cnio-CaixaResearch
FRONTIERS
MEETINGS

Madrid 9—10 May 2022

Molecular, Cellular and Organismal Drivers of Aging

Organisers

Maria Blasco
Spanish National Cancer Research Centre, CNIO, Madrid, Spain

Alejo Efeyan
Spanish National Cancer Research Centre, CNIO, Madrid, Spain

Thomas Rando
University of California, Los Angeles, US

Speakers

Steven Artandi
Stanford University, US

Fabrizio d'Adda di Fagagna
IFOM-FRC Institute of Molecular Oncology Foundation, Milan, Italy

Oscar Fernández Capetillo
Spanish National Cancer Research Centre, Madrid, Spain

Christine K. Garcia
Columbia University Irving Medical Center, New York, US

Vera Gorbunova
University of Rochester, New York, US

Jan Hoeijmakers
Erasmus MC Rotterdam, Netherlands

Juan Carlos Izpisua
Salk Institute for Biomedical Studies, La Jolla, US

William Mair
Harvard T.H. Chan School of Public Health, Boston, US

Brendan Manning
Harvard T.H. Chan School of Public Health, Boston, US

Pura Muñoz-Cánoves
Pompeu Fabra University (UPF), ICREA, Barcelona, and CNIC, Madrid, Spain

Angela Nieto
Institute of Neurosciences, CSIC-UMH, Alicante, Spain

Manuel Serrano
Institute for Research in Biomedicine, Barcelona, Spain

Dario R. Valenzano
Max-Planck Institute for Biology of Ageing, Cologne, Germany

EXCELENCIA SEVERO OCHOA 2012 - 2023

GOBIERNO DE ESPAÑA
MINISTERIO DE CIENCIA E INNOVACIÓN
Instituto de Salud Carlos III

cnio stop cancer

"la Caixa" Foundation

Madrid 9—10 May 2022

Molecular, Cellular and Organismal Drivers of Aging

Spanish National Cancer Research Centre (CNIO)
Madrid, Spain

cnio *stop cancer*

cnio-CaixaResearch
FRONTIERS
MEETINGS

Madrid 9—10 May 2022

Molecular, Cellular and Organismal Drivers of Aging

#CFM_Aging22
@CNIO_Cancer
@CaixaCiencia

EXCELENCIA SEVERO OCHOA 2012 - 2023

GOBIERNO DE ESPAÑA
MINISTERIO DE CIENCIA E INNOVACIÓN
Instituto de Salud Carlos III

cnio stop cancer

"la Caixa" Foundation

Madrid 9—10 May 2022

Molecular, Cellular and Organismal Drivers of Aging

Spanish National Cancer Research Centre (CNIO)
Madrid, Spain

cnio stop cancer

cnio-CaixaResearch
FRONTIERS
MEETINGS

Madrid 9—10 May 2022

Molecular, Cellular and Organismal Drivers of Aging

Summary

cnio stop cancer

Madrid 9—10 May 2022

Molecular, Cellular and Organismal Drivers of Aging

Spanish National Cancer Research Centre (CNIO)
Madrid, Spain

cnio stop cancer

cnio-CaixaResearch
FRONTIERS
MEETINGS

Madrid 9—10 May 2022

Molecular, Cellular and Organismal Drivers of Aging

Organisers and Speakers

cnio stop cancer

Madrid 9 — 10 May 2022

Molecular, Cellular and Organismal Drivers of Aging

Venue:

Spanish National Cancer Research Centre – CNIO Auditorium, Madrid, Spain

Chairpersons and organising committee:

Maria Blasco
Spanish National Cancer Research Centre, CNIO, Madrid, Spain

Alejo Efeyan
Spanish National Cancer Research Centre, CNIO, Madrid, Spain

Thomas Rando
University of California, Los Angeles, US

CNIO - CaixaResearch Frontiers Meeting

Speakers

Steven Artandi
Stanford University, US

Maria Blasco
Spanish National Cancer Research Centre, Madrid, Spain

Fabrizio d'Adda di Fagagna
IFOM-FRC Institute of Molecular Oncology Foundation, Milan, Italy

Alejo Efeyan
Spanish National Cancer Research Centre, Madrid, Spain

Oscar Fernández Capetillo
Spanish National Cancer Research Centre, Madrid, Spain

Christine K. Garcia
Columbia University Irving Medical Center, New York, US

Vera Gorbunova
University of Rochester, New York, US

Jan Hoeijmakers
Erasmus MC Rotterdam, Netherlands

Juan Carlos Izpisua
Salk Institute for Biomedical Studies, La Jolla, US

William Mair
Harvard T.H. Chan School of Public Health, Boston, US

Brendan Manning
Harvard T.H. Chan School of Public Health, Boston, US

Pura Muñoz-Cánoves
Pompeu Fabra University (UPF), ICREA, Barcelona, and CNIC, Madrid, Spain

Angela Nieto
Institute of Neurosciences, CSIC-UMH, Alicante, Spain

Thomas Rando
University of California, Los Angeles, US

Manuel Serrano
Institute for Research in Biomedicine, Barcelona, Spain

Dario R. Valenzano
Max-Planck Institute for Biology of Ageing, Cologne, Germany

cnio-CaixaResearch
FRONTIERS
MEETINGS

Madrid 9—10 May 2022

Molecular, Cellular and Organismal Drivers of Aging

Programme

cnio stop cancer

Monday May 9th 2022

09:00 - 09:30 *Registration (main hall)*

09:30 - 09:45 Welcome address

09:45 - 12:30 S #1 - SENESCENCE AND REGENERATION I
Chairperson: ***Manuel Serrano***

09:45 - 10:15 *"Aging and Regeneration"*
Juan Carlos Izpisua
Salk Institute for Biomedical Studies, La Jolla, US

10:15 - 10:45 *"Promoting regeneration of aged muscles"*
Pura Muñoz
Pompeu Fabra University and ICREA, Barcelona, Spain
& Spanish Center for Cardiovascular Research, Madrid, Spain

SHORT TALK 10:45 - 11:00 *"Harnessing senolytic CAR T cells to reverse and prevent aging"*
Corina Amor
Cold Spring Harbor Laboratory, New York, US

11:00 - 11:30 Coffee break & poster session (social room)

11:30 - 12:00 *"Mechanisms of longevity in long-lived mammals"*
Vera Gorbunova
University of Rochester, New York, US

12:00 - 12:30 *"Stem cell aging and mechanisms of epigenetic rejuvenation"*
Thomas Rando
University of California, Los Angeles, US

12:30 - 14:00 Lunch break (cafeteria)

Monday May 9th 2022

14:00 - 15:15 **S #2 - NUTRIENTS AND METABOLISM I**
Chairperson: ***Thomas Rando***

14:00 - 14:30 *"The nutrient – Rag GTPase axis as a driver of mammalian aging"*
Alejo Efeyan
Spanish National Cancer Research Centre, CNIO, Madrid, Spain

14:30 - 15:00 *"PI3K-mTOR signaling and the metabolic control of growth"*
Brendan Manning
Harvard T.H. Chan School of Public Health, Boston, US

SHORT TALK 15:00 - 15:15 *"Mitochondrial DNA variation and stress responses"*
Aurora Gómez Durán
Center for Biological Research (CIB) "Margarita Salas", Madrid, Spain

15:15 - 16:00 *Group picture (main door) and coffee break & poster session (social room)*

Monday May 9th 2022

16:00 - 17:15 **S #3 - NUTRIENTS AND METABOLISM II**
Chairperson: ***Thomas Rando***

SHORT TALK 16:00 - 16:15 *"Vitamin B12 is a limiting metabolite for reprogramming and tissue repair"*
Marta Kovatcheva
Institute for Research in Biomedicine, Barcelona, Spain

16:15 - 16:45 *"Efficacy of Longevity Interventions In C. elegans is Determined by Early Life Activity of RNA Splicing Factors"*
William Mair
Harvard T.H. Chan School of Public Health, Boston, US

16:45 - 17:15 *"Insights about Ageing Gained while Studying Neurodegeneration"*
Oscar Fernandez Capetillo
Spanish National Cancer Research Centre, CNIO, Madrid, Spain

17:15 - 18:15 Poster session – Snack for all participants (social room)

Tuesday May 10th 2022

09:30 - 12:00 S #4 - EPIGENETICS AND GENOME STABILITY I
Chairperson: ***Angela Nieto***

09:30 - 10:00 *"Transcriptional regulation of telomerase in aging and cancer"*
Steven Artandi
Stanford University, US

10:00 - 10:30 *"Telomerase Activation for the Treatment of Age-Related Diseases and Telomere Syndromes"*
Maria Blasco
Spanish National Cancer Research Centre, CNIO, Madrid, Spain

10:30 - 11:00 Coffee break & poster session (social room)

11:00 - 11:30 *"Evolutionary ecology of aging"*
Dario Valenzano
Max-Planck Institute for Biology of Ageing, Cologne, Germany

11:30 - 12:00 *"The contribution of DDR to telomere-driven age-related diseases"*
Fabrizio d'Adda di Fagagna
IFOM - FIRC Institute of Molecular Oncology Foundation, Milan, Italy

12:00 - 13:30 Lunch break (cafeteria)

Tuesday May 10th 2022

14:00 - 15:15 S #5 - EPIGENETICS AND GENOME STABILITY II

Chairperson: ***Juan Carlos Izpisua***

14:00 - 14:30 *"Genetics of Pulmonary Fibrosis: Inherited Susceptibilities and Personalized Prognostics"*
Christine K. Garcia
Columbia University Irving Medical Center, New York, US

14:30 - 15:00 *"DNA damage repair: understanding the process of aging and applications for medicine"*
Jan Hoeijmakers
Erasmus MC Rotterdam, Netherlands

15:00 - 15:15 *"When the non-coding codes: Mining the Microproteome for Novel Regulators of Cellular Plasticity"*
María Abad
Vall d'Hebron Institute of Oncology, Barcelona, Spain

15:15 - 15:45 Coffee break & poster session (social room)

Tuesday May 10th 2022

15:45 - 17:15 **S #6 - SENESCENCE AND REGENERATION II**
Chairperson: ***Oscar Fernandez Capetillo***

SHORT TALK 15:45 - 16:00 *"Cell senescence in Zebrafish development and tissue regeneration"*
Manuel Collado
Health Research Institute of Santiago de Compostela, IDIS, Spain

16:00 - 16:30 *"Cell plasticity as a driver or kidney fibrosis and regeneration"*
Angela Nieto
Institute of Neurosciences, CSIC-UMH, Alicante, Spain

SHORT TALK 16:30 - 16:45 *"How does time-dependent deterioration of T cells contribute to tissue senescence?"*
María Mittelbrunn
Spanish National Research Council (CSIC), Madrid, Spain

16:45 - 17:15 *"Understanding and controlling cellular reprogramming in vivo"*
Manuel Serrano
Institute for Research in Biomedicine, Barcelona, Spain

17:15 - 17:30 ***Prizes for best posters and best short talks – farewell***

Madrid 9 — 10 May 2022

Molecular, Cellular and Organismal Drivers of Aging

Monday May 9th 2022

Session #1
SENESCENCE AND REGENERATION I

Chairperson: ***Manuel Serrano***

Aging and regeneration

Juan Carlos Izpisua

Salk Institute for Biomedical Studies,
La Jolla, US

Ageing is characterized by the functional decline of tissues and organs and the increased risk of ageing-associated disorders. Several 'rejuvenating' interventions have been proposed to delay ageing and the onset of age-associated decline and disease to extend healthspan and lifespan. These interventions include metabolic manipulation, partial reprogramming, heterochronic parabiosis, pharmaceutical administration and senescent cell ablation. As the ageing process is associated with altered epigenetic mechanisms of gene regulation, such as DNA methylation, histone modification and chromatin remodelling, and non-coding RNAs, the manipulation of these mechanisms is central to the effectiveness of age-delaying interventions. I will discuss some of epigenetic changes that occur during ageing and the rapidly increasing knowledge of how these epigenetic mechanisms have an effect on healthspan and lifespan extension, and will outline questions to guide future research on interventions to rejuvenate the epigenome and delay ageing processes.

Promoting regeneration of aged muscles

Laura García-Prat[1,2], Sonia Alonso-Martín[2], Stefania Dell'Orso[3], Hong-Wei Sun[3], Eusebio Perdiguero[1], Vittorio Sartorelli[3] and **Pura Muñoz-Cánoves[1,2,4]**

[1]Department of Experimental and Health Sciences, Pompeu Fabra University (UPF) CIBER on Neurodegenerative diseases (CIBERNED), Barcelona, Spain
[2]Spanish National Center on Cardiovascular Research (CNIC), Madrid, Spain
[3]Laboratory of Muscle Stem Cells and Gene Regulation, National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), NIH, Bethesda, US
[4]ICREA, Barcelona, Spain

During ageing, tissue regenerative functions decline. Skeletal muscle regeneration depends on a normally quiescent population of stem cells (satellite cells). Upon injury, satellite cells either self-renew or differentiate to regenerate muscle. When and how these decisions are taken is not known. Here, we report that these alternative stem-cell fates are pre-determined in quiescence, before satellite cells encounter stress. The relative expression of a single gene, the CD34 surface marker, distinguishes two quiescent stem-cell states: $CD34^{high}$, with stemness properties, and $CD34^{low}$, more committed to myogenic differentiation. The $CD34^{high}$ quiescent stem-cell state is preserved into later life only succumbing in extreme old age, and this may reflect the cell's aspiration to maintain functional fitness.

SHORT TALK

Harnessing senolytic CAR T cells to reverse and prevent aging

Inés Fernández-Maestre[*1], William Pfohl[*2], Courtenay Graham[1], Riccardo Mezzadra[1], Judith Feucht[1,3], Kevin Chen[1], Ross Levine[1], Lee Jones[1], Michel Sadelain[1], Scott Lowe[1], **Corina Amor[2]**

[1]Memorial Sloan Kettering Cancer Center, New York, NY, US
[2]Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, US
[3]University Hospital Tuebingen, Tuebingen, Germany

Cellular senescence is a stress response program characterized by stable cell cycle arrest and the production of a proinflammatory secretory phenotype. Senescent cells accumulate over time and play a key role in the pathogenesis of organismal aging. Here we show for the first time that cellular therapy can successfully be used to effectively eliminate senescent cells in natural aging. Senolytic CAR T cells targeting uPAR are able to efficiently and safely remove senescent cells in aged mice improving their metabolic function and physical fitness. Importantly, the beneficial effects of senolytic CAR T cells are long lived and single administration of low doses is sufficient to mediate preventive long-term effects in physiological aging as well as in models of high-fat diet induced metabolic dysfunction. These results highlight the therapeutic potential of senolytic CAR T cells for age-related disorders.

Mechanisms of longevity in long-lived mammals

Vera Gorbunova
Doris Johns Cherry Professor of Biology and Medicine
Co-director Rochester Aging Research Center
University of Rochester
Department of Biology
Rochester, NY, US

Species of mammals differ dramatically in their maximum lifespan and cancer susceptibility. We investigate mammalian species that naturally evolved long lifespan and cancer resistance with the goal of understanding molecular mechanisms of longevity and cancer resistance and then applying them to benefit human health. Remarkably, long-lived animal species, in general, have more efficient DNA double-strand break repair. Recent study from our group, showed that the protein responsible for more efficient DNA repair in long-lived species is SIRT6. In long-lived rodents SIRT6 has higher biochemical activities. We identified centenarian variant of SIRT6 that is better at stimulating DNA repair than the wild type SIRT6, and is also more active as a tumor suppressor. We propose that specific SIRT6 activators may be developed for cancer prevention and lifespan extension.

Stem cell aging and mechanisms of epigenetic rejuvenation

Thomas Rando
University of California,
Los Angeles, US

Madrid 9 — 10 May 2022

Molecular, Cellular and Organismal Drivers of Aging

Monday May 9th 2022

Session #2
NUTRIENTS AND METABOLISM I

Chairperson: ***Thomas Rando***

The nutrient – Rag GTPase axis as a driver of mammalian aging

Alejo Efeyan
Metabolism and Cell Signalling Group Leader
Spanish National Cancer Research Centre, CNIO,
Madrid, Spain

The mechanistic target of rapamycin complex 1 (mTORC1) controls cellular anabolism, and genetic and pharmacological inhibition of mTORC1 extend longevity across eukaryotes. Moreover, suppression of mTORC1 and dietary restriction are at least partially epistatic. Conversely, anomalous activation of mTORC1 has been unequivocally linked to aging, but modelling increased mTORC1 activity in mice has been challenging because of detrimental, pleiotropic consequences of mTORC1 activation, which have limited the analysis of mechanisms of aging governed by mTORC1 in mammals.

We have engineered knock-in mice expressing active mutant variants of RagC, a GTPase that signals nutrient sufficiency to mTORC1. Cells from heterozygous RagC-mutant mice show a mild increase in mTORC1 activity, and RagC-mutant mice exhibit multiple features of a premature aging phenotype. To our knowledge, this is the first genetic system with an increased nutrient signaling – mTORC1 axis in mice to understand cellular and molecular underpinnings that link this pathway to aging. The shortened lifespan of RagC-mutant mice occurs with prominent senescence in peripheral organs and extensive features of inflammaging. Acute control of myeloid inflammation reverts some of the premature aging features, and extended suppression of myeloid cells extends survival of mice with increased nutrient – Rag GTPase signaling. I will discuss these observations and the implications of our work for human aging.

PI3K-mTOR signaling and the metabolic control of growth

Brendan D. Manning

Department of Molecular Metabolism,
Harvard T.H. Chan School of Public Health,
Boston, MA, US

Growth factor signaling through PI3K and Akt to mTORC1 results in a shift from catabolic processes to anabolic biosynthetic processes underlying cell, tissue, and organismal growth. Through unbiased genomic and metabolomic approaches, we have found that, in addition to its established roles in promoting protein synthesis and inhibiting autophagy, mTORC1 stimulates changes in specific metabolic pathways through transcriptional and posttranslational effects on metabolic enzymes. In this manner, mTORC1 serves to link growth signals to metabolic processes that promote the increase in biomass underlying growth, including enhanced synthesis of proteins, lipids, and nucleotides. Research in our lab is focused on understanding both how growth signals are propagated to control mTORC1 in different cell types and tissues, with a focus on the role of the TSC protein complex, and defining the molecular nature of the coordinated metabolic program downstream of mTORC1. I will describe new mouse models we have generated to genetically dissect this signaling network in vivo and a new downstream metabolic change driven by mTORC1 inhibition, related to adaptive changes in cellular lipid content.

SHORT TALK

Mitochondrial DNA variation and stress responses

Aurora Gomez-Duran[1,2,3] and Patrick Chinnery[2,3]

[1]MitoPhenomics Lab. Centro de Investigaciones Biológicas Margarita Salas. CSIC. Madrid, Spain
[2]MRC Mitochondrial Biology Unit, Cambridge Biomedical Campus, Cambridge, UK
[3]Department of Clinical Neurosciences, School of Clinical Medicine, University of Cambridge, UK

Mitochondrial DNA (mtDNA) variants influence the risk of rare and late-onset human diseases, but the reasons for this are poorly understood. Interestingly, the same variant exerts a great variability in disease penetrance in each individual, which suggests the existence of a complex system that does not necessarily imply the dysfunction of the energy synthesis. In here, through the combination of multi-omics approaches on several human models, we will describe how variations in oxidative phosphorylation system capacity (OXPHOS) driven by the mtDNA variants activate different types of stress responses and their possible role in late-onset disease. We will further show how these findings can be applied to pharmacogenomic discovery and search of new biomarkers.

Madrid 9 — 10 May 2022

Molecular, Cellular and Organismal Drivers of Aging

Monday May 9th 2022

Session #3
NUTRIENTS AND METABOLISM II

Chairperson: ***Thomas Rando***

SHORT TALK

Vitamin B12 is a limiting metabolite for reprogramming and tissue repair

Marta Kovatcheva[1], Elena Melendez[1], Dafni Chondronasiou[1], Federico Pietrocola[1,2], Raquel Bernad[1], Adria Caballe[1], Alexandra Junza[3,4], Camille Stephan-Otto Attolini[1], Neus Prats[1], Sylvere Durand[5-7], Oscar Yanes[3,4], Guido Kroemer[5-9], Manuel Serrano[1,10]

[1]Institute for Research in Biomedicine (IRB Barcelona), Barcelona, Spain
[2]Dep of Biosciences and Nutrition, Karolinska Institutet, Stockholm, Sweden
[3]Universitat Rovira i Virgili, Dep of Electronic Engineering, IISPV, Tarragona, Spain
[4]CIBER de Diabetes y Enfermedades Metabólicas Asociadas (CIBERDEM),ISC III,
[5]Metabolomics and Cell Biology Platforms, Inst Gustave Roussy, Villejuif Cedex, France
[6]Equipe labellisée par la Ligue contre le cancer, Centre de Recherche des Cordeliers, Inserm, Paris, France
[7]Pôle de Biologie, Hôpital Européen Georges Pompidou, AP-HP, Paris, France
[8]Suzhou Inst for Systems Medicine, Chinese Academy of Medical Sciences, Suzhou, China
[9]Karolinska Institute, Department of Women's and Children's Health, Karolinska University Hospital, Stockholm, Sweden
[10]Catalan Inst for Research & Advances Studies ICREA, Barcelona, Spain

Expression of OCT4, SOX2, KLF4 and MYC (OSKM) can reprogram differentiated somatic cells into pluripotent cells, albeit with low efficiency. Readily accessible interventions to promote *in vivo* reprogramming remain elusive. Here, we employ whole-genome sequencing of the murine microbiome during in vivo reprogramming to discover metabolic perturbations that affect both the host and the colonic microbiota. We have found that reprogramming entails an abnormally high consumption of vitamin B12 and amino acids used as precursors for one-carbon metabolism. Mechanistically, tissues and cells undergoing reprogramming upregulate the main B12 uptake receptor (CD320), as well as methionine synthase (MS), a B12-dependent enzyme essential for all methylation processes. Remarkably, supplementation of B12 significantly improves the efficiency of reprogramming both *in vivo* and *in vitro*. We find that vitamin B12 supplementation during reprograming enhances 3' accumulation of H3K36me3 and reduces spurious transcription from these genomic loci. Finally, we show that either brief OSKM induction or vitamin B12 supplementation promotes embryonic-like reprogramming of the colon, as marked by Sca1, and ameliorates regeneration after acute ulcerative colitis. We conclude that vitamin B12, through its essential role in methylation, can act as a non-toxic, gene-free, and easily administered metabolite to improve *in vivo* reprogramming, which can be harnessed for tissue repair.

Efficacy of longevity Interventions In *C. elegans* is determined by early life activity of RNA splicing factors

Sneha Dutta[1], Caroline Heintz[1], Maria C. Perez-Matos[1], Ayse Sena Mutlu[2], Mary E. Piper[3], Meeta Mistry[3], Arpit Sharma[1], Hannah J. Smith[1], Porsha Howell[1], Rohan Sehgal[1], Anne Lanjuin1, Meng C. Wang[2,4] and **William B. Mair[1*]**

[1]Department of Molecular Metabolism, Harvard T. H. Chan School of Public Health, Harvard University, Boston, Massachusetts, US
[2]Huffington Center on Aging, Baylor College of Medicine, Houston, US
Howard Hughes Medical Institute, Baylor College of Medicine, Houston, US
[3]Harvard Chan Bioinformatics Core, Harvard T. H. Chan School of Public Health, Boston, Massachusetts, US
[4]Howard Hughes Medical Institute, Baylor College of Medicine, Houston, US

Geroscience aims to target the aging process to extend healthspan. However, even isogenic individuals show heterogeneity in natural aging rate and responsiveness to pro-longevity interventions, limiting translational potential. Using in vivo mini gene reporters in isogenic *C. elegans*, we show that alternative splicing of mRNAs related to lipid metabolism in young animals is coupled to subsequent life expectancy. Further, activity of RNA splicing factors REPO-1 and SFA-1 early in life modulates effectiveness of specific longevity interventions via POD-2/ACC1 and regulation of lipid utilization. In addition, early inhibition of REPO-1 renders animals refractory to late onset suppression of the TORC1 pathway. Together these data suggest that activity of RNA splicing factors and the metabolic landscape early in life can modulate responsiveness to longevity interventions centered around metabolic homeostasis and may explain variance in treatment efficacy between individuals.

Insights about ageing gained while studying neurodegeneration

Oscar Fernandez-Capetillo[1,2]

[1]Genomic Instability Group, Spanish National Cancer Research Centre (CNIO), Madrid, Spain
[2]Science for Life Laboratory, Division of Genome Biology,
Department of Medical Biochemistry and Biophysics, Karolinska Institute, Stockholm, Sweden

For reasons that remain poorly understood, alterations in ribosome biogenesis, translation and nucleoli have a particular impact on neurons and hematopoietic cells. Accordingly, mutations associated to neurodegenerative diseases are frequently related to nucleolar biology. A specific example of this is ALS (amyotrophic lateral sclerosis), a fatal neurodegenerative disease lacking a cure. The most frequent mutation in ALS patients is an intronic repeat expansion in *C9ORF72*, which leads to the production of 2 types of arginine-rich dipeptide repeats (poly(PR) and poly(GR)) that cause nucleolar stress and cell death. We recently provided a mechanism that explains the toxicity of these peptides. By additional work, we have now discovered that these peptides trigger an accumulation of free ribosomal proteins and mTOR hyperactivation, a hallmark of ribosomopathies. In mice, we see that the systemic expression of these peptides causes nucleolar stress and accelerated ageing, which can be substantially alleviated by mTOR inhibition. In summary, this work illustrates that the most frequent type of ALS might be a particular type of ribosomopathy. Furthermore, our collective efforts, as well as data coming from other groups, suggests that the best approach to tackle neurodegenerative diseases might be to explore the value of strategies that can delay ageing as a whole. Our findings and ideas in this regard will be presented.

Madrid 9 — 10 May 2022

Molecular, Cellular and Organismal Drivers of Aging

Tuesday May 10th 2022

Session #4
EPIGENETICS AND GENOME STABILITY I

Chairperson: ***Angela Nieto***

Transcriptional regulation of telomerase in aging and cancer

Steven Artandi
Stanford University,
Stanford, US

Telomerase activation for the treatment of age-related diseases and telomere syndromes

Maria A. Blasco, PhD
Scientific Director, CNIO
President of SOMMa
Head, Telomeres and Telomerase Group (CNIO)
Spanish National Cancer Research Centre, CNIO
Madrid, Spain

Telomeres are nucleoprotein complexes which protect the ends of linear chromosomes and which play a pivotal role in cellular and organismal ageing. Over the past two decades short telomeres have been associated with a large disease spectrum including degenerative diseases and cancer. In addition, a number of diseases known as telomeropathies or telomere sydromes, including some cases of aplastic anemia and pulmonary fibrosis, are linked to mutations in telomere maintenance genes. Our laboratory has made significant contributions to dissect the role of telomerase and telomere length as one of the key molecular pathways underlying cancer and aging. We previously demonstrated that telomerase activation by means of transgenesis as well as vector-based gene therapy delays a variety of age-related pathologies and increases survival in wild-type mice. Here, I will discuss our more recent work validating the effectivity of telomerase gene therapy for the treatment of diseases related to the presence of short telomeres including models for myocardial infarction, aplastic anaemia, pulmonary fibrosis and renal fibrosis.

Evolutionary ecology of aging

Dario Valenzano
Max-Planck Institute for Biology of Ageing
Cologne, Germany

African killifishes have emerged over the past few years as a powerful model system to answer open questions in biology of aging, developmental biology and evolutionary biology. In my talk, I will share two main research themes pursued by our research group: 1) how studying killifish ecology and evolution has opened new perspectives to understanding how species' lifespan evolve as a function of past demographic constraints and 2) how an ecological perspective to killifish biology, which focuses on host-microbiome functional interactions, opens new insights into biology of aging, as well as offers novel opportunities for anti-aging interventions.

The contribution of DDR to telomere-driven age-related diseases

Fabrizio d'Adda di Fagagna
IFOM - the FIRC Institute of Molecular Oncology,
Milan, Italy

During aging, senescent cells accumulate in tissues and organs, which become unable to proliferate and function properly. Telomeric shortening and damage trigger most, if not all, the downstream pathways leading to senescence and disease. The DNA damage response (DDR) pathways are activated by short or damaged telomeres and are necessary for cellular senescence enforcement.

Recently, the role of RNA has emerged as a novel key regulator of DDR pathways. We have shown that damage-induced long non-coding RNAs (dilncRNAs) are generated at sites of DNA damage, including telomeres and are processed into shorter DNA damage response RNAs (DDRNAs). Antisense oligonucleotides (ASOs) against such RNAs allow site-specific DDR inhibition (Francia et al Nature 2012, Michelini et al Nature Cell Biology 2017, Pessina et al 2019).

Telomeric ASO (tASO) against RNA generated at short or damaged telomeres prevents DDR activation at dysfunctional telomeres in cultured cells and *in vivo* in mice (Rossiello et al. Nature Communications 2017).
In a mouse model of Hutchinson-Gilford Progeria Syndrome (HGPS), an accelerated aging condition, tASO treatment is sufficient to extend the proliferative capacity of patients' fibroblasts, and inhibit DDR, improve tissue homeostasis, reduce inflammation and extend lifespan (Aguado et al Nature Communications 2019).

Telomerase knockout mice bear short telomeres and show many pathological conditions associated with human aging, including lung fibrosis and altered hematopoiesis. Here, tASO reduce telomeric DDR, improves lung fibrosis and hematological defects.

We also recently observed that telomeric shortening or dysfunction cause an increase in the levels of ACE2, the SARS-CoV-2 receptor, in humans and in mice and that tASO-mediated telomeric DDR inhibition prevents it *in vivo* (Sepe et al. EMBO Reports).

We believe that many serious human conditions caused by telomere shortening and damage can be treated with tASO.

Madrid 9 — 10 May 2022

Molecular, Cellular and Organismal Drivers of Aging

Tuesday May 10th 2022

Session #5
EPIGENETICS AND GENOME STABILITY II

Chairperson: ***Juan Carlos Izpisua***

Genetics of Pulmonary Fibrosis: Inherited Susceptibilities and Personalized Prognostics

Christine K. Garcia

Columbia University Irving Medical Center,
New York, US

Unbiased genomic approaches, such as linkage, genome-wide association studies, and next generation sequencing, have been used to unravel the genetic underpinnings of idiopathic pulmonary fibrosis (IPF). IPF is a lethal scarring disease affecting older adults and is now the leading indication for lung transplantation in the United States. Genetic discoveries have implicated several different pathways as being relevant to IPF pathogenesis. In this talk, I will review variants that regulate telomere-related gene function and discuss how these variants are now being translated to the realm of patient care. Studies across various ILD centers have shown that peripheral leukocyte telomere length is a biomarker associated with several clinically relevant patient outcomes, such as, survival, rate of disease progression, development of adverse effects from immunosuppressive medications, and allograft function following lung transplantation.

DNA damage repair: understanding the process of aging and applications for medicine

Jan H.J. Hoeijmakers[1-3]

[1]Dept. of Molec. Genetics, Erasmus MC, Rotterdam, The Netherlands,
[2]Cecad Research Center, Cologne, Germany
[3]The Princess Máxima Center for Pediatric Oncology, Oncode, Utrecht, The Netherlands

Aging appears remarkably plastic: e.g. suppressing insulin signalling extends lifespan in numerous species. However, virtually all premature aging syndromes link with genome instability. We have generated DNA-repair-deficient mouse mutants which resemble human repair syndromes displaying wide-spread accelerated aging. For instance, *Ercc1*$^{\Delta/-}$ mice, carrying multiple repair defects show extensive multi-morbidity, limiting lifespan to 4-6 month. Simultaneously, they exhibit an anti-aging 'survival response', which suppresses growth and enhances maintenance, resembling the longevity response induced by dietary restriction (DR) as an attempt to delay the accelerated aging. Interestingly, subjecting these progeroid mutants to actual (30%) DR tripled lifespan, and drastically retarded accelerated aging, most notably neurodegeneration preserving 50% more neurons and maintaining full motoric function. The DR response in these mice resembled DR in wild-type animals including reduced insulin signaling. We found DR lowered DNA damage, explaining why DNA repair mutants overrespond to DR. Interestingly, *Ercc 01*$^{\Delta/-}$ liver expression profiles showed gradual decline of expression preferentially of long genes, consistent with genome-wide accumulation of stochastic, transcription-blocking lesions, which affect long genes more than short ones. This phenomenon was also prominent in normal aging of many post-mitotic tissues. DR largely prevented transcription stress, indicating that DR prolongs genome function. We will present phenotypes of conditional DNA repair models targeting aging to selected organs, striking parallels with Alzheimer's disease and the first remarkable results translating these concepts from mice to progeroid children. Our findings identify DNA damage as main cause of systemic aging, establish repair-deficient mice as powerful models for interventions to promote healthy aging, reveal untapped potential for reducing endogenous damage and transcription stress in neurodegeneration, explain the molecular anti-aging mechanism of DR and the aging component of proteinopathies based on transcription stress and promote counterintuitive DR-like interventions for progeroid syndromes, preventing neurodegenerative diseases and ischemia reperfusion damage in surgery and for improving chemotherapy outcome.

SHORT TALK

When the non-coding codes: Mining the Microproteome for Novel Regulators of Cellular Plasticity

Olga Boix, Emanuela Greco, Iñaki Merino, Marion Martínez, Elena Senís and **María Abad**

Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain

Recent findings have revealed that many RNA molecules annotated as non-protein coding (ncRNAs) actually contain small open reading frames that are transcribed and translated into evolutionary conserved, unannotated microproteins, also known as micropeptides or small-ORF encoded peptides (SEPs). Based on ribosome profiling, proteomics and phylogenetic analyses, the human genome hides thousands of evolutionary conserved microproteins that remain to be identified. These surprising observations open a whole new level of biological complexity, bearing enormous implications from basic research to the clinical setting.

The microproteins characterized to date play key functions in fundamental processes such as DNA repair, embryonic development and tissue regeneration. However, despite the growing interest in finding novel microproteins, their relevance in pathological settings such as cancer and age-related diseases has not been revealed so far. Interestingly, the translation of these sORFs is regulated by stress. My group is focused on the discovery of microproteins relevant for cellular plasticity. Using a computational method for phylogenetic analysis, we have identified 5 novel and evolutionary conserved microproteins regulated in cellular reprogramming and in cancer. We have experimentally validated their translation and characterized their molecular functions *in vitro* and *in vivo*. We will present our unpublished results that demonstrate that our identified microproteins are novel regulators of cellular plasticity with tumor suppressor activity. In particular, they act as guardians of cell identity by controlling different cellular processes such as calcium dynamics, cytoskeleton remodeling, mitochondrial metabolism and the EMT. More generally, our findings suggest that the proteome encoded by previously assumed non-coding RNAs can indeed be a source of new regulators of cell identity relevant for cancer and regenerative medicine.

Madrid 9 — 10 May 2022

Molecular, Cellular and Organismal Drivers of Aging

Tuesday May 10th 2022

Session #6
SENESCENCE AND REGENERATION II

Chairperson: ***Oscar Fernandez-Capetillo***

SHORT TALK

Cell senescence in Zebrafish development and tissue regeneration

Manuel Collado, Sabela Da Silva-Alvarez

Cell senescence, cancer and aging Lab.
Health Research Institute of Santiago de Compostela, IDIS.,
Santiago de Compostela, Spain

Cellular senescence is considered a stress response that limits the proliferation of damaged cells by establishing a permanent cell cycle arrest. Different stimuli can trigger senescence, but excessive production or impaired clearance of these cells leads to their accumulation during aging with deleterious effects. Despite this potential negative side of cell senescence, its physiological role as a pro-regenerative and morphogenetic force has emerged recently after the identification of programmed cell senescence during embryogenesis and during wound healing. Here, we explored the conservation of developmental and tissue injury-induced senescence in a lower vertebrate showing complex regeneration, the zebrafish.

We carried out a detailed characterization of senescence during zebrafish development and found it to be conserved and widespread. Apart from yolk and cloaca, previously described structures, we also identified senescence in the developing central nervous system, intestine, liver, pronephric ducts, and crystalline. Senescence at these developing structures disappeared upon treatment with senolytic compound ABT- 263, supporting their senescent identity and opening the possibility of studying the contribution of this process to development.

On the other hand, we observed how fin amputation in adult fish leads to the appearance of senescent cells at the site of damage, while their removal impairs tissue regeneration. Despite many conceptual similarities, this tissue repair response is different from developmental senescence.

Our results lend support to the notion that cell senescence is a positive response promoting tissue repair and homeostasis, and point to its evolutionary origin as a morphogenetic force operating during development. At the same time, they offer the prospect of identifying altered cell senescence responses as the molecular basis for developmental syndromes and diseases related with tissue damage, examples of which will be shown.

Cell plasticity as a driver of kidney fibrosis and regeneration

M. Ángela Nieto
Institute of Neurosciences (CSIC-UMH),
Alicante, Spain

Epithelial plasticity is at the core of crucial processes including embryonic cell migration, cancer progression, organ fibrosis and tissue repair. The epithelial to mesenchymal transition (EMT) triggers cell plasticity in all these contexts, highlighting its pleiotropy and intrinsic complexity. It is not a binary process or a single program, as it implies the generation of intermediate hybrid epithelial-mesenchymal (E/M) states that, very often, never reach the full mesenchymal state. Under those circumstances cells depict a hybrid phenotype expressing both epithelial and mesenchymal markers and from which they can reverse to the original state or move towards a more mesenchymal phenotype. Hybrid states favor beneficial coordinated cell migration during development, but they also enable the formation of clusters of migratory cancer cells with increased metastatic potential. Unlike the situation in cancer, where the hybrid phenotype is associated with a worse prognosis, the intermediate phenotype observed during organ fibrosis holds promise for new regenerative approaches, as inhibiting EMT attenuates established disease.

SHORT TALK

How does time-dependent deterioration of T cells contribute to tissue senescence?

Gonzalo Soto-Heredero, Gabriela Desdin-Mico, Elisa Carrasco, Enrique Gabande-Rodriguez, Manuel M. Gomez de las Heras and **María Mittelbrunn**[1]

[1]Centro de Biologia Molecular Severo Ochoa, Consejo Superior de Investigaciones Cientificas, Madrid, Spain

As in many other cells and tissues, cells of the immune system present mitochondrial decline with age. To investigate the consequences of the aging of the immune system, Mittelbrunn´s lab have induced age-associated mitochondrial dysfunction prematurely in T cell. Targeting mitochondrial function in T cells recapitulates metabolic, phenotypic and functional features of aged T cells, including susceptibility to infections and premature inflammaging. They found that inducing age-associated mitochondrial decline in T lymphocytes, does not only cause an immunometabolic dysfunction that drives T cell senescence, but actually causes a general, body-wide deterioration of health with multiple aging-related features, including metabolic, musculoskeletal, cardiovascular and cognitive alterations, altogether resulting in premature death. Thus, premature aging of T lymphocytes may be 'contagious', driving a generalized acceleration of aging throughout multiple organ systems. Their results place the metabolism of T cells at the crossroad between inflammation, senescence and aging, highlighting that immunometabolism can be a therapeutic target to delay aging. This presentation will decode the molecular mechanism by which T cells to contribute to inflammaging and age-related diseases and will discuss novel therapeutic opportunities to promote healthy aging.

Understanding and controlling cellular reprogramming *in vivo*

Manuel Serrano

Aging & Metabolism Group Leader
Institute for Research in Biomedicine - IRB Barcelona
Barcelona, Spain

We are interested in understanding cellular responses to stress and damage. An emerging theme in response to tissue injury is the acquisition of plasticity and progenitor properties by some cells. To study cell plasticity in vivo in a controllable manner, we have generated "reprogrammable" mice where it is possible to switch on-and-off the Yamanaka factors (Oct4, Sox2, Klf4 and Myc). We are using our "reprogrammable" mice to learn how to control *in vivo* cellular plasticity. We have found that indeed, damaged cells secrete factors, like IL6, that strongly promote cellular reprogramming *in vivo*. We have performed single-cell RNAseq of *in vivo* reprogramming tissues to understand the intermediate states. One important conclusion from these studies is that the path to reprogramming is conserved among different tissues. I will also present a novel intervention that greatly improves reprogramming by simply supplementing the diet with a particular vitamin. Finally, I will present data on the rejuvenating potential of a single cycle of transient reprogramming in naturally aged mice.

cnio-CaixaResearch
FRONTIERS
MEETINGS

Madrid 9—10 May 2022

Molecular, Cellular and Organismal Drivers of Aging

Organisers & Speakers' Biographies

cnio stop cancer

Steven Artandi

Director, Stanford Cancer Institute
Senior Associate Dean for Cancer Programs, Stanford School of Medicine
Chief Cancer Officer, Stanford Health Care,
Stanford, US

Steven Artandi, MD, PhD is the Laurie Kraus Lacob Director of the Stanford Cancer Institute and the Jerome and Daisy Low Gilbert Professor of Medicine and Biochemistry at Stanford University. He also serves as the inaugural Senior Associate Dean for Cancer Programs for Stanford School of Medicine and the Chief Cancer Officer for Stanford Health Care. He received his undergraduate degree from Princeton University, and MD and PhD degrees from Columbia University. He trained in Internal Medicine at Massachusetts General Hospital and in Oncology at Dana-Farber Cancer Institute before joining the Stanford faculty in 2000. Dr. Artandi is an oncologist and cancer biologist whose research work has focused on the role played by the enzyme telomerase in cancer, aging and stem cell function. His work has produced new insights into the origins of cancer, revealing how telomerase endows cells with immortal growth properties and how aspiring cancers circumvent critical bottlenecks encountered during carcinogenesis. He has received a number of awards including an Outstanding Investigator Award from the National Cancer Institute and is an elected member of the American Association for the Advancement of Science, the American Society for Clinical Investigation and the Association of American Physicians. He serves on the Editorial Boards of the journals Molecular Cancer Research and Stem Cells.

Maria A. Blasco
Scientific Director, CNIO
President of SOMMa
Head, Telomeres and Telomerase Group (CNIO)
Spanish National Cancer Research Centre, CNIO
Madrid, Spain

Maria A. Blasco is a molecular biologist devoted to the study of telomeres and telomerase and their role in cancer and aging, a field of research in which she excels worldwide. Her work has been published in high impact journals as, *Cell, Nature or Science*, among others.

Blasco has merited vast recognition, both national and international, as the Joseph Steiner Award of Switzerland, the EMBO Gold Medal, the Körber European Science Award of Germany, as well as the Spanish National Research Award in Biology *Santiago Ramón y Cajal* (2010) and the *Premio Jaume I*, among others.

Blasco was named Chair of SOMMa ('Severo Ochoa' Centres and 'María de Maeztu' Units of Excellence Alliance) and has received three Doctorate Honoris Causa in Spain: Universidad Carlos III of Madrid (2014), Universidad of Alicante (2017) and Universidad of Murcia (2018). In October 2017 received the *Generalitat Valenciana* Scientific Award.

Fabrizio d'Adda di Fagagna
IFOM - FIRC Institute of Molecular Oncology Foundation,
Milan, Italy

Fabrizio d'Adda di Fagagna is a cell and molecular biologist that studies the involvement of the DNA damage response (DDR) pathways in mammals in physiologically relevant processes, mainly aging and cancer. We demonstrated that replicative cellular senescence is the outcome of the direct recognition of critically-short telomeres by the DDR apparatus, and that oncogene activation is an intrinsically genotoxic event that, by altering DNA replication, causes DDR activation and cellular senescence. More recently, we discovered that the RNA polymerase II transcriptional apparatus is recruited to DNA lesions, including dysfunctional telomeres, and demonstrated that this allows for site-specific DDR inhibition.

Alejo Efeyan
Group Leader, Metabolism and Cell Signaling Lab,
Spanish National Cancer Research Centre, CNIO,
Madrid, Spain

After obtaining his BSc degree in Buenos Aires, Alejo Efeyan received his PhD from the Autonomous University of Madrid, for his studies on mechanisms of tumor suppression. His postdoctoral training was in the David M Sabatini Lab, studying the biology of mTOR and nutrient signaling. Alejo Efeyan settled his laboratory at the CNIO in 2016, and his team studies the links between nutrients and metabolic homeostasis and the impact of deregulated nutrient and growth factor signaling in cancer and aging.

Oscar Fernández Capetillo

Vicedirector of Spanish National Cancer Research Centre, CNIO,
Genomic Instability Group Leader
Madrid, Spain

Oscar Fernandez-Capetillo did his PhD in the University of The Basque Country working with mouse models of autoimmunity with Dr. Ana Zubiaga. For his postdoctoral stay he joined the group of André Nussenzweig, where he started to work on DNA repair, particularly focusing on the role of histone H2AX. In 2005, he joined CNIO to lead the Genomic Instability Group where he has been ever since. Initial works from the lab concentrated on exploring the role of replicative stress in cancer and ageing, for which the group combined cell biology, mouse models and drug development projects. More recently, the group has expanded to other areas such as mechanisms of drug resistance and neurodegenerative diseases. Since 2015 Oscar is also the Vicedirector of CNIO, and professor at the Karolinska Institute in Sweden.

Christine Kim Garcia

Frode Jensen Professor of Medicine
Chief, Division of Pulmonary, Allergy, and Critical Care Medicine
Columbia University Irving Medical Center, US

Christine Kim Garcia M.D., PhD., obtained her medical and Doctor of Philosophy degrees from the University of Texas Southwestern Medical Center and then trained in Internal Medicine and Pulmonary Medicine. She moved to Columbia University College of Physicians and Surgeons in 2019 to become the Frode Jensen Professor of Medicine. She is currently the Division Chief of Pulmonary, Allergy, and Critical Care Medicine.

Vera Gorbunova
Doris Johns Cherry Professor of Biology and Medicine
Co-director Rochester Aging Research Center
University of Rochester
Department of Biology
Rochester, NY, USA

Vera Gorbunova is an endowed Professor of Biology and Medicine at the University of Rochester and a co-director of the Rochester Aging Research Center. Her research is focused on understanding the mechanisms of longevity and on the studies of exceptionally long-lived mammals. Dr. Gorbunova pioneered comparative biology approach to study aging. She elucidated the mechanisms that control evolution of tumor suppressor mechanisms. She uncovered the function of the longevity gene Sirtuin 6 in regulating genome stability across species. She demonstrated the role of transposable elements in driving age-related inflammation. Her work received awards of from the Ellison Medical Foundation, the Glenn Foundation, AFAR, and NIH. Her work was recognized by the Cozzarelli Prize from PNAS, prize for research on aging from ADPS/ Alianz, France, Prince Hitachi Prize in Comparative Oncology, Japan and Davey Prize from Wilmot Cancer Center.

Jan H.J. Hoeijmakers
Erasmus MC Rotterdam,
Netherlands

Jan Hoeijmakers research focuses on DNA repair. His team made major contributions to cloning repair genes, elucidating underlying mechanisms, and generating numerous mouse mutants mimicking rare human repair syndromes. He discovered that accumulating DNA damage causes aging and triggers an anti-aging 'survival' response, that resembles calorie restriction (CR). Applying 30% CR dramatically delayed accelerated aging in mouse repair mutants by reducing DNA damage, explaining the anti-aging mechanism of CR. Translation to the first progeroid DNA repair patients even surpassed the enormous benefits in mice, revising nutritional guidelines for these syndromes. These clinical implications extend to counteracting neurodegeneration, side effects of chemo/radiotherapy, and surgery-related ischemia reperfusion injury. Jan Hoeijmakers heads research teams in the Erasmus Medical Center (Rotterdam), Princess Máxima Center for Pediatric Oncology (Utrecht), and CECAD (Cologne). For his scientific achievements he has obtained numerous (inter)national awards and distinctions.

Juan Carlos Izpisua
Salk Institute for Biomedical Studies,
La Jolla, US

Dr. Juan Carlos Izpisua Belmonte is the Roger Guillemin Chair and Professor in the Gene Expression Laboratory at Salk Institute for Biological Studies, Director of Altos Institute of Science in San Diego. During life's early stages cells display high levels of plasticity, regeneration and resilience against stress, disfunction and injury, which are key features of human health. Dr. Juan Carlos Izpisua Belmonte, has contributed towards understanding the molecular basis underlying embryogenesis and early postnatal life, as well as gained insights into how to program and rejuvenate adult and diseased cells. He is developing technologies to program cells to states similar to those observed in the early, healthy stages of life, with the objective of developing universal health therapeutics to overcome human.

William Mair
Associate Professor of Molecular Metabolism
Harvard T.H. Chan School of Public Health,
Boston, US

William Mair completed his BSc in Genetics and PhD in Biology at University College London, UK. He carried out his postdoctoral training at The Salk Institute for Biological Studies in La Jolla, before joining Harvard as an Assistant Professor in November 2011. He was promoted to Associate Professor of Molecular Metabolism in 2017.

The Mair lab studies mechanisms that mitigate the risks of aging, with a focus on metabolic flexibility and how changes to food intake can impact the aging process.

Brendan Manning
Harvard T.H. Chan School of Public Health,
Boston, US

Brendan Manning is a Professor and Acting Chair in the Department of Molecular Metabolism at the Harvard T.H. Chan School of Public Health and affiliated Professor in the Department of Cell Biology at Harvard Medical School, and a Faculty Member of the Dana-Farber/ Harvard Cancer Center. Professor Manning received his Ph.D. from Yale University and was a postdoctoral fellow in the laboratory of Lewis Cantley at Harvard Medical School. Research in the Manning laboratory is focused on defining the interface between cell signaling and metabolic networks, with an emphasis on PI3K-mTOR signaling in physiology, cancer, metabolic diseases, neurological disorders, and aging.

Pura Muñoz
Pompeu Fabra University and ICREA,
Barcelona, Spain
Spanish Center for Cardiovascular Research,
Madrid, Spain

Pura Muñoz-Cánoves studied Pharmacology at the University of Valencia. She obtained her PhD in Biology at the Madrid Autonomous University for work carried out at The Scripps Institute, and did postdoctoral work at University of California-San Diego and Scripps Institute, and in 1995 she joined the Cancer Institute in Barcelona. In 2002 she moved to the Center for Genomic Regulation, and became coordinator of the Cell Biology Unit at the Pompeu Fabra University, supported by ICREA, in 2009. She is an EMBO Member. Since 2016, she holds a double appointment at the Spanish National Cardiovascular Research Center (CNIC) in Madrid.

Angela Nieto
Institute of Neurosciences, CSIC-UMH,
Alicante, Spain

Angela Nieto is Full Professor at Institute of Neurosciences (CSIC-UMH) in Alicante, Spain. She is President of the International Society of Developmental Biology and Vicechair of EMBL Council. After her PhD in 1987 (*Universidad Autónoma*, Madrid) she worked at Institute for Biomedical Research (CSIC-UAM) in Madrid and at National Institute for Medical Research in London. She joined the Cajal Institute in Madrid in 1993, and from then on she has led a research group interested in cell plasticity. Their main contribution has been the impact that the reactivation of developmental programs has in adult disease, including tumour progression and organ degeneration.

Thomas A. Rando

Director of the Broad Stem Cell Research Center at the University of California, Los Angeles, US

Thomas A. Rando, MD, PhD is Director of the Broad Stem Cell Research Center at the University of California, Los Angeles, where he is Professor of Neurology and of Molecular, Cell and Developmental Biology. Research in the Rando laboratory concerns the basic biology of stem cells how their function is altered in degenerative diseases and during aging. Groundbreaking work from his laboratory using heterochronic parabiosis showed that the age-related changes in stem cell function can be reversed by a youthful environmental. Dr. Rando has received many awards including an NIH Director's Pioneer Award, and he is an elected member of the National Academy of Medicine and the American Academy of Arts and Sciences.

Manuel Serrano
Aging & Metabolism Group Leader
Institute for Research in Biomedicine - IRB Barcelona
Barcelona, Spain

Manuel Serrano is recognized in the fields of tumor suppression, senescence, aging and reprogramming. In 1993, he reported the discovery of the gene p16. This gene is among the most important anti-cancer genes but also a key inducer and marker of cellular senescence. Serrano pioneered the generation of genetically-modified mice resistant to cancer. Also, the Serrano laboratory demonstrated that cellular reprogramming into pluripotency is possible within tissues *in vivo* (Advance of the Year 2013, by Nature Medicine). The focus of his laboratory is to apply their knowledge on senescence and reprogramming to treat degenerative diseases and aging.

Dario R. Valenzano
Max-Planck Institute for Biology of Ageing
Cologne, Germany

Dario Riccardo Valenzano is full professor at the Friedrich Schiller University in Jena (Germany) and senior research group leader at the Leibniz Institute on Aging - Fritz Lipmann Institute (FLI).

He completed his PhD in neuroscience in Italy and did a postdoc with Anne Brunet at Stanford University. In 2013, he became group leader at the Max Planck Institute for Biology of Ageing and PI at the CECAD research center in Cologne.

The Valenzano lab studies how species in nature evolved short/long lifespans and explores the role of gut microbes during host aging. Their main model system is the naturally short-lived turquoise killifish (Nothobranchius furzeri), which they study in the lab and in their natural habitat in the African savannah.

cnio-CaixaResearch
FRONTIERS
MEETINGS

Madrid 9—10 May 2022

Molecular, Cellular and Organismal Drivers of Aging

Poster Session

cnio stop cancer

1 HIV-induced cellular senescence in patients living with HIV is decreased *ex-vivo* by Dasatinib + Quercetin senolytics

Nuria Climent[1], Víctor Casanova[1], Maria Jose Maleno[1], Andrea Rodríguez-Agustín[1], Sonsoles Sánchez-Palomino[1], Tània González[1], Carmen Hurtado[1], Esteban Martinez[2], Josep Mallolas[2], Juan Ambrosioni[2], Jose M. Miro[3] and **José Alcamí[2,4]**

[1]Fundació Clínic per a la Recerca Biomèdica (FCRB), Barcelona, Spain
[2]Hospital Clinic of Barcelona, Barcelona, Spain
[3]Hospital Clinic – IDIBAPS. University of Barcelona, Barcelona, Spain
[4]AIDS Immunopathogenesis Unit. Instituto de Salud Carlos III, Madrid, Spain

Background and objectives

Despite virologic suppression on antiretroviral therapy (ART), people living with HIV (PLWH) display chronic inflammation and accelerated aging that makes them more vulnerable to age-related diseases. Research in cellular aging has identified key biomarkers that define senescent cells (SC) and senolytic drugs. These markers include: SA-βGal, p16INK4a, ϒ-H2AX, IL-6, Bcl-II and uPAR/CD87. We studied SC biomarkers and the effect of ART in SC from PLWH with acute (PHI) or advanced (ADV) HIV-infection. Also we analyzed the impact of Dasatinib+Quercetin (D+Q) treatment on senescent cells from PLWH *ex vivo*.

Methods

PLWH, from two cohorts with PHI and ADV infection, before and after a year on ART, and a group of HIV-negative controls (NC) matched by sex and age were included. SC biomarkers, expression of HIV-Gag protein (KC57) and viability were assessed by flow cytometry on T-cells of those 3 cohorts (n=8). D+Q senolytic drugs were added during 3 days to PBMC cultures.

Results

SC markers such as SA-βGal, p16INK4a, ϒ-H2AX and Bcl-II were increased in CD4+ and CD8+ T-cells ($p<0.05$), especially in ADV vs PHI, and NC. One year on ART did not drop their levels. IL-6 was also higher in CD4+ and CD8+ T-cells from ADV, and ART could normalize these levels ($p<0.05$). D+Q senolytic drugs reduced the expression of SC markers as SA-βGal, ϒ-H2AX and IL-6 ($p<0.05$) in CD4+ T cells from PLWH when added to cell cultures "*ex vivo*". This fall was coupled to a rise in cell mortality induced by D+Q and a decrease in the number of infected CD4 lymphocytes as determined by the intracellular expression of HIV-Gag protein.

Conclusions

1. HIV-1 infection raises SC biomarkers in T cells. 2. ART cannot reverse biomarkers of cellular aging excepting IL-6 levels in T cells. 3. *Ex vivo* D+Q senolytic treatment decreased SC biomarkers and reduced the number of HIVinfected lymphocytes. 4. Senolytics could be useful to reverse cellular senescence, specially in advanced PLWH.

Supported by La Caixa Foundation, Gilead Sciences Fellowship, Spanish AIDS Research Network and HIV Unit, Hospital Clinic, Barcelona, Spain.

4EBP1 is a critical target for the efficacy of chimeric mTOR Inhibitors but is dispensable for feedback suppression of receptor tyrosine kinases.

Jacob A. Boyer, Neal Rosen

Molecular Pharmacology and Chemistry Program, Memorial Sloan Kettering Cancer Center, New York, US

mTOR kinase nucleates two distinct protein complexes: mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2). Each complex controls different aspects of cell growth and both are frequently hyperactivated in human cancer. Small molecule inhibitors of each complex are clinically employed but are limited by a number of factors. Allosteric inhibitor Rapamycin incompletely inhibits mTORC1 and activates mTORC2. ATP competitive inhibitors such as AZD8055, block mTORC1 and mTORC2 at equipotent doses but relieve feedback inhibition of receptor tyrosine kinases. Here we use newly developed chimeric mTOR inhibitors to show that mTORC1 and specifically eIF4E binding protein 1 (4EBP1) is a sufficient target for the efficacy of mTOR inhibitors. We also show that feedback reactivation of receptor tyrosine kinases results from mTORC2 but not mTORC1 inhibition. Such reactivation of Receptor Tyrosine Kinases requires de-novo protein translation, which can proceed in an eIF4E independent manner. Such information supports the development of mTORC1 selective inhibitors for treatment of mTOR dependent cancers.

3

A mechanism of mTORC1 activity modulation mediated by chaperones

Sofía Cabezudo[1], Natalia Cuervo[1], Marina Serna[1], Solip Park[2], Alejo Efeyan[3], Oscar Llorca1*

[1]Structural Biology Programme, Macromolecular Complexes in DNA Damage Group, Spanish National Cancer Research Centre (CNIO), Madrid, Spain
[2]Structural Biology Programme, Computational Cancer Genomics Group, Spanish National Cancer Research Centre (CNIO), Madrid, Spain
[3]Molecular Oncology Programme, Metabolism and Cell Signaling Group, Spanish National Cancer Research Centre (CNIO), Madrid, Spain
*Correspondence: ollorca[a]cnio.es

Cells are continuously adapting to changes in nutrients and energy availability to preserve their growth and survival. The communication between metabolic fluctuations, cellular sensors and downstream processes form a tightly modulated signaling cascade mainly orchestrated by the mammalian target of rapamycin complex 1 (mTORC1). The R2TP complex, one of the most elaborate HSP90 cochaperone, is essential for the stability, assembly and maturation of mTOR complexes, as well as all other members of the PIKK family of kinases. However, little is known about how mTOR is assembled into an active complex depending on the nutrient context. In this sense, components of the R2TP complex participate in the modulation of mTORC1 activity the context of glucose/glutamine (1). Moreover, WAC (WW domain containing adaptor with coiled-coil), a protein proposed as a tumor suppressor, is also involved in this modulation (2), although the molecular mechanism is not defined.

We have characterized the function of WAC and the R2TP chaperone system in the activation and modulation of mTORC1. In this sense, by using WAC deficient cells we have defined the modulatory role of WAC over mTORC1 activation in several nutrient contexts. Moreover, by combining endogenous protein interaction and mass spectrometry analysis we have characterized that WAC and components of the R2TP form a transient and regulatory complex with mTORC1, in response to specific nutrients, helping to preserve metabolic homeostasis. In addition, a comprehensive computational cancer genomic analysis suggests a synergistic role of this new modulator axis in tumorigenesis in different cancer types.

Overall, our results suggest a novel mechanism mediated by chaperones that regulates mTORC1 activation in the context of specific nutrients. We anticipate that a better characterization of this chaperone-mediated mechanism will have implications in understanding the role of this new modulatory axis in cancer.

1. Kim, S. G. et al. (2013) 'Metabolic Stress Controls mTORC1 Lysosomal Localization and Dimerization by Regulating the TTT-RUVBL1/2 Complex', Molecular Cell. Cell Press, 49(1), pp. 172–185. doi: 10.1016
2. David-Morrison, G. et al. (2016) 'WAC Regulates mTOR Activity by Acting as an Adaptor for the TTT and Pontin/Reptin Complexes', Developmental cell. NIH Public Access, 36(2), pp. 139–51. doi: 10.1016

Implicating cellular senescence in disease: Genetics as a bridge from molecular models to population data

Neil Robertson[1], Ryan Silk[1], Jo Mattocks[1], Colin Semple[1], Stefan Schoenfelder[2], **Tamir Chandra[1]**

[1]MRC Human Genetics Unit, University of Edinburgh, Edinburgh, UK
[2]The Babraham Institute, Cambridge, UK

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. Early results of senolytic studies of premature ageing phenotypes were promising, leading to investigations of acute pancreatitis, lung fibrosis and type-2 diabetes.

Nevertheless, directly implicating senescence in human disease 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 by using tissue specific interactions to connect candidate genes with disease variants and charting the overlap of tissue specific interactions and disease risk to link cell type and disease (for example the risk for multiple sclerosis could be explained by CD8 T-cell interactions but myeloid specific interactions). Large GWAS studies have accumulated, linking particular genetic loci to disease risks.

To bridge the gap between our molecular understanding of senescence and the relevance in human phenotypes, we have integrated PCHi-C in senescence with these large disease resources - exploring the roles of acute senescence in human disease states, leading to a prioritisation of conditions where senescence is involved. To further our mechanistic understanding, we compare the Hi-C interactions with single-cell ATAC seq data.

5

Reconstitution of chaperone complexes involved in the assembly and activation of mTOR complexes

Natalia Cuervo-Iturrioz[1], Marina Serna[1], Ana González-Corpas[1], Sofía Cabezudo[1] and Oscar Llorca

[1]Structural Biology Programme, Macromolecular Complexes in DNA Damage Group, Spanish National Cancer Research Centre (CNIO), Madrid, Spain

mTORC1 assembly and activation requires the participation of R2TP, a complex composed of RUVBL1, RUVBL2, RPAP3 and PIH1D1 proteins, working in concert with the HSP90 chaperone. This pathway needs of additional factors whose function is still poorly characterized. The TTI1-TTI2-TELO2 complex (TTT hereafter) for instance, participates in delivering mTOR to the R2TP-HSP90 chaperone complex and it also regulates R2TP-mediated ATP-hydrolysis (Pal M. et al., 2021, Cell Rep 36(1)). WAC (WW domain containing adaptor with coiled-coil) has also been implicated in the activation of mTORC1 and it has been proposed to form a complex with the R2TP complex based on pull-down experiments from cells. WAC also seems to participate in other cellular processes, such as the modulation of autophagy (David-Morrison et al., 2016, Dev Cell 36(2), 139-151) or the activation of Polo-like Kinase 1 (Qi et al., 2018, Cell Reports 24, 546–556).

We have cloned, expressed and purified WAC, testing their expression in E. coli, insect and mammalian cells, and characterizing which system behaves better to produce WAC protein in quality and quantity suitable for biochemical and structural studies. Purified WAC was used to analyze its direct interaction with several components of the R2TP system. *In vitro* and using purified proteins and pull-down experiments, recombinant WAC directly interacts with the RUVBL1-RUVBL2 complex in the presence and in the absence of RPAP3-PIH1D1 and, to a lesser extent with the RPAP3-PIH1D1 alone. WAC also interact with some of the components of the TTT complex. These results reveal that WAC forms a direct complex with the R2TP machinery implicated in mTORC1 assembly and activation. Further work will be required to elucidate what is the role of WAC in this system.

Mitochondrial DNA variants in oncogenesis

Cristina De Jesús-Sen[1*], Zoe J Golder[2,3*], Claudia Calabrese[2,3*], Yaobo Xu[*4], Iacopo Bicci[1,2], Lisa Tilokani[2], Julien Prudent[2], Gavin Hudson[4], Mauro Santibanez-Koref[4], Ihab Abdulkader[5], Jose Alberto Garcia-Sanz[1], Eduardo Ruiz-Pesini[6], Patrick F. Chinnery[2,3,$], Aurora Gomez-Duran[1,2,3,$]

[1]MitoPhenomics Lab. Centro de Investigaciones Biológicas, CSIC, Madrid, Spain
[2]MRC Mitochondrial Biology Unit, Cambridge, UK
[3]Department of Clinical Neurosciences, University of Cambridge, UK
[4]Institute of Genetic Medicine, Newcastle University, NE1 3BZ, UK.
[5]Servicio de Anatomía Patológica, Universidad de Santiago de Compostela, Santiago de Compostela, Spain
[6]Departamento de Bioquímica, Biología Molecular y Celular; CIBER de Enfermedades Raras (CIBERER). Universidad de Zaragoza, Zaragoza, Spain
[*]Correspondence to: aurora.gomez[a]cib.csic.es

Maternally inherited polymorphic variants of mitochondrial DNA (mtDNA) have been associated with the risk of developing a wide range of different diseases including several types of cancer. Here, by using a collection of different cancer cell lines, carrying some of this population variants in the mtDNA, and a mice model to develop xenografts, in order to understood how the subtle differences in the mtDNA can regulate oncogenesis and metastasis capacity *in vivo* and cell migration *in vitro*. We show that mTORC1 and HIF1a activation regulates a complex metabolic pathway involving mitochondrial biogenesis, autophagy, reactive oxygen species levels, cell growth and carcinogenesis. Furthermore, mtDNA variants can modify the sensitivity to different drug treatments, so mtDNA should have been taken into account in the cancer diagnosis and treatment.

7

Undiscovered of regulators of senescence-associated secretory phenotype mediated by small extracellular vesicles

Sergio Lucio-Gallego[1,&], Rocío Mato-Basalo[1,&], Carmen Alarcón-Veleiro[1], Mónica Carrera[2], Lola Gutiérrez[3], Concha Gil[3], Jesús Mateos[4], María C Arufe[1,*] and **Juan Fafián-Labora[1,*]**

[1]Grupo de Investigación en Terapia Celular y Medicina Regenerativa, Departamento de Fisioterapia, Medicina y Ciencias Biomédicas, Facultad de Ciencias de la Salud, Centro de Invesigaciones Científicas Avanzadas (CICA), Universidade da Coruña, INIBIC-Complejo Hospitalario Universitario A Coruña (CHUAC), Coruña, Spain
[2]Department of Food Technology, Institute of Marine Research (IIM), Spanish National Research Council (CSIC), Vigo, Spain
[3]Proteomics Facility-Complutense University and Scientific Park Foundation of Madrid, Madrid, Spain
[4]Grupo de Farmacología Clínica (FarmaCHUS). Instituto de Invest. Sanitaria de Santiago (IDIS), Hospital Clínico Universitario de Santiago de Compostela. Santiago de Compostela, Spain
[&]Shared the first author
[*]Corresponding author: maria.arufe[a]udc.es; juan.labora[a]udc.es

Cellular senescence is a process characterised by a stable cell-cycle arrest and the capacity to modify the microenvironment through the senescence-associated secretory phenotype (SASP), where cytokines, extracellular matrix proteins and proteases, as well as other factors that alter the behaviour of neighbouring cell have been found driving aging and age-related diseases. Small extracellular vesicles (sEV) are particles released by cells whose content is a mirror of the cells they come from. sEV are a new fashion intercellular communication way. In the last years, we reported that sEV are involved in the paracrine senescence transmission, denominated non-classical SASP. They have high potential to develop senomorphics, which are drugs that modulate SASP to treat age-related diseases.

In this project, we want to find a proteomic signature of the emerging non-classical SASP mediated by sEV. For that, we performed the identification, quantification, and comparison of proteome of senescent mesenchymal stem cells 1) with classical SASP (oncogenic induced senescence (OIS)), 2) with non-classical SASP (Knock-out RELA) and 3) without non-classical SASP (knock-out RAB27A (sEV biogenesis pathway) using the shotgun proteomic technique TMT. Comparative proteomic analysis identified 4099 proteins of which 25 were differentially regulated (11 down and 14 up) by non-classical SASP in comparison. The functional enrichment analysis indicated that metabolic pathways related to COPI-mediated anterograde transport, glycine degradation, Intra-Golgi traffic and retrograde transport at the Trans-Golgi-Network are involved in non-classical SASP.

This study has provided the first evidence about the importance that Golgi apparatus´ traffic and transport are involved in non-classical SASP. Altogether, these data collectively propose key that will be useful to design new therapeutic strategies in personalised medicine to increase their efficiency to treat age-related diseases.

Funding: JFL was funded by Proof-of-concept from ProteoRed-ISCIII (PPC2020) and Xunta de Galicia, Grant Number ED481D-2021-020. The proteomic analysis was performed in the Proteomics Unit of Complutense University of Madrid, a member of ProteoRed and is supported by grant PT17/0019, of the PE I+D+i 2013- 2016, funded by ISCIII and ERDF." MCA. received a grant from the Spanish National Health Institute Carlos III (PI20/00497).

Peripheral modulation of antidepressant targets MAO-B and $GABA_AR$ by IMDEA-C1 induces mitohormesis and delays aging

Luis Filipe Costa-Machado[1], Esther Garcia-Dominguez[2], Rebecca L. McIntyre[3], Andrea Tapia-Gonzalez[4], Álvaro Ballesteros-Gonzalez[5], Jose Luis Lopez-Aceituno[1], Tobias Eisenberg[6,7,8], Jesús Gomez[9], Adrian Plaza[1], Aranzazu Sierra-Ramirez[1], Manuel Perez[9], David Villanueva-Bermejo[10], Tiziana Fornari10, Gonzalo Herradon[11], Sebastian J. Hofer[6,7,8], Christoph Magnes[12], Frank Madeo[6,7,8], Isabel del Pino5, Maximo-Ibo Galindo[4,13,14], Riekelt H. Houtkooper[3], Diego Megias[9], Jose Viña[2], Mari Carmen Gomez-Cabrera[2], **Pablo J. Fernandez-Marcos[1,*]**

[1]Metabolic Syndrome Group – BIOPROMET. Madrid Institute for Advanced Studies - IMDEA Food, CEI UAM+CSIC, Madrid Spain.
[2]Freshage Research Group, Department of Physiology, Faculty of Medicine, CIBERFES, Fundación Investigación Hospital Clínico Universitario/INCLIVA, University of Valencia, Valencia, Spain.
[3]Laboratory Genetic Metabolic Diseases, Amsterdam Gastroenterology, Endocrinology, Metabolism, Amsterdam Cardiovascular Sciences, Amsterdam UMC, University of Amsterdam, Amsterdam, Netherlands.
[4]Developmental Biology and Disease Models Group, Centro de Investigación Príncipe Felipe, Valencia, Spain.
[5]Neural Plasticity Group, Centro de Investigación Príncipe Felipe, Valencia, Spain.
[6]Institute of Molecular Biosciences, NAWI Graz, University of Graz, Graz, Austria.
[7]BioTechMed Graz, 8010, Graz, Austria.
[8]Field of Excellence BioHealth – University of Graz, Austria.
[9]Confocal Microscopy Unit, Biotechnology Programme, Spanish National Cancer Research Centre (CNIO), Madrid, Spain.
[10]Department of Production and Characterization of Novel Foods, Institute of Food Science Research (CIAL UAM-CSIC), Madrid, Spain.
[11]Lab. Pharmacology, Faculty of Pharmacy, Universidad CEU San Pablo, Madrid, Spain.
[12]HEALTH-Institute for Biomedicine and Health Sciences, Joanneum Research Forschungsgesellschaft mbH, Graz, Austria.
[13]Instituto Interuniversitario de Investigación de Reconocimiento Molecular y Desarrollo Tecnológico (IDM), Universitat Politècnica de València, Universitat de València. Valencia, Spain.
[14]UPV-CIPF Joint Research Unit "Disease Mechanisms and Nanomedicine". Centro de Investigación Príncipe Felipe, Valencia, Spain.

Despite mounting evidence, the molecular link between metabolism and psychiatric status is not well understood. We show that IMDEA-C1, a metabolite belongind to a family plant-produced compounds with anti-depressant properties, improves mitochondrial function and metabolic parameters, and extends healthspan. Treatment with IMDEA-C1 induced a transient mitochondrial depolarization, a strong mitophagy response, and the AMPK compensatory pathway both in cultured C2C12 myotubes and in mouse liver, BAT and muscle. Mechanistically, simultaneous modulation of monoamine-oxidase B and GABA-A receptor, targets of IMDEA-C1, reproduced IMDEA-C1-induced mitochondrial improvements. Diet-induced pre-diabetic mice improved their glucose tolerance, liver steatosis and HOMA-IR after treatment with IMDEA-C1. IMDEA-C1 or a combination of MAO-B and $GABA_AR$ modulators extended the lifespan of *Caenorhabditis elegans* and *Drosophila melanosgaster*. Finally, 2 year-old mice treated with IMDEA-C1 delayed frailty onset by improving their glycemia, exercise performance and strength. Our results reveal a link between improved psychiatric status and healthspan extension through peripheral mitohormesis.

9

Dietary methionine sustains liver regeneration under ketogenic diet feeding

Herrera LV[1], Moral-Sanz J[2], Garrido M[1], Martin R[5], Colmarejo G[5], Gonzalez D[4], Diaz E[4], Fajardo P[4], Monge Patricia[6], Garrido Alvaro[6], Astudillo Alma M[6], Balsinde J[6,7], Cuenda A[4], Ikonomopoulou MP[2,3,8], **Manuel A. Fernandez-Rojo[1,3]**

[1]Hepatic Regenerative Medicine Laboratory, Madrid Institute for Advanced Studies (IMDEA) in Food, CEI UAM+CSIC, Madrid, Spain
[2]Translational Venomics Laboratory, Madrid Institute for Advanced Studies (IMDEA) in Food, CEI UAM+CSIC, Madrid, Spain
[3]School of Medicine, The University of Queensland, Brisbane, Herston, Australia
[4]Department of Immunology and Oncology, Centro Nacional de Biotecnología/CSIC, Madrid, Spain
[5]Bioinformatic Unit, Madrid Institute for Advanced Studies (IMDEA) in Food, CEI UAM+CSIC, Madrid, Spain
[6]Instituto de Biología y Genética Molecular, Consejo Superior de Investigaciones Científicas (CSIC), Valladolid, Spain
[7]Centro de Investigación Biomédica en Red de Diabetes y Enfermedades Metabólicas Asociadas (CIBERDEM), Madrid, Spain
[8]Institute for Molecular Bioscience, The University of Queensland, Brisbane, Herston, Australia

Methionine restriction (MR) protects against diet-induced obesity, ameliorates liver steatosis and improves glycemic control that translates in an extension of the lifespan together with a significant amelioration of age-related pathologies. Moreover, this is accompanied by alteration of the plasma concentrations of IGF-1, FGF-21, adiponectin and leptin, major nutrient- and stress-sensing hormones. Most importantly, the response to MR is conserved throughout phylogeny including humans. Our current investigations show that Ketogenic Diet (KD)-feeding is deleterious for overcoming the loss of liver mass after partial hepatectomy (aPHx) in healthy C57BL/6 mice. KD has been proposed as a nutritional intervention to reduce non-alcoholic fatty liver disease (NAFLD) and its progression to nonalcoholic steatohepatitis (NASH). However, KD does not restore liver regeneration in diet-induced-NASH (MCD-NASH) or Ob/Ob diabetic mice, both characterized by impaired liver regeneration, and the majority of them died between the 24-48h aPHx. KD is almost depleted of methionine, an essential amino acid involved in vital cellular functions. Accordingly, and related to methionine metabolism, RNAsequencing revealed that KD impairs the expression of major one-carbon and methionine metabolism-related genes in correlation with significant reduced protein levels of GNMT, a methyltransferase essential for successful liver regeneration, and Adenosylhomocisteinase (Ahcy), both regulating methylation reactions. Consistent with dietary methionine-deficiency underlying the deleterious effects of KD in liver regeneration, KD supplementation with methionine restored hepatic regeneration and maintained survival aPHx in healthy and MCD-NASH mice. Hence, our data support further studies to comprehend the molecular mechanisms underlying the specific significance of methionine supplementation on KD to promote liver regeneration in chronic liver diseases.

Combination of machine learning and senescence signatures predict the risk of myocardial infarction

10

Guangran Guo[1], Leon D'Cruz[2], Eamonn Cooper[1], Seodhna M. Lynch[1], Victoria McGilligan[1], Shu-Dong Zhang[1], Anthony Bjourson[1], Aaron Peace[1,3,4], Taranjit Singh Rai[1]

[1]Northern Ireland Centre for Stratified Medicine, Ulster University, Derry, Co Londonderry, Northern Ireland, UK
[2]Respiratory Medicine Department and Clinical Trials Unit, Queen Alexandra Hospital, Portsmouth, UK
[3]Cardiovascular Research and Improvement Science (CardioRISC), WHSCT, Northern Ireland, UK
[4]Department of Cardiology, Altnagelvin Hospital, WHSCT, Northern Ireland, UK

Acute coronary syndromes (ACS) are a group of cardiac conditions that reduced blood flow into the heart. One of these conditions is myocardial infarction (MI), which affects 26 million people and is responsible for 4 million deaths in Europe and more than a third of deaths from all causes in developed countries. 33% to 50% acute MI happens in patients >70 years old. Further, 80% acute MI caused death occurred in people over 65 years old implicating aging as biggest risk factor for MI. One cellular process that causes aging is cell senescence. We hypothesise accumulation of senescent cardiac cells may contribute to MI. Discovering specific senescence biomarkers may be able to predict MI risk or provide therapeutic targets. It is well known that senescent cells secrete SASP to enhance senescence and affect neighboring tissues causing further tissue damages and deepen diseases. In this study, ACS patients (n=171, mean age=65.61 ± 10.71) and control group (n=73, mean age=43.88 ± 10.48, 10-year cardiac-episode free) were recruited and their blood plasma was analyzed for senescence biomarkers by using Olink Bioscience. We found senescence biomarkers when combined with machine learning algorithms can accurately predict risk of Myocardial infarction (MI) independent of traditional risk factors, genetics and or environmental factors. To validate these findings in senescent cells we developed senescence cardiac cell models. We introduced senescence to human primary cardiac fibroblasts (from human donors) and human iPSC-derived cardiomyocytes, followed by SAGAL staining, DNA damage assays, proliferating assay to confirm the senescence state. Multi-omic analysis of cardiac cells confirmed the *in-vivo* findings showing a successful deployment of a bedside to bench model of cardiac disease. To conclude, our research not only provides potential senescence biomarkers for diagnostic and therapeutic target for MI patients but also an in vitro model to study these target proteins.

11

From laboratory to the wild: a non-invasive, Nanopore-based method for determining the epigenetic age of mice

Eveliina Hanski[1], Sarah Knowles[1], Susan Joseph[2], Tom Little[3]

[1]University of Oxford, Oxford, UK
[2]King's College London, London, UK
[3]University of Edinburgh, Edinburgh, UK

Age is a key characteristic of an organism, with various processes from immune maturation to reproduction being tied to it. Individuals are typically aged using chronological age, the amount of time passed from date of birth. However, epigenetic age may be more insightful due to its ability to capture inter-individual variation driven by genetic and environmental factors. Methods for acquiring epigenetic age are often invasive or destructive, and many studies have been limited to either laboratory or wild animals, rather than integrating the two. Using faecal samples as a source of mouse DNA, we sequenced bisulphite-converted DNA with Oxford Nanopore's MinION sequencing device to call SNPs and estimate methylation rates at 62 CpG sites across four genes associated with age. With this, we built an epigenetic clock using lab mice and then used it to age wild mice with unknown chronological age. We show that the rate of epigenetic aging is consistent in inbred lab mice living under stable conditions but highly variable in outbred wild mice exposed to changeable environmental factors. By considering established relationships between body mass and chronological age, our data suggest that wild mice are epigenetically multiple times older than lab mice in early life. These findings underline the potential effect of genetic and/or environmental factors on epigenetic aging. Our results demonstrate that epigenetic age can be measured non-invasively from faecal samples, opening possibilities for studying the drivers of epigenetic age over time not only in the laboratory but also in the wild.

Scallop: a novel computational method for the quantification of age-related loss of cell type identity at the single cell level

12

Olga Ibáñez-Solé, Alex M. Ascensión, Marcos J. Araúzo-Bravo, Ander Izeta

Tissue Engineering group, Biodonostia Health Research Institute Computational Biology and Systems Biomedicine group, Biodonostia Health Research Institute
Donostia - San Sebastián, Spain

Aging has been associated with a loss of identity of several cell types, presumably caused by cumulative DNA damage. This phenomenon has been referred to as an increase in cell-to-cell variability, heterogeneity or variation/noise, and measured using various computational methods in several tissues and organisms, with conflicting results. However, it was not clear whether the divergence between studies could be attributed to the methods used for the quantification of noise or to cell type-specific or tissue-specific effects. Single-cell RNA sequencing technologies have allowed quantitative measurements of transcriptional heterogeneity at the single-cell level in an increasing number of tissues. We developed Scallop, an computational method for the quantification of membership of single cells to their assigned cell type cluster, and show that cells with a greater membership are transcriptionally more stable. We used membership to clusters as a measure of transcriptional stability to determine whether there is a generalized age-associated loss of cell type identity, and found great variability between datasets, suggesting that increased transcriptional noise is unlikely to be a universal property of aged tissues. We then focused on the mammalian lung, and analyzed the cell type-specific changes in transcriptional noise and the changes in cell type composition that characterize its aging process, using four murine and two human scRNAseq datasets. We found no conserved pattern of transcriptional noise alteration across datasets. However, we found important changes in the cell type composition, particularly of the immune cell fraction. Plasma cells are enriched both in the murine and in the human aging lung. Alveolar macrophages suffer important changes in abundance, both in murine and in human lung. In humans, we found that distinct and transcriptionally stable subpopulations of alveolar macrophages with different surfactant expression profiles emerge with aging.

13

Inhibition of the neuromuscular acetylcholine receptor with atracurium activates FOXO/DAF-16-induced longevity

Rebecca L. McIntyre, Simone W. Denis, Rashmi Kamble, Marte Molenaars, Michael Petr, Bauke V. Schomakers, Mizanur Rahman, Siddhartha Gupta, Marton L. Toth, Siva A. Vanapalli, Aldo Jongejan, Morten Scheibye-Knudsen, Riekelt H. Houtkooper, **Georges E. Janssens**[1]

[1]Laboratory Genetic Metabolic Diseases, Amsterdam Gastroenterology, Endocrinology, and Metabolism, Amsterdam Cardiovascular Sciences, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands
[2]Center for Healthy Aging, Department of Cellular and Molecular Medicine, University of Copenhagen, Copenhagen, Denmark
[3]Core Facility Metabolomics, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands
[4]Dept. of Chemical Engineering, Texas Tech University, Lubbock, TX, USA.
[5]NemaLife Inc, Lubbock, US
[6]Bioinformatics Laboratory, Amsterdam UMC, University of Amsterdam, The Netherlands

Transcriptome-based drug screening is emerging as a powerful tool to identify geroprotective compounds to intervene in age-related disease. We hypothesized that, by mimicking the transcriptional signature of the highly conserved longevity intervention of FOXO3 (daf-16 in worms) overexpression, we could identify and repurpose compounds with similar downstream effects to increase longevity. Our *in silico* screen, utilizing the LINCS transcriptome database of genetic and compound interventions, identified several FDA-approved compounds that activate FOXO downstream targets in mammalian cells. These included the neuromuscular blocker atracurium, which also robustly extends both lifespan and healthspan in Caenorhabditis elegans. This longevity is dependent on both daf-16 signaling and inhibition of the neuromuscular acetylcholine receptor subunit unc-38. We found unc-38 RNAi to improve healthspan, lifespan, and stimulate DAF-16 nuclear localization, similar to atracurium treatment. Finally, using RNA-seq transcriptomics, we identify atracurium activation of DAF-16 downstream effectors. Together, these data demonstrate the capacity to mimic genetic lifespan interventions with drugs, and in doing so, reveal that the neuromuscular acetylcholine receptor regulates the highly conserved FOXO/DAF-16 longevity pathway.

Longitudinal dynamics of clonal haematopoiesis identifies gene-specific fitness effects

14

Neil A. Robertson[1], **Eric Latorre-Crespo[1],** Maria Terradas-Terradas[2,3], Jorge Lemos-Portela[4], Alison C. Purcell[2,3], Benjamin J. Livesey[1], Robert F. Hillary[5], Lee Murphy[6], Angie Fawkes[6], Louise MacGillivray[6], Mhairi Copland[7], Riccardo E. Marioni[5], Joseph A. Marsh[1], Sarah E. Harris[8,9], Simon R. Cox[8,9], Ian J. Deary[8,9], Linus J. Schumacher[4], Kristina Kirschner[2,3], Tamir Chandra[1]

1. MRC Human Genetics Unit, University of Edinburgh, Edinburgh, UK
2. Institute of Cancer Sciences, University of Glasgow, Glasgow, UK
3. Cancer Research UK Beatson Institute, Glasgow, UK
4. Centre for Regenerative Medicine, University of Edinburgh, Edinburgh, UK
5. Centre for Genomic and Experimental Medicine, Institute of Genetics and Cancer, University of Edinburgh, UK
6. Edinburgh Clinical Research Facility, University of Edinburgh, Edinburgh, UK
7. Paul O'Gorman Leukaemia Research Centre, Institute of Cancer Sciences, University of Glasgow, UK
8. Lothian Birth Cohorts, Department of Psychology, The University of Edinburgh, Edinburgh, UK
9. Department of Psychology, The University of Edinburgh, Edinburgh, UK

Clonal Haematopoiesis of Indeterminate Potential (CHIP) is defined as the expansion of HSCs in healthy aged individuals that results from genetic alterations. Although mostly inconsequential, the constant rate of the acquisition of mutations in HSCs (17 mutations/year) leads to an increasing probability, with respect to age, of a variant occurring in a gene that may alter the complex homeostasis of cell division and lead to the subsequent expansion of somatic clones [1]. As a result, CHIP has been shown to be a condition affecting more than 10% of the population over 65 years of age, with a prevalence that increases dramatically over subsequent decades [2,3]. Further, CHIP is a pre-malignant state linked with a ten-fold increase in the later onset of haematological cancers highlighting the importance of detecting fit clones and predicting their growth at an early stage [2,3]. CHIP is also associated with an increased risk for all-cause mortality, heart disease and ischemic stroke – pathologies where age is a primary risk factor [1]. Unprecedented access to longitudinal data following the dynamics of clonal haematopoiesis in time has allowed us to develop novel mathematical methods to detect and analyse the behaviour of rapidly expanding mutations [4]. First our novel likelihood-based filter for time-series data (LiFT) allows us to accurately detect fastgrowing mutations with before they grow large. LiFT surpasses the current standard of clinical diagnosis of CHIP by detecting highly pathogenic mutations at an early stage of their clonal expansion that would have been missed otherwise. Further, longitudinal data allows us to infer stem cell fitness, or clonal growth speed, associated to cells carrying any mutation or combination of mutations that are unique to each individual. This in stark contrast with previous attempts where the fitness associated to CHIP mutations could only be associated to highly recurrent mutations and was assumed to be uniform across individuals. Our longitudinal approach therefore opens the possibility of personalised clinical management. Finally, we find that there exist gene-specific fitness effects that overcome individual variation. This crucial insight can serve as a basis to inform the screening of CHIP in a clinic.

References:
1 - Jaiswal, Siddhartha, and Benjamin L. Ebert. "Clonal hematopoiesis in human aging and disease." Science 366.6465 (2019): eaan4673.
2 - Jaiswal, Siddhartha, et al. "Age-related clonal hematopoiesis associated with adverse outcomes." New England Journal of Medicine 371.26 (2014): 2488-2498.
3 - Genovese, Giulio, et al. "Clonal hematopoiesis and blood-cancer risk inferred from blood DNA sequence." New England Journal of Medicine 371.26 (2014)
4 - Robertson, Neil A., et al. "Longitudinal dynamics of clonal hematopoiesis identifies gene-specific fitness effects." bioRxiv (2021).

15

Integrated stress response activation is variant specific in mitochondrial disease

Carmen Linares-Andujar[1], Ignacio Monar-Redondo[1], Virginia García-Calvo[1], Aurora Gomez-Duran[1]

[1]MitoPhenomics Lab. Centro de Investigaciones Biológicas Margarita Salas. CSIC, Madrid, Spain
*Correspondence to: Aurora Gomez-Duran: aurora.gomez[a]cib.csic.es

Mitochondrial diseases (MDs) are metabolic disorders characterised by the disruption of the oxidative phosphorylation (OXPHOS), which can be caused by mutations in both mitochondrial (mtDNA) or nuclear genomes. mtDNA is polyploid, several alleles can coexist inside each mitochondrion and cell, in a state called heteroplasmy. Studies on MDs models have recently pointed to the Integrated Stress Response (ISR) as a common stress response in these disorders. However, little is known about the activation of ISR in disease human models or whether it plays a role in mtDNA heteroplasmy regulation. Here, by using several primary cell lines carrying nDNA and heteroplasmic mtDNA variants causing MDs, we studied the role of ISR in MD as well as in heteroplasmy regulation. Our results confirmed high complexity in these responses being pathway as well as variant and complex specific, but independent of mtDNA heteroplasmy load and other bioenergetic parameters. Our findings indicate that further analyses are needed to confirm the role of these responses in MDs and their applicability to the treatment of these disorders.

Senescence biomarkers for predicting risk in COVID-19 patients

16

Seodhna M. Lynch[1], Eamonn Cooper[1], Guangran Guo[1], Victoria E. McGilligan[1], Elaine K. Murray[1], Steven Watterson[1], Priyank Shukla[1], Shu-Dong Zhang[1], Magda Bucholc[1], Darren Mc Daid[1], Joseph McLaughlin[1], Andrew English[1], Rachelle E. Irwin[1], David S. Gibson[1], Colum P. Walsh[2], Anthony J. Bjourson[1], Aaron Peace[1,3], Maurice O'Kane[1,4], Taranjit Singh Rai[1,*]

[1]Northern Ireland Centre for Stratified Medicine, School of Biomedical Sciences, Ulster University, C-TRIC Building, Altnagelvin Area Hospital, Glenshane Road, Derry, UK
[2]Biomedical Sciences Research Institute, University of Ulster, Coleraine, UK
[3]Department of Cardiology, Altnagelvin Hospital, WHSCT, Northern Ireland, UK
[4]Clinical Chemistry Laboratory, Altnagelvin Hospital, Derry~Londonderry, UK
*Correspondence: t.rai[a]ulster.ac.uk; Tel.: (+44) 02871675459.

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has resulted in a global pandemic associated with substantial morbidity and mortality worldwide, with particular risk for severe disease and mortality in the elderly population. Indeed, senescence and aging together, are believed to play a central role in COVID-19 severity and pathogenesis. A deeper understanding of COVID-19 pathophysiology and the involvement of senescence associated secretory phenotype (SASP) is therefore required as a foundation to help identify patients, at an early stage, who are more susceptible to acquiring a more clinically severe COVID-19 infection. This early detection remains a major challenge however largely due to limited understanding of SARS-CoV-2 pathogenesis.

In this study, we investigate whether expression of specific SASP proteins found within plasma of COVID-19 patients can be utilised to predict severity. We performed proteomic profiling of plasma from 400 COVID-19 patients using the Olink Explore 384 Inflammation Panel. Data analysis was performed to identify differentially expressed proteins, which are linked to senescence, whilst taking into account patient hospitalisation status, age and their WHO clinical progression score. We identified molecular changes in the plasma of hospitalised patients compared to non-hospitalised patients. We also identified molecular changes which were associated with increased age. Furthermore, we also identified molecular changes in the plasma of mild patients compared to patients classified as severe according to their WHO clinical progression score.

This study has revealed characteristic protein changes, or specific senescent endotypes (or "sendotypes"), in the plasma of COVID-19 patients, which can used as determinants for predicting COVID-19 severity. We propose that the identification of such sendotypes could be exploited for therapeutic intervention via senolytics in COVID-19.

17

A mouse model for Li-Fraumeni-Like Syndrome with cardiac angiosarcomas associated to POT1 mutations

Paula Martínez, Raúl Sánchez-Vázquez, Rosa Serrano and Maria Blasco

Telomeres and Telomerase Group, Molecular Oncology Program, Spanish National Cancer Centre (CNIO), Madrid, Spain

The shelterin protein POT1 has been found mutated in many different familial and sporadic cancers, however, no mouse models to understand the pathobiology of these mutations have been developed so far. To address the molecular mechanisms underlying the tumorigenic effects of POT1 mutant proteins in humans, we have generated a mouse model for the human POT1R117C mutation found in Li-Fraumeni-Like families with cases of cardiac angiosarcoma by introducing this mutation in the Pot1a endogenous locus, knock-in for Pot1aR117C. We find here that both mouse embryonic fibroblasts (MEFs) and tissues from Pot1a+/ki mice show longer telomeres than wild-type controls. Longer telomeres in Pot1a+/ki MEFs are dependent on telomerase activity as they are not found in double mutant Pot1a+/ki Tert-/- telomerase-deficient MEFs. By using complementation assays we further show that POT1a pR117C exerts gain of function and dominant-negative effects at telomeres. As in human Li-Fraumeni patients, heterozygous Pot1a+/ki mice spontaneously develop a high incidence of angiosarcomas, including cardiac angiosarcomas, and this is associated to the presence of abnormally long telomeres in endothelial cells as well as in the tumors. The Pot1a+/R117C mouse model constitutes a useful tool to understand human cancers initiated by POT1 mutations.

Iron deposition in tissues drives senescence, inflammation and fibrosis

18

Mate Maus[1], V.P. Lopez[1], A.M. Manonelles[2], A.M. Sola[2], Miguel Lafarga[3], K. Meyer[1], F. Hernandez[4], S. Chaib[1], M. Rovira1, M. Sanchez[5], G. Albaiceta[6], R. Fahner[4], A. Agusti[4], J.M. Cruzado[2], M. Serrano[1]

[1]Institute for Research in Biomedicine (IRB), Barcelona, Spain
[2]Nephrology Unit, Bellvitge University Hospital, (IDIBELL), Hospitalet de Llobregat, Spain
[3]Department of Anatomy and Cell Biology, University of Cantabria-IDIVAL, Santander, Spain
[4]Department of Respiratory Medicine, Institut Clínic Respiratori, IDIBAPS, Barcelona, Spain
[5]Department of Basic Sciences, Universitat Internacional de Catalunya (UIC), Sant Cugat del Vallès, Spain
[6]Department of Biología Funcional, Universidad de Oviedo, Spain

Estimates are that fibrotic diseases account for 45% of all mortality in the elderly population of the western world. Fibrosis is the progressive replacement of healthy tissues by a scar tissue that can affect any organ. Anti-fibrotic therapies achieve slow-down in progression, however, lack of biomarkers for early detection of fibrogenesis limits their utility in clinics. Here, we find that fibrotic tissues accumulate iron. We demonstrate that iron accumulation alone is sufficient to explain various hallmarks of fibrotic diseases, including activation of myofibroblasts, collagen deposition, inflammation, infiltration of neutrophils and macrophages, vascular rarefaction, and accumulation of senescent cells. We find that disrupted vascular barrier function, disrupted blood flow and associated hemolysis are drivers of tissue iron deposition in fibrosis models. Additionally, we find that senescent cells also secrete and accumulate iron and thereby promote inflammation and tissue remodeling. Finally, we show that magnetic resonance imaging (MRI)-based iron detection is a powerful tool for predicting fibrosis in chronic kidney disease patients outperforming currently used clinical biomarkers. In summary, we find that tissue iron accumulation is a key driver of fibrosis with diagnostic and therapeutic relevance.

19

A mouse model for the Néstor-Guillermo Progeria Syndrome phenocopies bone alterations associated with aging

Pablo Mayoral[1,2,#], Clea Bárcena[1,#], Pedro M. Quirós[1,2], Francisco Rodríguez[1], Daniel Maeso[1], José M. P. Freije[1,2,*], and Carlos López-Otín[1,2,*]

[#]P.M. and C.B. contributed equally to this study
[*]Correspondence to J.M.P.F. and C.L.O.
[1]Departamento de Bioquímica y Biología Molecular, Facultad de Medicina, Instituto Universitario de Oncología (IUOPA), Universidad de Oviedo, Oviedo, Spain
[2]Centro de Investigación Biomédica en Red de Cáncer (CIBERONC), Spain

Néstor-Guillermo Progeria Syndrome (NGPS) is an accelerated-aging disease that phenocopies features of classical progeria such as growth retardation, lipodystrophy and alopecia; however, the bone phenotype is more severe and survival is extended compared to HGPS patients, developing a chronic progeria-like syndrome where bone alterations constitute the greatest challenge for their life quality and lifespan.

NGPS is caused by homozygous c.34G>A (p.Ala12Thr) mutation in BANF1, which encodes a protein called barrier-to-autointegration factor 1 (BAF). BAF interacts with DNA and nuclear lamina related proteins, being implicated in nuclear envelope assembly and generating profound nuclear abnormalities when mutated. Recently, BAF has been related to DNA damage responses in oxidative stress, through the binding and inhibition of PARP1, and DNA double-strand breaks (DSB) repair pathways, by regulating non-homologous end joining (NHEJ). However, the Other Information: molecular basis that underlies the progeroid phenotype seen in humans remains poorly understood.

In this work we have generated mouse models with different Banf1 alterations, including a mouse that carries the NGPS mutation. Banf1A12T/A12T mice show a milder phenotype compared to human with no changes in lifespan or mortality compared to WT littermates. However, mutant mice resemble the bone alterations seen in NGPS in physiological and stress conditions as ovariectomy-derived osteoporosis, iron overdose and aging. Further, the NGPS mutation in a LmnaG609G progeria background elicits an extreme phenotype with reduced lifespan and severe bone alterations. Currently, we are performing RNA-seq analysis in bone and bone marrow to determine the transcriptional changes responsible of these bone alterations. Together, our results validate Banf1A12T/A12T as an appropriate mouse model of NGPS and to study bone phenotype of premature aging, may contributing to develop new intervention strategies in these patients.

A genetic model of enhance nutrient signaling drives premature aging

20

Ana Ortega-Molina[1,2*], Cristina Lebrero-Fernández[1,2], Alba Sanz[1], Patricia Gonzalez[3], Eduardo Caleiras[3], María Casanova-Acebes[4], Alejo Efeyan[1*]

[1]Metabolism and Cell Signaling Laboratory. Spanish National Cancer Research Centre (CNIO), Madrid, Spain
[2]Metabolism in cancer and aging Laboratory, Immune system development and function Department. Centro de Biología Molecular Severo Ochoa (CBMSOCSIC), Madrid, Spain
[3]Histopathology Unit. Spanish National Cancer Research Centre (CNIO), Madrid, Spain
[4]Cancer Immunity Laboratory. Spanish National Cancer Research Centre (CNIO), Madrid, Spain

mTOR signaling pathway plays a significant role in longevity regulating several hallmarks of aging. Genetic or pharmacological inhibition of mTOR signaling with rapamycin/rapalogs has been reported to increased lifespan. Moreover, one of the most efficient interventions against aging is the restriction of dietary intake (DR) that results not only in extended longevity but also delays the onset of age-related pathologies. The beneficiary effects of DR is thought to be, due to inhibition of mTOR signaling. In the presence of cellular nutrients, the Rag GTPases, are responsible for the activation of the mTOR pathway, but there is no genetic proof to support its connection with the modulation of aging. The Rag GTPases work as heterodimeric complexes composed of RagA and RagC and relay information on cellular nutrient levels to mTORC1. In the presence of plentiful nutrient levels, RagA undergoes GTP loading and RagC loads GDP, and this nucleotide configuration allows the binding and recruitment of mTORC1 to the lysosome, an essential step for kinase activation. We used CRISPR/Cas9 technology to engineer a novel mouse strain that expresses a RagC activating mutation (S74N). This mutation has been previously reported to confer higher affinity for GDP rather than GTP and this correlates with increased mTORC1 activity in the absence of amino acids *in vitro*. RagCS74N/+ mice show decreased survival, but surprisingly this is not accompanied with enhance development of tumors. RagCS74N/+ old mice present multiple features of accelerated aging including an imbalance between lymphoid and myeloid populations and augmented inflammation in several tissues together with increased senescence and SASP in damaged tissues. In addition, we also observe increased inflammatory cytokines in blood of RagCS74N/+ old mice related with enhance neutrophil function. When neutrophils are depleted using a specific blocking antibody *in vivo*, RagC S74N/+ old mice extend their survival compared to non-treated mice. These beneficial effects correlate with reduced pro-inflammatory cytokines and reversion of some of the premature aging features. Together, we present the first genetic study where moderate increased activation of mTOR signaling showed a premature aging phenotype that can be alleviated by diminishing circulating myeloid cells.

21

Nutrient and hormonal signaling to mTORC1 as an hepatic GPS

Ana Belén Plata-Gómez[1], Lucía de Prado Rivas[1], Celia De la Calle Arregui[1], Alba Sanz[1], Eduardo Caleiras[2], Ajay Jain[3], Alejo Efeyan[1]

[1]Metabolism and Cell Signaling Group, Molecular Oncology Programme, Spanish National Cancer Research Centre (CNIO), Madrid, Spain
[2]Histopathology Unit, Spanish National Cancer Research Centre (CNIO), Madrid, Spain
[3]Division of Pediatric Gastroenterology, Hepatology and Nutrition, Saint Louis University, Saint Louis, US

The mechanistic target of rapamycin complex I (mTORC1) is a central regulator of metabolism, lifespan and aging by the integration of two major regulatory inputs: nutrients, which activate mTORC1 pathway through the family of Rag GTPases, and growth factors (GFs), which inhibit the Tuberous Sclerosis Complex 1 (TSC1) to allow mTORC1 activation. To understand how the mTOR pathway integrates signals by two related but independent cues, and how mTOR orchestrates metabolism accordingly, we have engineered a mouse model in which systemic and cellular nutrient signaling are deregulated in hepatocytes (Li-TSC1KO RagAGTP/-mice). Our results show that while single activation of mTORC1 through either nutrients or GFs dominantly activates the mTORC1 pathway and abrogates fasting metabolism, simultaneous genetic activation of nutrient and hormonal cues disrupt the zonal identity of central and portal hepatocytes. This perturbation of zonation is correlated with an abrogation of the spatial differences of the programs executed downstream of mTOR. In particular, we have found alterations in the Wnt/βcatenin signaling pathway, which is the major controller of hepatic organogenesis, as well as in the metabolic functions of the liver that depends on hepatocyte segregation. These results indicate that correct nutrient and hormonal signaling to mTORC1 are needed to define hepatocyte identity and properly stablish liver zonation. In parallel, we have addressed a context of total parenteral nutrition, in which the information of nutrient fluctuations to hepatocytes is blurred since the nutritional products are given intravenously. The same abrogation of the zonation as in our genetic model is found in this scenario, manifesting the relevance of the proper sensing of the feeding by the hepatocyte in the establishment of the metabolic architecture of the liver. We are currently deepening in the molecular determinants involved in the development of this aberrant zonation.

Transcriptional reprogramming for cellular rejuvenation

22

Alexandru Plesa

Harvard Medical School,
Boston, US

Aging is the major risk factor for multiple human disorders such as cancer, cardiovascular disease, and neurodegeneration. While the causes of the aging are still being investigated, several cellular functions have emerged as key hallmarks of aging organisms. However, widely used aging assays either focus on specific processes such as senescence and DNA damage, or have little interpretability due to their use of DNA methylation patterns of unknown function. Subsequently, despite recent reports showing the malleability of the aging process, the lack of a comprehensive, scalable, and interpretable aging assay has impeded the discovery of novel age reversal interventions. To address this, here we use current knowledge of cellular biology and gene annotations to build a functional transcriptomic interpretable multi-tissue ensemble (TIME) predictor. Our RNA clock reveals the relative significance of different cellular processes in aging, as well as cell line specific age-related signatures. Moreover, to showcase the utility of our high throughput aging assay, we performed a large-scale age reversal screen in primary human dermal fibroblasts which identified novel cellular rejuvenation targets. Using our functional TIME predictor, we characterized the transcriptomic landscape of fibroblast aging and designed combination genetic interventions for comprehensive rejuvenation. These findings present a new paradigm for aging as a transcriptional state and provide tools for developing cellular rejuvenation therapies.

23

In vitro genetic screen for age reversal in human neurons

Michael Shadpour

MIT Biology, Wyss Institute,
Cambridge, US

Aging is a complex degenerative process that creates great suffering for people, increases the probability of diseases ranging from Alzheimer's to cancer, and places a huge economic burden on global healthcare systems. The ability to reverse or delay age-associated phenotypic changes and diseases would enable people to enjoy longer lives with a higher quality of life in their adult years. To understand these phenotypic changes and how they relate to gene expression, a genetic-phenotypic mapping of primary human cells is needed. Perturb-seq, a pooled CRISPR based screening method single cell sequencing readouts, has been used to form such maps in human cancer cell lines.To create a comprehensive atlas of cell states associated with changes in expression of a given gene, we are performing a genome-wide perturb-seq screen in induced human neurons with single cell RNA and epigenetic sequencing readouts. Despite recent advances in cell therapy and xenotransplantation, progress on neural rejuvenation therapies has lagged due to the brain's complexity and irreplaceability. To help bridge this gap, we are performing this screen in neurons transdifferentiated from primary dermal fibroblasts, which have been shown to preserve key biomarkers of aging. The data generated by this screen will create a first of its kind cell atlas of primary human cells that can be used to gain new insights into fundamental systems biology. In parallel, our group is developing a single cell transcriptomic clock to complement recent advances in single cell epigenetic aging clocks. Applying these aging clocks to the cell atlas, will enable the discovery genetic perturbations that slow or reverse cellular aging. The top putative age reversal perturbations will then be functionally profile to identify improvements key cellular processes. Finally, we will identify and validate combinations of these perturbations to achieve a comprehensive cellular rejuvenation.

Sirt3 dimorphic role in development of hepatocellular carcinoma

24

Arantzazu Sierra-Ramirez, Adrián Plaza, José Luís López-Aceituno, Andrés Pastor-Fernández, Cristina Pantoja, Marta Barradas, Pablo José Fernández-Marcos

Metabolic Syndrome Group – BIOPROMET. Madrid Institute for Advanced Studies - IMDEA Food, Madrid Spain.

One of the most promising targets for anti-ageing approaches are sirtuin proteins. In mammals, Sirtuins are a family of 7 proteins with deacylase or ADP-ribosyltransferase activities, that use NAD^+ in its oxidized form as co-substrate. The equilibrium between NAD^+ and its reduced form (NADH) determines the redox status of the cell; thus, a low redox cellular status will activate sirtuins, that trigger different energy generation pathways. In our laboratory we are focused on the role of the mitochondrial SIRT3 in the development of liver carcinoma.

We have observed that female mice with the *Sirt3* gene specifically ablated in hepatocytes ($Sirt3^{hep-/-}$) were more prone to hepatocellular carcinoma (HCC) development after treatment with the liver carcinogen diethylnitrosamine (DEN) at day 15 and chronic high-fat diet (HFD) feeding, losing the female-specific protection already described in female mice and humans. Our hypothesis is that Sirt3 ablation alters the well-described liver sexual dimorphism, regulated by the transcription factor STAT5b, by which WT females are protected from HCC development. To explore this, we first measured liver function and gene expression in adolescent (15 days) and young (12 weeks) mice and did not detect any effect in the absence of liver Sirt3. We then analyzed livers of mice treated with DEN at day 15, fed in a HFD since weaning, and sacrificed at 8 months of age, when the first liver tumors appear. At this age, female Sirt3-deficient livers had more liver triglycerides and more lipid vacuoles, strong risk factors for HCC development. We next analyzed liver gene expression and found that $Sirt3^{hep-/-}$ female mice showed reduced expression in their livers of Stat5b mRNA, and altered expression of inflammation markers, including cytokines as *Cxcl10, Ccl5, Tgfb, Tgtp1* and the *Stat5b* target *Socs2*. We also observed increased levels of liver fibrosis markers in $Sirt3^{hep-/-}$ females, as *Col1a1*. Interestingly, we found the same alterations in $Sirt3^{hep-/-}$ female mice during liver regeneration after partial hepatectomy, indicating that liver Sirt3 deficiency specifically in females disrupts liver homeostasis during stress situations, such as liver damage/regeneration and tumorigenesis.

25

Effect of human extracellular vesicles-depleted serum in the senescence response of mesenchymal stem cells

Bianca Simonassi-Paiva[1,2], Lana Ribeiro Aguiar[1], Patricia Malard[1,3], João Henrique, Moreira Viana[4], Juliana Lott de Carvalho[1,5], Mark Lynch[2], Neil Rowan[2], Robert Pogue[1,2]

[1]Department of Genomic Sciences and Biotechnology. Catholic University of Brasília, Brasília, Brazil
[2]Biosciences Research Institute. Technological University of the Shannon: Midlands Midwest, Athlone, Ireland
[3]Biocell Laboratory Celular Therapy, Brasília, Brazil
[4]Embrapa Genetic Resources and Biotechnology, Brasília, Brazil
[5]Faculty of Medicine, University of Brasília, Brasília, Brazil

Due to their immunomodulatory potential, mesenchymal stem cells (MSCs) are a relevant tool in cell therapy. The translation of cell culture into a therapeutic environment has enhanced concerns regarding toxicological and adverse immunological effects cells may present for patients, especially if cultured with animal-derived supplements, such as fetal bovine serum (FBS). Human serum (HS) has been shown to be a potential substitute for FBS. Another concern for clinical use of MSCs is the in vitro expansion prior to therapy, which can lead to cellular senescence. Extracellular vesicles (EVs) are naturally secreted by all cell types and are suggested to have immunotherapeutic potential. The aim of this study was to characterize cellular senescence of human MSCs upon treatment with human serum depleted of extracellular vesicles (DHS), in comparison to HS and FBS. To this end, a pool of human serum from six donors was prepared, and depletion of EVs was performed by ultracentrifugation. MSCs from three donors were treated with FBS, HS and DHS starting from passage 4, and senescence was evaluated at passages 5, 7, 9 and 11 by the SA-β-gal assay. Cells were photographed and the program Image J was used for analysis of the percentage of senescent cells at each passage with each treatment. Cultures supplemented with DHS presented with fewer senescent cells than those cultured with HS at all evaluated passages, and fewer senescent cells than those cultured with FBS at passages 5, 7 and 11. Overall, there was no statistical difference between cells supplemented with FBS and HS, but the number of senescent cells after culture with DHS was significantly lower. Furthermore, a difference in response among the three MSCs donors was observed, suggesting that individual cell variability may play a role in senescence response. Our results also showed that DHS did not affect differentiation potential of MSCs, and had a similar profile in cell proliferation as HS.

Robust age prediction based on average methylation per genomic region

26

Daniel J. Simpson[1], Qian Zhao[1], Jan Dabrowski[1], Eric Latorre Crespo[1], Xiao Xiao Sylvie[2], Riccardo E. Marioni[2], Tamir Chandra[1]

[1]MRC Human Genetics Unit, MRC, Institute of Genetics and Cancer, University of Edinburgh, Edinburgh, UK
[2]Centre for Cognitive Ageing and Cognitive Epidemiology, Centre for Genomic and Experimental Medicine, Institute of Genetics and Cancer, University of Edinburgh, Edinburgh, UK

Recent studies suggest that rejuvenation can be achieved via partial reprogramming. To effectively test partial reprogramming, mouse models are the safest alternative. However, we have found that the recent epigenetic clocks developed for mouse RRBS data have variable success rates. We tested multiple mouse epigenetic clocks on various datasets and found significantly poor correlations between predicted and chronological age. Among the datasets we predicted epigenetic age, we observed that coverage and read depth varied dramatically, which may explain the poor age prediction. We have developed RRBS mouse clocks that use average methylation over large regions (termed regional epigenetic clocks), rather than individual CpGs. We have demonstrated that a window size between 2 and 6 Kb will generate a robust epigenetic clock that is transferable across multiple RRBS platforms and experiments, and outperforms current RRBS mouse clocks.

27

Exploring the role of nucleolar stress in ageing and neurodegeneration

Oleksandra Sirozh, Vanesa Lafarga, Anabel Saez-Mas, Oscar Fernandez-Capetillo

Spanish National Cancer Research Centre, CNIO,
Madrid, Spain

Amyotrophic lateral sclerosis (ALS) is a deadly neurodegenerative disease with no cure, characterised by the progressive death of spinal motor neurons and subsequent paralysis. One of the most common ALS-driving mutations is a hexanucleotide repeat expansion in C9ORF72. Translation of this region gives rise to a series of dipeptide repeats (DPRs) out of which two, poly(PR) and poly(GR), are toxic. Although these arginine-rich (R-rich) peptides were shown to accumulate at nucleoli, and to disturb RNA metabolism, the mechanism of toxicity remained elusive.

Our previous work *in vitro* revealed that R-rich DPRs avidly bind to nucleic acids, displacing chromatin and RNA-binding factors from DNA and RNA, respectively. This leads to cell death through inhibition of multiple processes using nucleic acid substrates, the most prominent of which are ribosome biogenesis and translation. To evaluate the effects of R-rich DPRs *in vivo*, we developed a novel mouse model which enables organism-wide expression of (PR)97. Surprisingly, expression of the peptide led to a lethal premature ageing phenotype within 3 months. Molecular and cellular biology analyses revealed an accumulation of nucleolar stress and ribosomal proteins, suggesting that the pathology is reminiscent to a class of diseases known as ribosomopathies.

Supporting this view, DPR toxicity *in vitro* is ameliorated by the mTOR inhibitor rapamycin, or by downregulation of MYC, both of which are known to reduce ribosome biogenesis and to extend lifespan in mammals. Importantly, rapamycin extends the survival of (PR)97 mice.

Altogether, we describe a novel mouse model with nucleolar-stress driven ageing, revealed that the pathology caused by poly(PR) DPRs is parallel to ribosomopathies, and identified the nucleolus as a possible therapeutic target in ALS.

cnio-CaixaResearch
FRONTIERS
MEETINGS

Madrid 9—10 May 2022

Molecular, Cellular and Organismal Drivers of Aging

Previous CNIO Frontiers Meetings and CNIO Cancer Conferences

cnio stop cancer

2019

HETEROGENEITY AND EVOLUTION IN CANCER

23/09/2019 – 25/09/2019

Organisers: Fátima Al-Shahrour, Arnold Levine, Solip Park, Raúl Rabadán

STRUCTURAL AND MOLECULAR BIOLOGY OF THE DNA DAMAGE RESPONSE

20/05/2019 – 22/05/2019

Organisers: Oscar Llorca, Rafael Fernández Leiro, Laurence H. Pearl, Titia Sixma

2018

MOLECULAR, CELLULAR AND ORGANISMAL HALLMARKS OF AGING

07/05/2018 – 09/05/2018

Organisers: Maria A. Blasco, Alejo Efeyan, Kathleen Collins, Thomas Rando

FRONTIERS IN IMMUNOMODULATION AND CANCER THERAPY

09/07/2018 – 11/07/2018

Organisers: Victoria Aranda, Nabil Djouder, Joao Monteiro, Marisol Soengas, Laurence Zitvogel

2017

PRIMARY AND SECONDARY BRAIN TUMORS

19/02/2017 – 22/02/2017

Organisers: Massimo Squatrito, Manuel Valiente, Richard Gilbertson, Michael Weller

MOLECULAR CHAPERONES IN CANCER

02/05/2017 – 04/05/2017

Organisers: Nabil Djouder, Wilhelm Krek, Paul Workman, Xiaohong Helena Yang

2016

CANCEROMATICS III – TUMOR HETEROGENEITY

13/11/2016 – 16/11/2016

Organisers: Fátima Al-Shahrour, Núria Malats, Alfonso Valencia, Chris Sander

2015

METASTASIS INITIATION: MECHANISTIC INSIGHTS AND THERAPEUTIC OPPORTUNITIES

28/09/2015 - 30/09/2015

Organisers: David Lyden, Yibin Kang, Gemma Alderton, Victoria Aranda, Li-kuo Su, Héctor Peinado

NEW TRENDS IN ANTICANCER DRUG DEVELOPMENT

22/03/2015 - 25/03/2015

Organisers: Manuel Hidalgo, Alberto Bardelli, Lillian Siu, Josep Tabernero

2013

CHROMOSOME INSTABILITY AND ANEUPLOIDY IN CANCER

27/05/2013 - 29/05/2013

Organisers: Robert Benezra, Ana Losada, Marcos Malumbres, René Medema

2012

ALLOSTERIC REGULATION OF CELL SIGNALLING

17/09/2012 - 19/09/2012

Organisers: Francesco Gervasio, Ermanno Gherardi, Daniel Lietha, Giulio Superti-Furga

2011

RECAPTURING PLURIPOTENCY: LINKS BETWEEN CELLULAR REPROGRAMMING AND CANCER

07/11/2011 - 09/11/2011

Organisers: Maria A. Blasco, Konrad Hochedlinger, Manuel Serrano, Inder Verma

CANCEROMATICS II : MULTILEVEL INTERPRETATION OF CANCER GENOME

28/03/2011 - 30/03/2011

Organisers: Søren Brunak, Stephen Chanock, Núria Malats, Chris Sander, Alfonso Valencia

BREAST CANCER

07/02/2011 - 09/02/2011

Organisers: Joaquín Arribas, José Baselga, Miguel Ángel Piris, Lajos Pusztai and Jorge Reis-Filho

2010

CANCER PHARMACOGENETICS: PERSONALIZING MEDICINE

22/11/2010 - 24/11/2010

Organisers: Javier Benítez, William E. Evans, Miguel Martín and Magnus Ingelman-Sundberg

MOLECULAR CANCER THERAPEUTICS

08/03/2010 - 10/03/2010

Organisers: Gail Eckhardt, Roy S. Herbst and Manuel Hidalgo

2009

THE ENERGY OF CANCER

02/11/2009 - 04/11/2009

Organisers: Toren Finkel, David M. Sabatini, Manuel Serrano and David A. Sinclair

CANCER-OM-ATICS : MULTILEVEL INTERPRETATION OF CANCER GENOME DATA

06/07/2009 - 08/07/2009

Organisers: Søren Brunak, Núria Malats, Chris Sander and Alfonso Valencia

STEM CELLS AND CANCER

23/02/2009 - 25/02/2009

Organisers: Elaine Fuchs, Maria A. Blasco, Eduard Batlle and Mirna Pérez-Moreno

2008

SIGNALLING UPSTREAM OF mTOR

03/11/2008 - 05/11/2008

Organisers: Dario R. Alessi, Tomi P. Mäkelä and Montserrat Sánchez-Céspedes

STRUCTURE AND MECHANISMS OF ESSENTIAL COMPLEXES FOR CELL SURVIVAL

23/06/2008 - 25/06/2008

Organisers: Niko Grigorieff, Eva Nogales and Jose María Valpuesta

DEVELOPMENT AND CANCER

04/02/2008 - 06/02/2008

Organisers: Konrad Basler, Ginés Morata, Eduardo Moreno and Miguel Torres

2007

LINKS BETWEEN CANCER, REPLICATION STRESS AND GENOMIC INTEGRITY

05/11/2007 - 07/11/2007

Organisers: Oskar Fernández-Capetillo, Jiri Lukas, Juan Méndez and André Nussenzweig

MYC AND THE TRANSCRIPTIONAL CONTROL OF PROLIFERATION AND ONCOGENESIS

11/06/2007 - 13/06/2007

Organisers: Robert N. Eisenman, Martin Eilers and Javier León

MOLECULAR MECHANISMS IN LYMPHOID NEOPLASM

19/02/2007 - 21/02/2007

Organisers: Elias Campo, Riccardo Dalla-Favera, Elaine S. Jaffe and Miguel Angel Piris

2006

TELOMERES AND TELOMERASE-CNIO / JOSEF STEINER CANCER CONFERENCE

13/11/2006 - 15/11/2006

Organisers: Maria A. Blasco and Jerry Shay

MEDICINAL CHEMISTRY IN ONCOLOGY

02/10/2006 - 04/10/2006

Organisers: Fernando Albericio, James R. Bischoff, Carlos García-Echeverria and Andrew Mortlock

INFLAMMATION AND CANCER

22/05/2006 - 24/05/2006

Organisers: Curtis Harris, Raymand Dubois, Jorge Moscat and Manuel Serrano

PTEN AND THE AKT ROUTE

08/05/2006 - 10/05/2006

Organisers: Ana Carrera, Pier Paolo Pandolfi and Peter Vogt

2005

CANCER AND AGING

07/11/2005 - 09/11/2005

Organisers: Maria A. Blasco, Kathy Collins, Jan Hoeijmakers and Manuel Serrano

MAP KINASES AND CANCER

30/05/2005 - 01/06/2005

Organisers: Philip Cohen, Roger Davis, Worcester, Chris Marshall and Ángel Nebreda

ANIMAL TUMOUR MODELS AND FUNCTIONAL GENOMICS

07/03/2005 - 09/03/2005

Organisers: Allan Balmain, Mariano Barbacid, Anton Berns and Tyler Jacks

2004

CADHERINS, CATENINS AND CANCER

29/11/2004 - 01/12/2004

Organisers: Amparo Cano, Hans Clevers, José Palacios and Franz Van Roy

STRUCTURAL BIOLOGY OF CANCER TARGETS

27/09/2004 - 29/09/2004

Organisers: Ernest Laue, Guillermo Montoya and Alfred Wittinghofer

2003

APOPTOSIS AND CANCER

01/12/2003 - 03/12/2003

Organisers: Gabriel Nuñez, Marisol Soengas and Scott Lowe

SMALL GTPases IN HUMAN CARCINOGENESIS

16/06/2003 - 18/06/2003

Organisers: Juan Carlos Lacal, Channing Der and Shuh Narumiya

TARGETED SEARCH FOR ANTICANCER DRUGS

17/03/2003 - 19/03/2003

Organisers: Amancio Carnero and David H. Beach

2002

MECHANISMS OF INVASION AND METASTASIS

18/11/2002 - 20/11/2002

Organisers: Joan Massagué and Richard Hynes

THE CELL CYCLE AND CANCER

30/09/2002 - 02/10/2002

Organisers: Marcos Malumbres, Charles Sherr and Jiri Bartek

CANCER EPIGENETICS : DNA METHYLATION AND CHROMATIN

29/05/2002 - 31/05/2002

Organisers: Manel Esteller and Stephen B. Baylin

cnio - CaixaResearch
FRONTIERS
MEETINGS

Madrid 9 — 10 May 2022
Abstract submission deadline: April 11, 2022
Registration deadline: April 15, 2022

Molecular, Cellular and Organismal Drivers of Aging

Organisers

Maria Blasco
Spanish National Cancer Research Centre, CNIO, Madrid, Spain

Alejo Efeyan
Spanish National Cancer Research Centre, CNIO, Madrid, Spain

Thomas Rando
University of California, Los Angeles, US

Speakers

Steven Artandi
Stanford University, US

Shelley Berger
The Perelman School of Medicine at the University of Pennsylvania, US

Fabrizio d'Adda di Fagagna
IFOM-FRC Institute of Molecular Oncology Foundation, Milan, Italy

Oscar Fernández Capetillo
Spanish National Cancer Research Centre, Madrid, Spain

Christine K. Garcia
Columbia University Irving Medical Center, New York, US

Vera Gorbunova
University of Rochester, New York, US

Jan Hoeijmakers
Erasmus MC Rotterdam, Netherlands

Juan Carlos Izpisua
Salk Institute for Biomedical Studies, La Jolla, US

William Mair
Harvard T.H. Chan School of Public Health, Boston, US

Brendan Manning
Harvard T.H. Chan School of Public Health, Boston, US

Pura Muñoz-Cánoves
Pompeu Fabra University (UPF), ICREA, Barcelona, and CNIC, Madrid, Spain

Angela Nieto
Institute of Neurosciences, CSIC-UMH, Alicante, Spain

Manuel Serrano
Institute for Research in Biomedicine, Barcelona, Spain

Dario R. Valenzano
Max-Planck Institute for Biology of Ageing, Cologne, Germany

Centro Nacional de Investigaciones Oncológicas (CNIO).
Melchor Fernández Almagro 3, 28029 Madrid

*CNIO reserves the right to close registration and abstract submission when we reach full capacity.

For further information and to apply please go to www.cnio.es/events

"la Caixa" Foundation

cnio stop cancer

cnio - CaixaResearch FRONTIERS MEETINGS

Madrid 24 — 26 October 2022

Early fee until June 20, 2022

Abstract submission deadline: September 12, 2022

Registration deadline: October 3, 2022

Diet, Nutrition and Cancer Cell Metabolism

Organisers

Nabil Djouder
Spanish National Cancer Research Centre, CNIO, Madrid, Spain

Nikla Emambokus
Cell Press, Cambridge, US

Allyson Evans
Cell Metabolism, Cambridge, US

Valter Longo
IFOM, Milan, Italy

Marcos Malumbres
Spanish National Cancer Research Centre, CNIO, Madrid, Spain

Speakers

Yasmine Belkaid
National Institute of Allergy and Infectious Diseases (NIH), Bethesda, US

Rafael de Cabo
National Institutes of Health (NIH), Bethesda, US

Lewis C. Cantley
Weill Cornell Medicine, New York, US

Sabrina Diano
Yale University School of Medicine, New Haven, US

Ana Domingos
University of Oxford and Howard Hughes Medical Institute International Research Scholar, UK

Lluis Fajas
Center for Integrative Genomics (CIG), Lausanne, Switzerland

Mark A Febbraio
Monash Institute of Pharmaceutical Sciences, Monash University, Victoria, Australia

Douglas R. Green
St. Jude Children's Research Hospital, Memphis, US

Gökhan S. Hotamışlıgil
Harvard T.H. Chan School of Public Health, Boston, US

Guido Kroemer
The Cordeliers Research Centre (CRC), Paris, France

Tak Mak
Princess Margaret Cancer Centre (UHN), Toronto, Canada

Núria Malats
Spanish National Cancer Research Centre, CNIO, Madrid, Spain

Marina Pollán
National Center for Epidemiology (ISCIII), Madrid, Spain

Ana Ramírez de Molina
IMDEA Food Institute, Madrid, Spain

Romeo Ricci
IGBMC, Illkirch-Graffenstaden, France

M. Celeste Simon
Abramson Family Cancer Research Institute, University of Pennsylvania Perelman School of Medicine, US

Dana Small
Yale School of Medicine, New Haven, US

John R. Speakman
University of Aberdeen, King's College, Aberdeen, Scotland

Bruce M. Spiegelman
Harvard Medical School, Boston, US

Yu-Hua Tseng
Harvard Medical School, Joslin Diabetes Center, Boston, US

Matthew Vander Heiden
Koch Institute for Integrative Cancer Research, (MIT), Cambridge, US

Karen Vousden
The Francis Crick Institute in London, UK

Jihye Yun
Baylor College of Medicine; Houston, US

Centro Nacional de Investigaciones Oncológicas (CNIO). Melchor Fernández Almagro 3, 28029 Madrid

*CNIO reserves the right to close registration and abstract submission when we reach full capacity.

For further information and to apply please go to www.cnio.es/events

"la Caixa" Foundation

cnio stop cancer

cnio-CaixaResearch
FRONTIERS
MEETINGS

Madrid 9—10 May 2022

Molecular, Cellular and Organismal Drivers of Aging

Notes

cnio stop cancer

NOTES

NOTES

cnio-CaixaResearch
FRONTIERS
MEETINGS

Madrid 9 — 10 May 2022

Molecular, Cellular and Organismal Drivers of Aging

Centro Nacional de Investigaciones Oncológicas (CNIO)
Spanish National Cancer Research Centre
Melchor Fernández Almagro, 3
28029 Madrid, Spain
www.cnio.es

Coordination and edition:
Mercedes Moro, CNIO, Madrid, Spain
Production of art and design by Juan Agüera / Soda Graphics
Photographic archive CNIO

Printed in Spain

#CFM_Aging22
@CNIO_Cancer
@CaixaCiencia

cnio stop cancer

As a non-profit organisation, we would like to thank all those who sponsored this conference. Such contribution helps us to ensure that our conferences will continue to establish the CNIO as a point of reference for the international cancer research community.

#CFM_Aging22 @CNIO_Cancer @CaixaCiencia

EXCELENCIA SEVERO OCHOA 2012 - 2023

GOBIERNO DE ESPAÑA | MINISTERIO DE CIENCIA E INNOVACIÓN | ISC Instituto de Salud Carlos III

cnio stop cancer

"la Caixa" Foundation