BIOLOGY OF AGEING

Ulysseus EUROPEAN UNIVERSITY

UNIVERSITÉ CÔTE D'AZUR | GRADUATE SCHOOL LIFE AND HEALTH SCIENCES

IRCAN

ipmc

institut Valrose Biologie

WINTER SCHOOL BIOLOGY OF AGEING

Organizing Committee

Coordinators:

- Paula Pousinha and Alexandre Ottaviani

Staff support:

EUR Life:

- Clemence Benoit
- Tatiana Masson
- Line-Aurore March
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- Yacine Gouaich
- Stephane Ngo Mai

Reception and sessions:

- Aurore ribera
- Camille Girolet

Funding:

- EUR Life
- Ulysseus
- Research UniCA Institutes (IRCAN, IPMC, iBV)

Campus Valrose, 11th – 15th December

Over the last century, human life expectancy has dramatically increased, and aged individuals will represent 22% of the world's population by 2050. **These profound demographic changes have placed "the aging process" as a major challenge for scientific research nowadays**. **Université Côte d'Azur (UniCA) is a pivotal university the field of Biology of Ageing**, with (i) a dedicated institute (IRCAN), (ii) multiple pluridisciplinary teams developing research related to the aging process at different associated laboratories (IRCAN, IPMC, iBV), and (iii) aging-focused international initiatives and networks (UlyssEUs' Innovation Hub, OncoAGe, InterAging).

<u>We will cover the following topics:</u>

The morning sessions will consist in thematic modules with didactic presentations from UniCA researchers (20 min) and keynote seminars from invited speakers (45 min). In the afternoon workshops, we propose active learning sessions to improve the participants' learning experience.

SEMINARS (mornings) – Open to all

- Genomic instability and telomers maintenance
- Cellular stresses and ageing
- Mitochondrial dysfunction in ageing
- Cellular senescence
- Stem cell in ageing
- Regeneration and ageing
- Immuno-ageing
- Aging and environment
- Intercellular communication dysregulation
- Age-related disorders
- Entrepreneurship in ageing
- Healthy ageing keys

IMMERSED EDUCATION (afternoons) – only for registered students who will be present full week.

- Innovative experimental models of ageing
- Soft skills training:
    - Critical Thinking
    - Science communication
    - Deliverable Innovation
    - Speech and body perception

Internal Scientific Contributions (UniCA)

IRCAN

- Aaron Mendez-Bermudez
- Aldine Amiel
- Alexandre Ottaviani
- Aurélien Doucet
- Cedric Gaggioli
- Delphine Benarroch-Popivker
- Dmitry Bulavin
- Eirini Trompouki
- Eric Gilson
- Eric Röttinger
- Gilles Pagès
- Julien Chrfilis
- Maeva Dufies
- Marie-Josèphe Giraud Panis
- Marina Shkreli
- Miguel Godinho Ferreira
- Nicolas Haupaix
- Soline Estrach
- Aurore Ribera
- Bernard Mari
- Fanny Eysert
- Guillaume Cinquanta
- Maeva Meynier
- Mounia Chami
- Paula Pousinha

iBV

- Anne-Sophie Rousseau
- Florence Besse
- Valentina Cigliola

LP2M

- Claudine Blin

LAMHESS

- Stephane Ramanöel

C3M

- Nathalie Boulet

Ulysseus

- John Rowel

IPMC

External Scientific Contributions

- Björn Schumaker (Cologne, Germany)
- Deepak Kumar Sinai (Bangalore, India)
- Emilio di Maria (Genova, Italy)
- Mario Pende (Paris, France)
- Praneet Soi (Amsterdam, Neatherlands)

WEEK SCHEDULE

	Monday 11th	Tuesday 12th	Wednesday 13th	Thursday 14th	Friday 15th
	Grand Château Théâtre	Grand Château Salle des Actes	Grand Château Théâtre	Fizeau Salle Olivier Chesneau	Grand Château Théâtre
9h00	**Presentation Biology of Ageing Winter School**	**Mitochondrial dysfunction in Aging**		**Intercellular communication dysregulation**	**Regeneration and Aging** (90 min)
	A. Ottaviani P. Pousinha	**M. Chami A. Mendez-Bermudez**		**M. Godinho Ferreira P. Pousinha**	**V. Cigliola E. Röttinger C. Blin**
10h	**Genomic Instability and Telomeres maintenance**	**Cellular senescence**	**Immuno-Aging**	**Age-related disorders I**	**Centenarians** (25 min)
	A. Doucet M-J. Giraud-Panis	**D. Bulavin**	**J. Cherfils E. Trompouki**	**B. Mari G. Pagès**	**E. Di Maria**
10h45	Coffee break	Coffee break	Coffee break	Coffee break	Coffee break
11h	**Cellular stresses and Aging**	**Stem cell in Aging**	**Keynote session**	**Age-related disorders II**	**Art and Business in Aging**
	F. Besse D. Benarroch	**M. Shkreli S. Estrach**	**GPCR signaling in Senescence D. Kumar Saini**	**AS. Rousseau S. Ramanoël**	**M. Dufies Praneet Soi**
12h		**Keynote session**	**Keynote session**	Lunch	**Keynote session**
	Deliverable Innovation J. Rowell	**Aging and Environment E. Gilson**	**Metabolism and Ageing M. Pende**		**Genome Stability B.Schumacher**
13h	Lunch	Lunch	Lunch	**Fizeau Salle Olivier Chesneau**	Lunch
	IRCAN	**Fizeau Salle Olivier Chesneau**	**Fizeau Salle Olivier Chesneau**		**Fizeau Salle Olivier Chesneau**
14h30	**Innovative experimental models of aging** Immersion in Lab (IRCAN)	**Theater Role Play** Soft skills with Theater Company With S. Eichenholc	**Exploratory Research Design** Scientific observations guided by researchers	**Exploratory Research Design** Development guided by researchers	**My idea in 180s**
					WS closing P. Pousinha A. Ottaviani
18h30		**Social Event (Secret Address)**			

EXTENDED PROGRAM

Monday December 11th

MORNING SESSIONS

9am Winter School Presentation

Coordinators: Paula Pousinha *(Associate Professor, UniCA)* **and Alexandre Ottaviani** *(Associate Professor, UniCA)*

10am

Aurelien Doucet
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Research Associate, IRCAN, Institute for Research on Cancer & Aging, Nice, CNRS 7284, INSERM 1081, Université Côte d'Azur

"Human transposable elements at the crossroad of genomic instability and aging"

The human genome contains an average of a hundred copies of active LINE-1 transposable elements. These genetic entities have the ability to move from one locus to another through a process known as retrotransposition. This process involves the ORF2p protein encoded by LINE-1, which harbors endonuclease and reverse transcriptase enzymatic activities. Both activities are essential for LINE-1 mobility but can also have detrimental effects on the cell. Retrotransposition is a source of insertional mutagenesis, but it can also lead to genomic instability and induce cellular senescence through DNA damage and the triggering of the interferon response. These effects of LINE-1 activity are being particularly studied in the context of cancer and aging.

Marie-Josèphe Giraud Panis
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Research Associate, IRCAN, Institute for Research on Cancer & Aging, Nice, CNRS 7284, INSERM 1081, Université Côte d'Azur

"Telomeres: safeguards of genome stability"

Telomeres constitute the ends of all linear chromosomes. Their main role is to protect chromosomes extremities against nucleolytic degradation and to avoid the recognition of these ends as double strand breaks. Indeed, if recognized as breaks, the DNA damage signaling and the repair pathways are activated leading to telomeres fusions, dicentric chromosomes and rampant genome instability, thus causing cell senescence/death or generating cancer. Hence, it is vital for genome stability and cell survival to maintain telomeric functions. Unfortunately, telomeres of somatic cells shorten at each round of cell division causing, with age, accumulation of senescent cells and an increase of cell death. Consequently, telomeres shortening is one of the hallmarks of aging. In cancer cells, restoring telomere maintenance is a prerequisite for full transformation and is achieved by reactivating telomere elongation pathways (reactivation of telomerase or recombination pathways). Thus telomeres, the safeguards of genome integrity, are at the crossroad between aging and cancer. Our team (Pr. Eric Gilson's) has been working on telomeres for more than 30 years and was seminal in several discoveries such as the essential telomeric protein TRF2, its partner Apollo or the link between telomeres and pericentromeres in the onset of senescence. After a short presentation of the biology of telomeres, I will present some of the past and present achievements of the team.

11am

Florence Besse

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Research Director, Director of Institute of Biology Valrose, UMR CNRS 7277, INSERM U1091

“Condensation of translationally-repressed mRNAs in the aging brain”

Formation of membrane-less condensates enriched in functionally related biological molecules has recently emerged as a major principle enabling dynamic cell compartmentalization.

In the healthy nervous system, collections of dynamic condensates enriched in RNA and associated proteins have been identified. In late onset neurodegenerative diseases, in contrast, accumulation of static RNA-protein aggregates with aberrant composition has been reported and linked to disease progression. To explore if and how physiological aging impacts on neuronal RNA- condensates independently of disease context, we analyzed in vivo condensation in the aging brain. Our work uncovered a progressive recruitment of selected mRNA species into large condensates that repress mRNA translation. These results suggest that co-condensation of selected mRNAs and translation regulators into repressive condensates contribute to the specific post-transcriptional changes in gene expression observed in the course of aging, opening new perspectives on age-dependent regulation of gene expression. "

Delphine Benarroch - Popivker

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"Effects of Glucocorticoids on telomeres and cellular senescence"

Several types of stress can accelerate telomere shortening leading to cellular senescence. The mechanisms linking stress response, involving stress hormones or oxidative stress, to telomere homeostasis and function are still poorly understood. I will present data showing the short-term effect of cell treatment by dexamethasone (a synthetic stress hormone) on DNA Damage Response (DDR) activation and on telomere maintenance. The treatment of immortalized human fibroblasts (BJ-Helt) and colon cancer cells (HCT116) by dexamethasone triggered an increase in telomere protection, as revealed by a decreased frequency of telomere DNA damage (TIFs). Conversely, knocking-down the glucocorticoid receptor expression led to a decreased telomere protection. In both situations, the global amount of DNA damages did not change. No change was also observed in telomere length in BJ-Helt cells after short-term glucocorticoid activation or inhibition. The use of glucocorticoids does not change telomere capping function in young human primary fibroblasts (WI38) unless the cells are downregulated for a telomere protein called TRF2, leading to telomere dysfunctional cells, and in BJ-Helt cells which are invalidated for the catalytic subunit of the telomerase. These results suggest that a short-term use of glucocorticoid protects against specific types of telomeres deprotection events. We can hypothesize that glucocorticoids behave as a "first aid" in coping with a stress situation, reinforcing telomere protection and maybe preventing senescence.

12pm

John Rowell

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Innovation hub Manager, Ulysseus European University

"Cultivating Innovation in Ageing Research: Empowering the Next Generation"

Abstract: The field of ageing biology is at a critical juncture, poised to tackle the multifaceted challenges of an aging population. In this workshop, we explore the pivotal role of innovation in advancing ageing research and addressing pressing societal needs. Emphasizing the imperative for future researchers to wield innovation as a powerful tool, we will explore strategies for integrating inventive thinking into fundamental research and fostering entrepreneurial mindsets. Through this, we aim to equip the next generation with the tools and inspiration needed to drive transformative change in the landscape of ageing research.

2:30pm AFTERNOON WORKSHOP

Students will be divided into four groups, who will rotate in the different workshops.

A. Anti-aging platform

Aldine Amiel (IRCAN)

B. Zebra fish as a model of aging

Miguel Godinho Ferreira Lab (Research Director INSERM, IRCAN)

C. Innovative in vitro models to study aging and neurodegenerative disorders

Organoids and spheroids screening platform (Cedric Gaggioli, Research Director INSERM, IRCAN)

Brain organoids (Aurore Ribera, PhD student and Guillaume Cinquanta, PhD student, IPMC)

Microfluidic chambers and iPSCs (Fanny Eysert, Researcher CDD, IPMC)

Tuesday December 12th

MORNING SESSIONS

9am

Mounia Chami

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Research Associate, Université Côte d'Azur, CNRS UMR7275, Institute of molecular and cellular pharmacology, Laboratory of excellence DistALZ, 06560, Sophia-Antipolis, Valbonne, France.

"Mitochondria structure, function and mitophagy alterations in Alzheimer's disease: molecular mechanisms and a therapeutic approach"

Mitochondria structure and function alterations are major features of Alzheimer's disease (AD). In addition, impairments in mitophagy, the process of selective mitochondrial degradation by autophagy leading to a gradual accumulation of defective mitochondria, have also been reported in neurodegenerative diseases including AD. Specifically, mitochondria dysfunctions and mitophagy failure have been mostly linked to toxic Amyloid beta (Aβ) peptides. Several lines of recent evidence also indicate that the amyloid precursor protein-derived C-terminal fragments (APP-CTFs) are etiological triggers of AD pathology. However, their genuine contribution to mitochondrial dysfunction and mitophagy process were unknown.

In my presentation, I will provide an overview of recent data showing the specific contribution of the amyloid precursor protein-derived C-terminal fragments (APP-CTFs) to mitochondrial structure, function, and mitophagy defects. These evidences have been reported in cellular and mice models mimicking familial forms of AD. Importantly, our data also provide evidences that mitophagy failure molecular signature correlates with APP-CTFs accumulation in post-mortem human sporadic AD (SAD) brains, and demonstrated altered mitochondrial structure and function and mitophagy failure in a cohort of fibroblasts isolated from SAD patients. I will then focus on our latest data demonstrating the impact of the bioenergetic sensor, AMP-activated protein kinase (AMPK) on mitochondrial dysfunctions, mitophagy and neuroinflammation in cellular, ex vivo and mice AD study models. Together, these studies unraveled new molecular mechanisms underlying AD development and provide future directions for AD therapeutics.

Aaron Mendez-Bermudez

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Researcher CDD, IRCAN, Institute for Research on Cancer & Aging, Nice, CNRS 7284, INSERM 1081, Université Côte d'Azur

"The interplay between telomeres and mitochondria function during senescence and ageing"

Ageing is characterized by the overall decline in physiological integrity leading to progressive failure in maintaining tissue function and consequently favouring the appearance of age-related diseases such as atherosclerosis, cardiovascular disorders, arthritis, osteoporosis, Alzheimer's disease and cancer among others. Evidence suggests that the accumulation of senescent cells in tissues is a key driver of ageing and consequently, it is likely that cellular senescence is one of the main determinants that contribute to aging and thus to tissue deterioration. Senescence is described as an irreversible cell-cycle arrest state that can be triggered by various types of stresses such as telomere attrition, oxidative stress, oncogene activation and mitochondria dysfunction among others. This process is accompanied by changes in the metabolism, chromatin, gene expression and the release of numerous molecules named senescence-associated secretory phenotype (SASP).
Oxidative stress resulting from mitochondrial dysfunction and telomere shortening are prominent senescence-inducing stimuli that occur during normal and pathological ageing and are risk factors for the decline of regenerative potential and age-associated pathologies. Growing evidence shows an interplay between the function of these senescence stimuli highlighting the importance of the stability of these structures to prevent a detrimental feedback loop which could lead to cellular senescence. The implications of the connection between mitochondria and telomeres will be discussed.

10am

Dmitry Bulavin

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Research Director, IRCAN, Institute for Research on Cancer & Aging, Nice, CNRS 7284, INSERM 1081, Université Côte d'Azur

"Senescence and Aging"

The accumulation of senescent cells can drive many age-associated phenotypes and pathologies. Consequently, it has been proposed that removing senescent cells might extend lifespan. Here I will discuss the recent development in the field of senescence to highlight both detrimental but also beneficial functions of senescent cells under different conditions and during aging.

11am

Soline Estrach

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Research Assoiate, IRCAN, Institute for Research on Cancer & Aging, Nice, CNRS 7284, INSERM 1081, Université Côte d'Azur

"Aging and Stem Cells: a skin tale"

Tissue homeostasis is achieved through a strictly controlled balance of growth and regression. To fulfil this task, a subset of stem cells (SCs) in the epithelium remain in a quiescent state between their recruitment. To study physiological tissue regeneration, we use the mouse hair follicle (HF) as the model of choice, which alternates between phases of growth and regression, maintaining a pool of stem cells (HFSCs) to sustain tissue regeneration and repair. HFSCs drive the hair regeneration cycle via niche interactions. The niche refers to the fine location where the stem cells are located. In the skin, they are located in the region below the sebaceous gland, the so-called bulge, which is enriched with specific ECM components. Aging is a physiological process. It affects tissues homeostasis and their repair capacity. We are interested in the effects of aging on skin maintenance and repair and in particular how it affects HFSC function. We have shown that biophysical properties are affected by aging and that it affects epidermal homeostasis. We are currently investigating the effects of aging on the pattern of stem cell markers and how it affects their function, opening up new avenues of thought for rejuvenation therapy. Stem cell and aging research comprises a promising new field of research in the light of societal developments.

Marina Shkreli

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Research Associate, IRCAN, Institute for Research on Cancer & Aging, Nice, CNRS 7284, INSERM 1081, Université Côte d'Azur

"Stimulation of intrinsic regenerative capacities in the adult kidney by telomerase"

Tissue homeostasis and regeneration represent critical processes for maintaining organ functionality and extending longevity. During the multifactorial process of aging, certain tissues or organs lose their capacities to maintain homeostasis and to regenerate leading to age-related diseases. Thus, understanding the cellular and molecular events that initiate, drive, and coordinate homeostasis as well as regeneration has an important potential to develop novel strategies to fight against age-related diseases. Notably, these processes involve various cellular mechanisms such as cellular plasticity or adult stem cell engagement. But importantly, proper tissue maintenance depends upon mobilization of progenitor cells and activation of cellular proliferation within the adult organism. Understanding key molecular and cellular mechanisms controlling tissue homeostasis and regeneration, and the forces that constrain or unleash these processes in mammals, represents a major challenge for therapeutic approaches aiming to restore tissue maintenance in adulthood or with aging. Here, we will address these different mechanisms in the context of kidney maintenance in the adult organism. We will see how telomerase modulates an intrinsic regenerative potential in the adult kidney.

12pm Keynote lecture

Eric Gilson

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Director of IRCAN, PU-PHCE, IRCAN, Institute for Research on Cancer & Aging, Nice, CNRS 7284, INSERM 1081, Université Côte d'Azur

"Telomere and aging: problem or solution ?"

2:30 pm

Theater Role Play

Theater Company Arkadia

With Stephane Eichenholc

Wednesday December 13th

MORNING SESSIONS

10am

Julien Cherfils

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Research Associate, IRCAN, Institute for Research on Cancer & Aging, Nice, CNRS 7284, INSERM 1081, Université Côte d'Azur

"Targeting the Senescence associated Immune Checkpoint to blunt age-related diseases and cancers"

Aging is at the origin of a significant number of diseases and cancers, for which the epistemological link is increasingly detailed. At the cellular level, the accumulation of senescent cells (SC) in tissues emerges as a key factor in aging. It is now well established that SC can be either eliminated by our immune system (pre-oncogenic SC for instance) but also can accumulate progressively during life and be tolerated in our tissues. We still do not know the molecular events regulating senescence immune clearance. Those SC, appearing even during the youth (i.e., the melanocytic naevi), are not eliminated despite a potent immune system and can be maintained for decades. This suggests that immune checkpoints expressed by SC must regulate their immunogenicity.

We show that SC, elicited by various stressors other than oncogenic activation, triggers immune escape toward natural killer (NK) cells. We reveal that SC reshuffle their glycocalyx composition, toward a marked increase in the ganglioside content, including the appearance of disialylated ganglioside GD3. The high level of GD3 leads to a strong immunosuppressive signal affecting NK cell-mediated immunosurveillance. In lung fibrosis mouse model, senescent cell-dependent NK cell immunosuppression is blunted by in vivo administration of anti-GD3 monoclonal antibodies leading to a clear anti-fibrotic effect. Moreover, targeting GD3 by mAbs in old mice significantly attenuate age-related diseases including natural lung fibrosis or osteoarthritis and significantly increase healthspan. These results demonstrate that GD3 upregulation in SC drives a switch from immune clearance toward immune tolerance. Therefore, we propose that GD3 level acts as a Senescence Immune Checkpoint (SIC) that determine senescent cell fate.

Eirini Trompouki

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Research Director, IRCAN, Institute for Research on Cancer & Aging, Nice, CNRS 7284, INSERM 1081, Université Côte d'Azur

"Repetitive elements as signals for developmental hematopoiesis and aging"

Repetitive elements like transposable elements (TEs) and other simpler repeats are dispersed throughout the genome and consist more than one third of it in multiple species. For many years this part of the genome was considered as "junk", but it has lately become clear that many functions can be attributed to repetitive elements. Developmental processes and cellular states exhibiting high plasticity are often accompanied by expression of repetitive elements. Here we show that repetitive elements are transcribed during hematopoietic stem cell development and aging. Repetitive element RNAs act as signals for innate immune receptors of the RIG-I-like receptor family. Activation of these receptors titrates the induction of sterile inflammatory signals that enhance hematopoietic stem cell development and participates in aging phenotypes. Thus, RNA sensing of repetitive elements actively shapes cellular transitions.

11am

Keynote lecture

Deepak Kumar Saini

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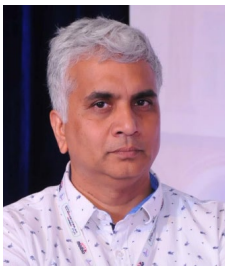
Professor

Department of Developmental Biology and Genetics, Department of Bioengineering. Indian Institute of Science. Bangalore, INDIA

Coordinator

MSc Life Sciences program and Franco-Indian Campus on Health.



"GPCR signaling in Senescence"

Senescence is typically associated with enhanced inflammation, oxidative and nitrosative stress, persistent damage to cellular components, and changes in signalling. As organisms age, their ability to clear out senescent cells reduces, leading to organ and tissue dysfunction. GPCRs, like CXCR1/2, are essential for the activation and trafficking of inflammatory mediators along with tumour progression. Interestingly, the chemokine receptor CXCR4 involved in the homeostasis of the adult hematopoietic system, mainly homing in aged neutrophils, is upregulated during cellular senescence. The induction is part of DNA-damage response and is dependent on activation of the ATM kinase - HIF1α axis. This induction is necessary for increasing inflammation during DNA damage which can promote cell clearance or causes senescence if left uncleared. In sync with this, in cells which have entered senescence and escaped clearance, there is change in CXCR4 signaling and we recorded that in these cells calcium oscillations are impaired, and signalling is altered after ligand stimulation.

Typically, the CXCR4 receptor signals through the Gai G-protein which reduces cAMP and enhances inflammation. In this talk, I will present evidence of how altered lipid metabolism changes the CXCR4 receptor output from pro to anti-inflammatory arm of signalling. I will present experimental and computational evidences of altered CXCR4 signalling and propose potential implications on the pharmacological interventions tailored for geriatric populations.

12pm

Keynote lecture

Mario Pende

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Research director, Inserm U845 - Institut Necker, Paris - France

"Metabolism and Ageing"

The control of growth and ageing by nutrients and the mTOR pathway will be discussed, describing how caloric restriction and mTOR inhibition promote healthy longevity. I will present recent data from the lab revealing the metabolic rewiring of senescent cells.

2:30 pm AFTERNOON WORKSHOP

Exploratory Research Design Scientific observations guided by researchers

Maeva Meynier (Researcher CDD)

Nicolas Haupaix (Researcher CDD)

Nathalie Boulet (Associate Professor)

Thursday December 14th

MORNING SESSIONS

9am

Paula Pousinha

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Associate Professor, Université Côte d'Azur, CNRS UMR7275, Institute of molecular and cellular pharmacology, Laboratory of excellence DistALZ, 06560, Sophia-Antipolis, Valbonne, France.

"What happens to excitatory synapses as we age?"

In the hippocampus, NMDARs mainly contain GluN2A and/or GluN2B regulatory subunits. The amyloid precursor protein (APP) has emerged as a putative regulator of NMDARs, but the impact of this interaction to their function is largely unknown. By combining patch-clamp electrophysiology and molecular approaches, we unravel a dual mechanism by which APP controls GluN2B-NMDARs, depending on the life stage. We show that APP is highly abundant specifically at the postnatal postsynapse. It interacts with GluN2B-NMDARs, controlling its synaptic content and mediated currents, both in infant mice and primary neuronal cultures. Upon aging, the APP amyloidogenic-derived C-terminal fragments, rather than APP full-length, contribute to aberrant GluN2B-NMDAR currents. Accordingly, we found that the APP processing is increased upon aging, both in mice and human brain. Interfering with stability or production of the APP intracellular domain normalized the GluN2B-NMDARs currents. While the first mechanism might be essential for synaptic maturation during development, the latter could contribute to age-related synaptic impairments.

Miguel Godinho Ferreira

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Research director, IRCAN, Institute for Research on Cancer & Aging, Nice, CNRS 7284, INSERM 1081, Université Côte d'Azur

"Telomere elongation in the intestine extends lifespan of zebrafish"

As in humans, zebrafish gut is one of the organs with the fastest rate of telomere decline, triggering early tissue dysfunction during normal zebrafish aging and in prematurely aged telomerase mutants. However, whether telomere-dependent aging of an individual organ, the gut, causes systemic aging remains unknown.

We show that preventing telomere shortening in the gut through tissue-specific telomerase expression rescues premature aging of tert. Induction of telomerase rescues gut senescence and low cell proliferation, while restoring tissue integrity, inflammation, and age-dependent microbiota dysbiosis. Averting gut aging causes systemic beneficial impacts rescuing aging of distant organs, such as reproductive and hematopoietic systems. Conclusively, we show that gut-specific telomerase expression extends lifespan of tert by 40 %, while ameliorating natural aging. Our work demonstrates that delaying telomere shortening in the gut is sufficient to systemically counteract aging in zebrafish.

10am

Bernard Mari

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Research Director, Non-Coding Genome & Lung Disorders, Université Côte d'Azur, CNRS UMR7275, Institute of molecular and cellular pharmacology, Laboratory of excellence DistALZ, 06560, Sophia-Antipolis, Valbonne, France.

"Aging and pulmonary fibrosis: the microvascular trail?"

Lung regeneration is hampered by aging, which increases susceptibility to pathologies such as fibrosis. I will present our recent data presenting a whole picture of cell dynamic changes in lungs from young and aged mice during fibrosis formation and resolution, using notably a combination of single-cell and spatial transcriptomics. We found that transcriptomic alterations in specific cell subpopulations correlated with a delayed fibrosis resolution in aged mice. In particular, we characterized the appearance of pro-angiogenic pulmonary capillary endothelial cells (PCEC) subpopulations associated with the alveolar regeneration process. In aged mice, recruitment of these PCEC subpopulations is delayed whereas in human IPF biopsies, these pro-angiogenic progenitors are not detected, suggesting that age-associated transcriptomic alterations in specific PCEC subpopulations may interfere with the lung progenitor differentiation associated with a normal repair process and contribute to the persistent fibrotic process typical of the human pathology.

Gilles Pagès

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Research Director, IRCAN, Institute for Research on Cancer & Aging, Nice, CNRS 7284, INSERM 1081, Université Côte d'Azur

"Navigating Renal Cell Carcinoma: Exploring the Synergy of Immunotherapy and Anti-Angiogenic Drugs and Assessing the Impact of Age as a Treatment Criterion"

Metastatic renal cell carcinoma is managed through a synergistic approach involving a combination of immunotherapies and anti-angiogenic drugs. Following a comprehensive overview of the targets and mechanisms of these therapeutic agents, our exploration will extend to discerning the nuanced specificity of these treatments tailored for both young and elderly patients

11am

Anne-Sophie Rousseau

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Full Professor, Institute of Biology Valrose, UMR CNRS 7277, INSERM U1091

"Immunometabolism, exercise and healthy ageing: does T cell metabolism determined vitality capacity?"

Vitality capacity (VC) is the physiological determinant of our intrinsic capabilities that enable healthy ageing. It results from the interaction of factors related to metabolism, neuromuscular function, immunity, and stress response. Immunometabolism plays a central role in this new concept. Regulatory T cells (Tregs) a regulatory component of our adaptive immune system, are involved in maintaining the functions of adipose and muscle tissues (key organs responsible for whole body energy homeostasis). However, the diversity of Tregs with ageing hinders our understanding of the effects of subpopulations on VC. Physical inactivity is the main contributor of the decrease in physiological intrinsic capacities with the advancing age. The question addressed here is whether exercise or metabolic modulators that "mimics" endurance exercise at skeletal muscle level, by increasing fatty acid oxidation (FAO) and redox status, alter CD4+T cells metabolism and Tregs. Our recent work in mice and preliminary data in humans establish a link between T cell metabolism, Tregs characteristics, body composition, and, most importantly, the maintenance of aerobic physical abilities with age. Physiological and pathological situations that disrupt the overall metabolism of the body, such as physical exercise or obesity, could determine the metabolic program of Tregs and be linked to VC and its protective physiological effects.

Stephen Ramanoël

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Associate Professor, Université Côte d'Azur, LAMHESS, Nice, France

"The cerebral correlates of visual perception and spatial navigation processing in healthy ageing"

The 21st century is marked by a demographic "greying" of the global population. In this context, spatial navigation as a complex behavior encompassing perceptual, cognitive and motor processes, provides an ideal framework for the study of normal and pathological ageing. Older adults exhibit prominent impairments in their capacity to navigate efficiently, reorient in unfamiliar environments or update their path when faced with obstacles. These changes in navigation capabilities reduce older adults' autonomy and mobility, resulting in an increased risk of progression of age-related disorders such as Alzheimer's disease. This decline in navigational capabilities has traditionally been ascribed to memory impairments and dysexecutive function whereas the impact of visual ageing has often been overlooked. To address this issue, we implemented a highly interdisciplinary approach, bringing together clinical, psychophysical, biological, and behavioral screening as well as neuroimaging paradigms and virtual reality. During this presentation, I will summarize some experimental results from healthy young and older participants using an integrative neurocognitive approach from passive perception of visual scenes to active navigation tasks combined with functional magnetic resonance imaging methods. This work helps towards a better comprehension of the neural dynamics subtending visual and navigation processing and it provides new insights for the development of innovative remediation methods, such as visual devices or spatial environment designs, in order to improve the autonomy and healthcare of these populations.

2:30 pm AFTERNOON WORKSHOP

Exploratory Research Design Development guided by researchers

Maeva Meynier (Researcher CDD)

Nicolas Haupaix (Researcher CDD)

Nathalie Boulet (Associate Professor)

Friday December 15th

MORNING SESSIONS

9am

Eric Rottinger

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Research Director, IRCAN, Institute for Research on Cancer & Aging, Nice, CNRS 7284, INSERM 1081, Université Côte d'Azur

"*Nematostella vectensis*, a cnidarian research model to gain insight into stress-response, whole body regeneration and longevity"

Certain cnidarians (e.g., sea anemones, corals) display impressive stress-resistance and whole-body regenerative capacities, associated with a virtually unlimited lifespan. Inspired by these features, we developed a series of experimental approaches to decipher cellular and molecular mechanisms underlying stress-response and regeneration, to gain insight into the longevity strategies deployed by this marine animal. The presentation will provide an overview of these capacities, with a particular focus on the tissular, cellular and molecular dynamics that are induced following injury and that lead to the reformation of lost body part.

Valentina Cigliola

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Chair Professor, Institute of Biology Valrose, UMR CNRS 7277, INSERM U1091

"Innate Mechanisms of Spinal Cord Regeneration"

Spinal cord (SC) regeneration is negligible in adult mammals, yet zebrafish regenerate and recover motor function after a paralyzing injury. In a pro-regenerative factor screen, we discovered a major role for Hb-egfa in zebrafish SC regeneration. Epigenetic profiling revealed a hb-egfa cis-regulatory element sufficient to trigger gene expression during zebrafish SC regeneration. This element also directed expression following mouse SC injury and could increase axon density in the lesioned mouse SC when delivered via viral vectors for targeted HB-EGF delivery. Our results reveal cross-species functions for Hb-egf during SC repair and suggest strategies to awaken SC regeneration in adult mammals.

Claudine Blin

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Research Director, LP2M, UMR7370 CNRS, Université Côte d'Azur

"Aging in osteoimmunology: the bone-immune system connection"

The bone and immune systems are tightly interconnected and regulate each other. These interactions define a new field of research called osteoimmunology. Immune cells regulate bone remodeling by bone-forming osteoblasts and bone-resorbing osteoclasts while bone cells participate in bone niches that regulate the maintenance and differentiation of immune cells and their hematopoietic progenitors.

Throughout life, the two systems evolve in parallel. With age, the immune system progresses towards a low-grade inflammatory state characterized by a myeloid skewing. This affects the differentiation of bone cells, in particular osteoclasts that are of myeloid origin. On the other hand, the differentiation and activity of bone cells are also altered, resulting in reduced bone formation and increased bone resorption, and consequently decreased bone mass. Such alterations also impact bone marrow niches and the immune system.

This presentation will address the aging process of the bone-immune axis and its pathophysiological consequences on the bone tissue.

10:30am

Emilio Di Maria

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Associate Professor, MD PhD; Department of Health Sciences, University of Genova, Italy
University Unit of Medical Genetics, Galliera Hospital, Genova, Italy

Centenarians and oldest-olds in Liguria – COOL: investigation on cognitive status in centenarians from Genova. A multidisciplinary approach to investigate the genetic determinants of cognitive well-being in the oldest population.

Educational attainments, socioeconomic status and mentally stimulating activities, significantly affect late-life cognitive phenotypes, thus leading to the paradigm called "cognitive reserve". However, recent studies demonstrated that cognitive reserve might have a relevant effect in subpopulations with high prior risk of dementia. Thus, the paradigm may be no longer valid in healthy oldest-old. As compared to the body of literature on risk factors for dementia, little is known on protective genetic factors associated with a favourable cognitive profile in the oldest population.

Across the European countries, Italy has a leading position with a swelling population of centenarians. In the Italian map of longevity, Liguria region has the highest ratio incidence of over centenarians (3.3 per 100,000). The COOL study is aimed at identifying genomic biomarkers of healthy ageing in centenarians, with specific focus on cognitive status.

We designed a not-for-profit, multicentric cohort study involving a series of centenarians (aged >99) living in the Genova area. The relevant phenotype (primary endpoint) is cognitive status; genomic biomarkers will be retrospectively investigated as predictors. Cognitive functions are deeply explored by the mean of a set of neuropsychological tests. Personal history, clinical history, genomic variants, and their interactions with environmental variables will populate a model (or different models) allowing us to interpret healthy aging and variance in cognitive performance. The diverse profiles of genomic variants in the study cohort will eventually allow to test different multivariate models to interpret the distribution of cognitive performance among centenarians.

The work plan implies a close collaboration between skills: the family doctors are pivotal in the process of information and enrolment of participants; chief medical officers supervise the enrolment and data collection processes, which is carried out by all the investigators; clinical neurologists and neuropsychologists contribute with their expertise for the assessment of cognitive profile; clinical pharmacologists are in charge for the analysis of drug prescription and intake; the clinical geneticists (included the PI) examine the family history data and design the investigation of genomic biomarkers.

As to September 2023, 54 participants had been reached as eligible; 49 (age range: 99-108) were enrolled in the study after informed consent. Centenarians are mostly female (84%) and are well distributed between institutional household and private home residents. To date, 36 participants underwent the full neuropsychological assessment (details will be presented). The genomic analyses will be carried out after the completion of the enrolment phase and may eventually reveal new clues about the genetic determinants of cognitive well-being.

Expected impact: Liguria is the most aged region in Italy; thus the characterization of long-lived subjects provides crucial data for the health policies. The achievement of the project objectives will allow to establish fruitful partnerships with existing initiatives. The definition of ageing profiles is relevant both at a scientific and at the health policy levels, including innovative campaigns to promote choices that favour healthy ageing processes. The results will be disseminated to the scientific community and the general population, in order to improve the knowledge on healthy aging. The multidimensional data set on the cohort of centenarians will constitute a scientific standpoint to explore novel research questions.

11am

Maeva Dufies

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CEO Roca Therapeutics and CNRS Researcher

"Development of First-In-Class small molecules for a personalized treatment of uveal melanoma and ocular complication- from lab to start-up creation"

Uveal melanoma (UM) is a highly aggressive cancer. Treatment of UM consists of proton therapy (100% of patients). Although effective, this treatment stimulates the development of blood vessels, leading to neovascular glaucoma and enucleation (removal of the eye) in 30% of patients. In addition, around 50% of patients will develop liver metastases, which are currently incurable and lethal within 2 years.

We have demonstrated that ELR+CXCL cytokines play a key role in resistance to anti-VEGF therapies. These cytokines (CXCL1,2,3,5,6,7,8) are pro-angiogenic/pro-inflammatory. They exert their effects via the G protein-coupled receptor CXCR2. This receptor is physiologically expressed by endothelial and immune cells, and aberrantly by tumor cells. These cytokines are just as important as VEGF in stimulating angiogenesis and inflammation in UM. In contrast to the recognized phenomena of VEGF-dependent angiogenesis and primary inflammation, these cytokines are involved in the exacerbated/anti-VEGF-resistant form of angiogenesis (VEGF-independent), as well as in immunosuppressive inflammation.

We have demonstrated, in two independent cohorts of uveal melanoma (UM) patients, that the presence of these cytokines in the primary tumor correlates with the development of liver metastases and shorter survival. Moreover, they are over-expressed in the aqueous humor of UM patients (PROTECT clinical trial conducted by Nice University Hospital).

With our colleagues chemists, from the Institut de Chimie de Nice (ICN, Dr Ronco and Dr Benhida), we carried out a rational structure/activity design (SAR) of small molecule CXCR2 inhibitors. Three rationally designed series, representing more than 300 compounds, were synthesized and enabled us to select our lead molecules: RCT001 (UM) and RCT002 (neovacular glaucoma).

Our patented innovation involves the development of competitive CXCR2 inhibitors capable of concomitantly and selectively neutralizing several mechanisms responsible for neovascular glaucoma and the aggressiveness of UM:

i. VEGF-independent exacerbated/resistant angiogenesis, involved in the metastatic process and in neovascular glaucoma

ii. harmful immunosuppressive inflammation involved in tumor escape from the anti-tumor immune system

iii. Autocrine loops of ELR+CXCL and CXCR1/2 expression by tumor cells stimulating UM cell proliferation and survival (metastasis)

iv. Oxidative stress, through a significant increase in ROS (Reactive Oxygen Species)

These molecules have been patented by SATT Sud-Est. With the aim of continuing the development of these molecules in order to bring them into the clinic and hope to treat patients, we created the start-up Roca Therapeutics in 2021, a spin-off from the University of Nice.

Our aim is to develop drug candidates that will significantly improve the therapeutic management of patients suffering from Uveal Melanoma. More specifically, our drug candidates will treat currently fatal liver metastases (RCT001) and/or complications associated with UM (a side effect of proton therapy), notably neovascular glaucoma (RCT002).

Praneet Soi

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Born in 1971 in Kolkata, Praneet Soi completed a bachelor's and master's of fine arts in painting at the Faculty of Fine Arts, Maharaja Sayajirao University of Baroda, after which he worked briefly in the advertising industry in New Delhi. He went on to do a second master's at the University of California at San Diego.

Soi's works reside in important collections in Europe and India. These include the permanent collections of the Van Abbe Museum, Eindhoven, the Kiran Nadar Museum of Art, New Delhi, The Irish Museum of Modern Art in Dublin and the Stedelijk Museum, Amsterdam. In 2014 Soi was commissioned to create a permanent work for the HCL headquarters in Chennai. In 2011 he was one of 4 artists representing India at the Indian Pavilion in Venice.

Art and Ageing

12pm Keynote lecture

Björn Schumacher

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Head of CECAD, Full Professor Faculty of Medicine, University of Cologne

"Genome Stability in aging and inheritance: new insights from C. elegans"

Institute for Genome Stability in Aging and Disease, Medical Faculty, Cologne Excellence Cluster for Cellular Stress Responses in Aging-Associated Diseases (CECAD) Research Centre and Center for Molecular Medicine (CMMC), University of Cologne, Joseph-Stelzmann-Str. 26, 50931 Cologne, Germany

The demographic change is one of the greatest challenges of our time. Age is the biggest risk factor for a wide range of chronic diseases including dementia, cardiovascular diseases, cancer, and frailty. It is therefore of utmost importance to understand the biology of aging. While the soma ages over the course of an individual's lifespan, germ cells can be indefinitely perpetuated.

The genome contains all information for building and maintaining cells, tissues and thus the organism. The DNA is constantly exposed to damage but, in contrast to any other macromolecules, it cannot be replaced but instead requires constant repair. DNA repair mechanisms are thus essential for life and the maintenance of health. DNA repair defects accelerate human aging in rare progeroid syndromes. While the DNA in somatic tissues only needs to be maintained for an individual's lifespan, germline genomes require indefinite maintenance. We will here discuss new concepts of genome maintenance mechanisms in the germline.

First, we investigated the genome quality control in the germline. We uncovered unexpected transgenerational consequences of DNA damage in paternal genomes. We show that DNA damage in mature sperm leads to structural variants that are generated by maternal Theta-mediated endjoining (TMEJ), which consequently results in genome instability in the progeny. The progeny is incapable to repair the damage due to heterochromatization leading to transgenerational embryonic lethality. Alleviation of the heterochromatization, in contrast, allows access for homologous recombination repair (HRR) thus resolving the genome instability and reversing the transgenerational lethality. We thus uncovered a novel mechanism of the specific consequences of paternal DNA damage and the restrictive repair types fueling genome instability in the consequent generation.

Third, we investigated the mechanisms underlying the limited DNA repair capacities of somatic cells compared to the germline. We found that the DREAM complex represses DNA repair gene expression in somatic cells thus curbing somatic genome maintenance. DREAM inactivation leads to induction of

the expression of DNA repair genes in all DNA repair systems consequently enhancing DNA repair kinetics and conferring DNA damage resistance to the soma. We show the DREAM inhibition also in human cells and in mice elevates DNA damage resistance. We propose the DREAM as the first master regulator of somatic DNA repair capacities whose inhibition could augment genome maintenance thus alleviating a fundamental cause of aging.