treating comorbidities is an interesting strategy. Sleep apnea syndrome is common in elderly subjects and is accompanied by intermittent hypoxia that may cause stress-induced premature aging and cognitive decline. But the role of cellular senescence in these mechanisms remains largely unknown. To determine whether intermittent hypoxia causes premature brain aging and accelerates neurodegeneration, 3- and 12-month-old wild-type and transgenic mice were exposed to intermittent hypoxia or normoxia for 6 weeks. Our results indicate that hypoxia exposure induced cognitive impairments and increased the expression of senescence markers, specifically in different brain structures affected in Alzheimer's disease. Cellular senescence mediated by the sleep apnea syndrome could be a potential target for Alzheimer's prevention.

Marco Malavolta

Non-invasive longitudinal quantification of physical function and frailty in geriatric mice: a tool to assess health in intervention studies with senotherapeutics

I am a researcher in the Advanced Technology Center in Aging Research at IRCCS INRCA, the Italian Institute for Health and Science of Aging (Ancona, Italy). My research interests lie in the field of Biogerontology and Geroscience. I'm currently focused on the development and validation of treatments (mostly targeting senescent cells, such as senolytics) that can ameliorate frailty and extend health and lifespan in geriatric mice.

Abstract

The elderly affected by age-related diseases are expected to be the primary beneficiary of the new generation of therapies, including senotherapeutics, that is currently being developed based on the Geroscience hypothesis. This requires careful preclinical studies that may be able to evaluate short and long-time benefits as well as adverse effects. Here we present, in a large cohort (n = 441) of naturally ageing C57BL/6J mice, an innovative and non-invasive scoring method of physical function that resume the five criteria proposed in the Fried's frailty phenotype. This score can be easily integrated with the clinical frailty index to provide an overall score (Vitality Score) for the accurate quantification of health in geriatric mice. We also show preliminary data from the application of this tool in longitudinal intervention studies with innovative senotherapeutics.

Mohamed ElGhazaly

Pathogen manipulation of the infection niche by rewiring the secretome of senescent cells

Mohamed ElGhazaly gained his PhD at the University of Sheffield in 2021 where he is a Postdoctoral Research Associate in the School of Biosciences in the laboratory of Dr Daniel Humphreys. His research characterises senescence-like responses to the typhoid toxin of Salmonella enterica, a bacterial pathogen causing acute typhoid fever, chronic infections, and gallbladder carcinoma in low- and middle-income countries. His work has been published in high-impact journals including Nature Communications (2019), Cells (2021) and another on bioRxiv. He was awarded first prize for his work in numerous national and international conferences, most notably UK Cell Microbiology, yICSA and Scientist.

Abstract

How bacterial pathogens interact with senescence innate defences is not understood. Here, we reveal that cells damaged by the typhoid toxin of Salmonella enterica undergo evolution of DNA damage responses (DDR). Initial DNA replication stress is replaced by concomitant cellular distention, enlarged γH2AX and 53BP1 foci that identify toxin-induced senescent cells (txSCs). Unidentified factors in host secretions from txSCs elicit widespread paracrine senescence and promote infection in bystander cells - toxin-associated SASP (txSASP). Transcriptomics of txSCs and proteomics of the txSASP revealed a role for the TGFβ pathway and activation of target SMAD transcription factors in establishing paracrine senescence. Mechanisms of paracrine senescence were conserved with chemical DDR inducers, yet the txSASP was divergent: the txSC secretome contained Wnt5a that mediated crosstalk with the TGFβ pathway, caused paracrine senescence and augmented macrophage infections. The findings reveal how bacterial toxins rewire the infection niche through damaged cells that elicit senescence responses.

Paula Carpintero-Fernandez

Connexin43 increases CDK4/6 inhibitors efficacy reinforcing the senescent phenotype in breast cancer models

Dr.Carpintero got her PhD in Biomedical Sciences (2015) under the supervision of Dr. Mayán. During her PhD she got a grant from Fundación Barrié to visit Yale University. In 2017, she joined Dr. O´Loghlen´s lab for her postdoc thanks to a Postdoctoral Fellowship from Xunta de Galicia. In June 2019 she joined back the CellCOM group at INIBIC where she started her researcher line based on the discovery of new biomarkers to predict CDK4/6 inhibitors response in breast cancer patients. In March 2021 she got a Postdoctoral Fellowship from Xunta de Galicia.

Abstract

Cancer cells naturally avoid senescence however, CDK4/6 inhibitors (CDK4/6i) become an attractive strategy to induce cell cycle arrest in tumour cells. Connexins are channel-forming proteins involved in cell-to-cell communication. Connexin43 (Cx43) can modulate the tumour microenvironment and enhance senescence via channel dependent/independent functions. Our results demonstrated that restoration of Cx43 in breast cancer cells enhance senescence and sensitizes these cells to cell death by apoptosis. Also, we obtained similar results using sEVs-enriched in Cx43, in combination with CDK4/6i, which significantly increased CDK4/6i efficacy. Further, the combination of Cx43, CDK4/6i and senolytics, resulted in the best strategy to enhance senescence, reduce proliferation significantly increasing CDK4/6i efficacy. We propose a new and effective drug combination strategy based on the use of Cx43 to increase CDK4/6i efficacy in breast cancer. These results could impact in the manage and treatment of tumours that respond to CDK4/6i with a potential clinical benefit in patients.

Sarah Pringle

Are senescent epithelial progenitor cells a defining feature of autoimmune diseases?

Abstract

The autoimmune/inflammatory diseases primary Sjögren's syndrome (pSS), cutaneous lupus erythematosus (CLE), and Crohn's disease (CD) are united by impaired function of epithelial organs, namely the salivary glands (SGs), skin and intestine respectively. Progenitor cells resident in these tissues normally maintain homeostasis by self-renewal and differentiation. Cells in SG organoids (SGOs) cultured from pSS SG biopsies maintain shorter telomeres lengths and were less able to proliferate and differentiate than age-matched controls. Expression of p16 in SG progenitor cell niche of pSS patients was correlated with lack of SG function. Significantly more p16+ and p21+ cells in the skin progenitor cell niche were detected in CLE skin lesions, compared to controls. In intestines of patients with CD, p16 expression was observed in the progenitor cell niche, and p21 in the transient amplifying cell zone. Senescent epithelial progenitor cells may thus represent therapeutic targets in organs affected by autoimmune disease.

Scott Haston

Clearance of senescent macrophages ameliorates tumorigenesis in KRAS-driven lung cancer

Scott Haston is a postdoctoral research fellow at the Institute of Child Health (UCL) studying the role of cellular senescence during tumourigenesis and in ageing using novel genetically engineered mouse models. Scott obtained a BSc in Anatomy from the University of Dundee in 2013 and a PhD in genetics and cell biology from UCL in 2019, before continuing post-doctoral research in the laboratory of Professor Juan Pedro Martinez-Barbera (UCL). Currently, Scott is investigating the tumour promoting effects of senescent cell populations during adult lung and paediatric brain tumourigenesis and whether this is therapeutically targetable to prevent or restrict tumourigenesis.

Abstract

Accumulation of senescent cells in the tumour microenvironment can drive tumourigenesis in a paracrine manner through the senescence-associated secretory phenotype (SASP). Using a new mouse model, termed p16-FDR, we show that macrophages and endothelial cells are the predominant senescent cell types in murine KRAS-driven lung tumours. Single cell transcriptomics identify a population of tumour-associated macrophages, expressing a unique array of pro-tumourigenic SASP factors and surface proteins, that are also present in normal aged lungs. Ablation of senescent cells with diphtheria toxin or the senolytic ABT-737 results in a significant reduction in tumour burden and increased mouse survival of KRAS-driven murine lung cancer models. Of translational relevance, we show the presence of macrophages with senescent features in human lung premalignant lesions, but not in adenocarcinomas. Together, our results identify a population of macrophages contributing to the initiation and progression of lung cancer, and open potential therapeutic avenues and cancer preventative strategies.

Staffan Strömblad

PAK4 governs Kras-driven premalignant pancreatic acinar cell reprogramming

I have almost 35 years of experience in research in Cancer biology. My research aims to improve the fundamental understanding of how cancer develops and progresses, in particular to unravel functional mechanisms of cancer at the cellular and molecular levels with a focus on cell-matrix interactions, cellular signaling and cellular senescence.

My current position and engagements include
2009- Professor of Clinical Molecular Biology at Karolinska Institutet
2007- Director of the Live Cell Imaging Core Facility at Karolinska Institutet
2021- Director of the Breast Cancer Theme Center at Karolinska Institutet
2022- Member of the Nobel Assembly at Karolinska Institutet

Abstract

We previously found that p21-activated kinase 4 (PAK4) promotes passage through the senescence barrier in breast cancer models and that the prevalent cancer PAK4 overexpression blocks cellular senescence (Costa et al. Nat Commun 2019). However, the potential function of PAK4 in the development of other cancer types remains unclear. Here, we show that PAK4 is amplified in pancreatic ductal adenocarcinoma (PDAC) patients and overexpressed in patient samples. In the Pdx-Cre;KrasG12D mouse PDAC model, increased PAK4 expression peaks at the stage of acinar to ductal metaplasia (ADM) lesions. Importantly, PAK4 gene depletion in Pdx-Cre;KrasG12D mice causes accumulation of ADM lesions combined with loss of subsequent PanIN formation. This halt of acinar reprograming is accompanied by inhibited proliferation, decreased apoptosis and increased expression of p16 and p21CIP1. Consequently, PAK4 gene ablation markedly reduces advanced PDAC. In conclusion, PAK4 promotes acinar cell reprogramming during Kras-driven PDAC development, plausibly by inhibiting cellular senescence.

Tamir Chandra

Implicating senescence in human health

Tamir earned his Ph.D. in Oncology and Cancer Biology from Cancer Research UK at the University of Cambridge in 2011. He earned his Bachelor's Degree of Science in Biochemistry from The Goethe University Frankfurt in 2007. Tamir did his Postdoctoral Research between 2012 and 2016 at The Babraham Institute, where he began with research in understanding cellular aging. He finished with his Postdoc in 2016, before becoming a Chancellor's Fellow and tenure track Group Leader at MRC Human Genetics Unit.

Abstract

Senescence is the finite capability of cells to proliferate and offers a cellular model with which to study organismal ageing. The area of senescence has recently been energised by observations, in mouse, that clearance of senescent cells (senolysis) leads to improved health outcomes and an extension of healthy lifespan.

Nevertheless, directly implicating senescence in human ageing has proved a significant challenge, because to date, most evidence has emerged from cell culture or mouse models. Promoter Capture Hi-C (PCHi-C) has proven to be a powerful tool in the analysis of GWAS studies.

We have integrated PCHi-C in senescence with genetic resources - exploring the roles of senescence in human health. The outcome is an easily adaptable framework to prioritise human conditions based on their susceptibility to the senescence phenotype.

Tomaz Rozmaric

Characterization of cellular senescence in development, ageing and wounding of mouse skin by creation and exploration of the largest sc-RNA-seq database of murine skin cells

My name is Tomaz Rozmaric and I am a Ph.D. student at Ludwig Boltzmann Research Group SHoW - Senescence and Healing of Wounds under the mentorship of Dr. Mikolaj Ogrodnik. My thesis is focused on cellular senescence and ageing. I have obtained my master's degree in Biochemistry at the University of Ljubljana in 2018. During my master's degree I have established methods such as DNA nanopore sequencing, bisulfite sequencing and EWAS studies based on NGS, MBD and MeDIP. I also helped in the improvement of the Austrian Newborn Screening by establishing VitB12 screening.

Abstract

Senescent cells, induced by various stressors, present a heterogenous population of irreversibly cell cycle arrested cells, which are present in higher frequencies during development, regeneration and in ageing. Drugs used to eliminate senescent cells (senolytics) are known to target pathways which are differentially activated in various cell types. To identify novel senolytics applicable in skin, it is necessary to decipher senescence signatures of various cell types.

Here we present our preliminary in silico results on defining and characterizing phenotypes of senescent skin cells. We generated a database consisting of 19 studies with publicly available 10x genomics single-cell-RNA-sequencing (sc-RNA-seq) datasets of mouse skin from the developmental stage, regeneration, and the aging process. To our knowledge this is the biggest sc-RNA seq dataset of mouse skin generated to date. This dataset was used to unravel the phenotypic characteristics related to cellular senescence of different populations of mouse skin cells.

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Senescence Therapeutics

Rubedo


BIOAGE

Bio-Connect

Poster Presenters

Abraham Mathew

PhD student, Indian Institute of Science

Understanding the role of hydrogen sulfide in regulating redox homeostasis during cellular senescence

Emmanuelle Born

Post-doctoral fellow, INSERM DR PARIS 06

Eliminating senescent cells can promote pulmonary hypertension development and progression

Matej DURIK

Post-Doc, CERBM Gie IGBMC

Investigating novel features of the cellular senescence program

Donghee Kang

Post-doc, Inha University

TRIM22 promotes cellular senescence by targeting PHLPP2 for proteasomal degradation

Karen Castaño

PhD candidate, UMCG

The contribution of cellular senescence to age-related hearing loss

Chrysiida Baltira

PhD student, Netherlands Cancer Institute

Characterization of treatment induced senescence in glioblastoma by targeted inhibition of the PI3K, MEK, and CDK4/6 pathways

Amal Albati

Phd Student, University of Leicester

BTK Inhibition as a potential strategy to improve Cardiac health in aged population

Aina Calls Cobos

UPF

Role of cellular senescence in cardiac muscle dystrophy

Naomi Veeningen

PhD student, Hasselt University

Spinal cord injury induces premature immune aging in mice

Vanessa Lopez-Polo

PhD Student, IRB Barcelona

Exploring mitochondrial vulnerabilities in senescent cells

Daniel SAMPAIO GONCALVES

PhD Student, CERBM Gie IGBMC

Functional investigation of a novel senescence-regulating transcription factor

Sofian Al Shboul

Assistant professor, *The Hashemite University*

Neoadjuvant Chemotherapy Induces the Expression of a Therapy-Induced Senescence Profile in Human Breast Cancer

Timothy Cash

Chief Scientific Officer, *Rejuveron Senescence Therapeutics*

Development of monoclonal antibody directed against a sensecent cell surface protein for therapeutic use in oncology

Teodora Gheorghe

PhD student, *ERIBA*

Repurposing calcium channel blockers for use in senolytic therapies

Andres Cisneros Fernández

PhD Student, *UPF*

scRNA-seq characterization of cells undergoing senescence in skeletal muscle during Duchenne muscular dystrophy

Sebastian Mackedenski

PhD student, *ERIBA*

lncRNA PURPL is a pro-survival factor in senescent cells

Petr Svoboda

Postdoctoral researcher, *Institute for Clinical and Experimental Medicine, Prague*

The effect of three SGLT-2 inhibitors on metabolic parameters, insulin sensitivity and development of senescence in hereditary hypertriglyceridemic rats

Barbora Judita Kasperova

PhD student, *Institute for Clinical and Experimental Medicine*

SGLT-2 inhibitors alleviates markers of senescence in subcutaneous and epicardial adipose tissue in heart failure subjects

SABELA DA SILVA ALVAREZ

Postdoctoral Researcher, *FUNDACION IDIS*

ANALYSIS OF SENESCENCE MARKERS IN LIQUID BIOPSIES TO GUIDE CANCER TREATMENT

Anna Ingeborg Eisenmenger

Student, *Centre for Healthy Longevity (CHL), National University Health System, Healthy Longevity Translational Research Programme (HLTRP), National University of Singapore*

Diet and dietary compounds and their impact on cellular senescence in human and animal models: A systematic review

MARIA PILAR PICALLOS RABINA

PhD Student, *FUNDACION IDIS*

Identification of Cardiac Glycosides as a novel class of senolytic compounds

Jan Fröhlich

Researcher, *St.Anne´s University Hospital Brno*

Untangling the role Growth differentiation factor 11 (GDF11) in cellular senescence

Hannah Smith

PhD student, *University of Leicester*

Novel Markers of Senescence in the Liver in Ageing and in Response to Senotherapies

Paloma Kalegari

PhD Student, *CRCHUM / Université de Montréal*

Induction of senescence in cancer cells followed by GPX4 inhibition, a promising one-two punch therapy in pancreatic cancer

Matt Yousefzadeh

Research Assistant Professor, *University of Minnesota*

Failure to repair endogenous DNA damage in ß-cells causes adult onset diabetes

Louise Pitcher

PhD Candidate, *University of Minnesota iBAM*

Characterization of cellular senescence induced by space radiation: implications for space travel

Thomas Brand

PhD student, *Utrecht University*

Senescence influences liver differentiation through the SASP

Marta Varela Eirin

Postdoctoral researcher, *ERIBA, UMCG*

Role of palmitic acid in the inflammatory exacerbation of cellular senescence

Pujan Engels

PhD Student, *Universitätsklinikum Tübingen*

Therapy-induced senescence and SASP heterogeneity influence innate immune responses in liver cancer

Mariem Alsharief

PhD candidate, The University of Sheffield

Does pericyte senescence contribute to oral cancer progression? Mariem Al-Sharief, Syed Ali Khurram, Daniel W

Mohamad RIMA

Scientist, StarkAge Therapeutics

Identification of senescent cell surface markers as immunotherapeutic targets

Laura Kuil

Postdoc, NKI

Therapy-induced cognitive impairment: is senescence involved?

Clara Fia Gøricke Laursen

PhD student, Nordic Bioscience

Circulating levels of endotrophin, a fragment derived from collagen type VI, are associated with worse health conditions in a self-reported health questionnaire

Belén Pan Castillo

Postdoctoral fellow, Starkage Therapeutics

Extracellular vesicles-based identification of lung fibrosis-associated biomarkers for targeted therapies

Abel Soto-Gamez

Postdoctoral Researcher, RUG / UMCG

A role for HGF in adipose-derived mesenchymal stem cell attenuation of radiation-induced senescence of salivary gland organoids

Alba Escriche

PhD student, *Vall d'Hebron Institute of Oncology (VHIO)*

Impact of therapy-induced senescence (TIS) on the tumor microenvironment

Sarah Gough

PhD student, *Cancer Research UK Cambridge Institute*

Senescence-specific adaptive immune response to oncogene-induced-senescence (OIS) within the murine liver

Hyunjung Hwang

Post-doc, *Inha University*

FLRT2 regulates vascular aging by modulating ITGB4 phosphorylation

Danis Thomas

PhD student, *University of Cambridge CRUK Cambridge Institute*

Characterising p53 response to centrosome loss and senescence that follows

Lucy Martin

Cross Disciplinary Research Fellow, *University of Edinburgh*

The role of senescence in glioblastoma radiation therapy

Ioana Olan

Research Associate, *University of Cambridge*

The three-dimensional chromatin gradient and cellular plasticity

Mariana Ascensao-Ferreira

PhD student, *Instituto de Medicina Molecular*

Profiling the alternative splicing landscape of senescent cells

Jordan Guillon

post doctoral student, *University of Montreal (CRCHUM)*

Characterization of resistance mechanisms to FOLFIRINOX-induced senescence in pancreatic tumor models

Isabelle LE ROUX

PhD, permanent CNRS researcher, *Paris Brain Institute*

Cellular senescence in malignant cells promotes tumor progression in mouse and patient Glioblastoma

Soňa Štemberková Hubáčková

Deputy head in Laboratory of Translational and Experimental Diabetology and Obesitology, *Institute of Clinical and Experimental Medicine*

Targeting senescence as a promising approach to treatment of type 2 diabetes mellitus and its comorbidities

Inês Tomé Ribeiro

PhD student, *University of Coimbra / CNC_UC-Biotech*

Pharmacological clearance of senescent cells with Navitoclax reverses HFpEF hallmarks

María Mayán Santos

Group Leader, *Fundación Profesor Novoa Santos*

Connexin 43 peptides target dedifferentiation and senescence in osteoarthritis

Fabio J. Ferreira

Junior Researcher, *IBMC - i3S*

The FOXM1/AP-1 axis: an enhancer hub at the center of chromatin accessibility in senescence

Meriem ELOUAFY

PhD Student, *IMOPA - UMR 7563 - CNRS UL*

Senescence and immunomodulatory properties of mesenchymal stromal cells are related with the clinical outcome of patients with MDS and AML after hematopoietic stem cell transplantation

Tomaz Rozmaric

Ph.D. Student, *Ludwig Boltzmann Research Group SHoW - Senescence and Healing of Wounds*

Characterization of cellular senescence in development, ageing and wounding of mouse skin by creation and exploration of the largest sc-RNA-seq database of murine skin cells

Julie MacDonald

Postdoctoral Fellow, *Dana Farber Cancer Institute*

Senescence and apoptotic priming: poised between life and death

Adelyne Chan

Research Associate, *Cancer Research UK Cambridge Institute*

Oncogenic RAS dosage and the Senescence Spectrum

Maayke Kuijten

Research scientist, *Erasmus Medical Center*

A lamin-based reporter system to study senescence in cancer

Romain Perouf

PhD Student, *IMOPA - UMR 7563 - CNRS UL*

Senescent mesenchymal stromal cells show decreased mitochondrial transfer and immunomodulation capacity

Andrew Baker

PhD Student, *University of Cambridge*

NanoJagg Nanoparticles as a Multimodal Contrast Agent for the Detection of Senescent Cells

Loren Kell

PhD Student (2nd Year), *University of Oxford*

Investigating DNA repair and mTOR inhibition in the senescence of human fibroblasts and T cells

Sarah Kent

PhD student, *University of Edinburgh*

Investigating the role of microglial senescence in central nervous system injury and repair

Madeleine Tancock

PhD student, *PeterMac/Monash*

High-grade serous ovarian cancer cells that undergo therapy-induced senescence engage in an enhanced inflammatory phenotype

LJiljana Fruk

Associate Professor, *University of Cambridge*

Organic Nanostructured Probes for In vivo Detection of Senescence burden

Florence Chainiaux

Dr, *University of Namur*

UVB-induced senescence impacts amino acids balance in normal human keratinocytes

Antonella Lettieri

post-doctoral fellow, *Università degli studi di Milano*

In vitro study of p300 role in cellular senescence

Larissa Lipskaia

Senior Researcher, *INSERM DR PARIS 06*

Induction of telomerase in p21-positive cells counteracts capillaries rarefaction and preserves lung function of aging mice

Andrew Jarjour

Associate Principal Scientist, *Merck Sharp & Dohme*

Identification of novel senolytic targets in replicatively-senescent rat astrocytes

Blake Monroe

Postdoctoral Fellow, *University of Minnesota Twin Cities*

Reactive Lipid Aldehydes Induce Cellular Senescence

Elizabeth Thompson

Research Support Manager, *University of Minnesota*

Spatial transcriptomics of human liver to characterize senescence with aging and fibrosis

Paula Carpintero-Fernández

Postdoctoral Researcher, *INIBIC. A Coruña*

Connexin43 increases CDK4/6 inhibitors efficacy reinforcing the senescent phenotype in breast cancer models

Sharmilla Chandrasegaran

PhD Researcher, *Newcastle University*

Modelling The Spatiotemporal Dynamics Of Senescent Cells In Wound Healing And Tissue Repair

Bethany Bartlett

PhD student, *MRC Human Genetics Unit, University of Edinburgh*

Regulation of the senescence-associated secretory phenotype by the nucleoporin TPR

Bethany Hughes

PhD student, Blizard Institute of Cel land Molecular Science, Queen Mary University of London, London, UK

Building a machine learning model to identify deep senescence of human dermal fibroblasts

Vanessa Smer Barreto

Cross-disciplinary post-doctoral fellow, *University of Edinburgh*

Discovery of new senolytics using machine learning

Haoran Zhu

Research Associate, *CRUK CI*

In vivo model of Dose-Dependency in the Oncogene-Induced Senescence

Andrea Postmus

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Doxorubicin-induced p16Ink4a-positive senescent cells do not promote long-term cardiometabolic effects in an atherosclerosis-prone mouse model

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Investigating the Effect of Ribosomal Stress-induced Senescence on p16-positive Basal-like Breast Cancer

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RSK3 prevents senescence of epithelial cells following mesenchymal transition: role of proteasomes and of the NF-kappaB pathway

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Loss of Pla2r1 decreases cellular senescence and age-related alterations caused by aging and Western diet

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Exploring the potential of senescence-inducing therapy in genetically distinct models of hepatocellular carcinoma

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p16 as a transcriptomic marker of cell senescence regulation

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A role of the Caspase-Activated DNAse (CAD) in senescence

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The ATF6 arm of the Unfolded Protein Response is involved in the establishment of UVB-induced premature senescence

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Eliminating senescence: more ways to kill death resistant cells from novel senolytics to immune based therapeutics

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Role of STING in intracellular IL-6 signaling in two tumor models of senescence

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Hunt for novel senotherapeutics by drug screening and drug design

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Effect of therapy-induced senescence on the efficacy of HER2-directed Antibody Drug Conjugates

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Modelling senescence in osteoarthritis: Combining irradiation and mechanical loading in human osteochondral explants

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PAK4 governs Kras-driven premalignant pancreatic acinar cell reprogramming

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Functionality of mutant p53 in early tumorigenesis

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Clearance of senescent macrophages ameliorates tumorigenesis in KRAS-driven lung cancer

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Study of treatment induced senescence (TIS) in head and neck squamous cell carcinoma (HNSCC) according to the HPV status

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Human cytomegalovirus infection drives a cellular senescence-like phenotype in kidney epithelial cells

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Investigating MRTF-dKO induced senescence

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Characterization of oncogene-induced-senescence as a potential adverse event in HSPCs gene therapy

Yaan Frey
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Accelerated replication senescence of ataxia-telangiectasia skin fibroblasts is retained at physiologic oxygen levels, with unique and common transcriptome patterns

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Time dependent changes in EVs secretion by senescent vascular smooth muscle cells

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Cellular senescence Impacts vascular smooth muscle cells phenotypic switch and promotes accumulation in de-differentiated phenotype

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Identifying genes involved in geroconversion

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Dynamic characterization of the p53 interactome during senescence using proximity labelling

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Abemaciclib restricts the pro-tumorigenic effects and toxicity of therapy-induced senescent cells

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p21 (CDKN1A) regulates the microenvironment of senescent cells and promotes lung fibrosis

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Investigating the modulation of non-coding RNAs associated to senescence using computational and biological approaches

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Identification of a novel mechanism of paracrine senescence induction via miR-23b-5p targeting MICAL2, as delivered by replicatively senescent exosomes

Jamil Nehme

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PARP signaling regulates cell fate decision between senescence and death during oxidative stress events

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Time-resolved proteomic profiling of plasma membrane damage-induced senescent cells

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The role of telomeric DDR and the impact of its inhibition in age-related diseases

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Fisetin does not alleviate cholangiopathy in Cyp2c70-deficient mice with a hydrophobic bile acid pool despite modulation of cellular senescence

Julio Aguado
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Senotherapies alleviate premature brain aging and virus-induced senescence in human brain organoids.

Panagiotis Galanos
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Aberrant p21 expression drives escape from senescence through chronic replication stress and metabolic reprogramming.

Roel Goldschmeding
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CCN2/CTGF as a driver of senescence and kidney fibrosis

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RNA accumulation in aged endothelial cells links an interferon gene signature to cellular senescence

Kevin Hascup
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Sexual Dimorphic Responses to Oral Fisetin or Dasatinib and Quercetin Treatment in C57BL/6 Mice.

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Impaired virus clearance of 3D cultured bronchial epithelium from aged donors

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PD-L2 suppression cooperates with genotoxic chemotherapy in the control of experimental tumors

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Immune checkpoints impair immune surveillance of senescent cells

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The Impact of a senotherapeutics molecule, peptide 14, in the progression of senescent cells using single- cell analysis

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The p-rpS6-zone delineates markers of cellular senescence during healing

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De novo mitochondrial DNA synthesis in senescent endothelial cells sustains sterile inflammation and Doxorubicin cardiotoxicity

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Aberrant induction of p19Arf-mediated cellular senescence contributes to neurodevelopmental defects

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High-throughput screening to identify pro-senescence therapies for p16-positive basal-like breast cancer: A novel therapeutic innovation

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Senescent cells enhance newt limb regeneration by promoting muscle dedifferentiation

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Senescence modulation reduces tumourigenesis in mouse models of paediatric craniopharyngioma

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Characterization of oncogene-induced-senescence as a potential adverse event in HSPCs gene therapy

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