ICSA

International Cell Senescence Association

Conference 2018

Cellular Senescence: Geroscience, Cancer and beyond

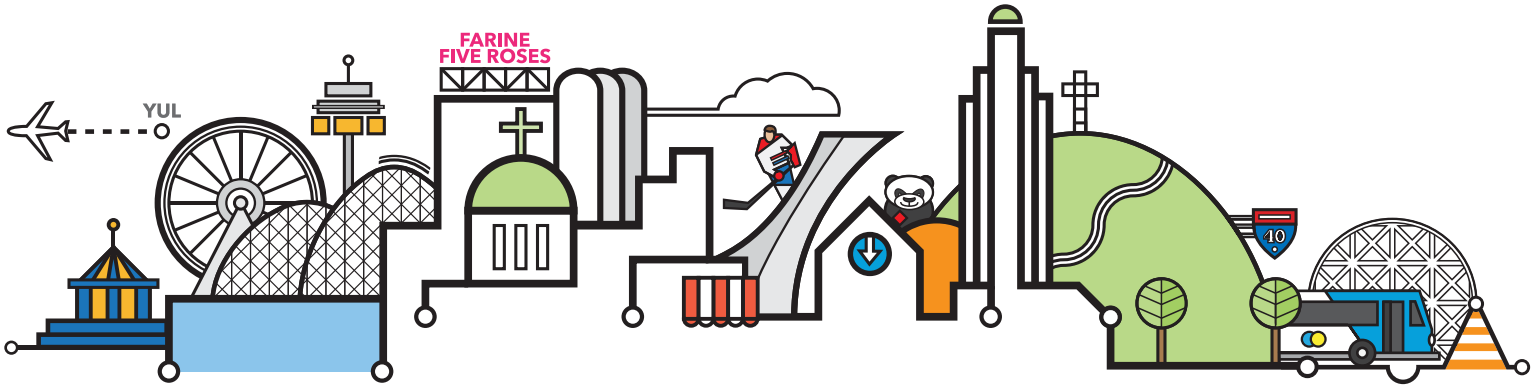
Montreal - July 8-11th 2018

CHUM Research Center

Program and Conference Information

Organizers

Gerardo Ferbeyre - g.ferbeyre@umontreal.ca
Francis Rodier - rodierf@mac.com
Daohong Zhou - DZhou@uams.edu



Université de Montréal

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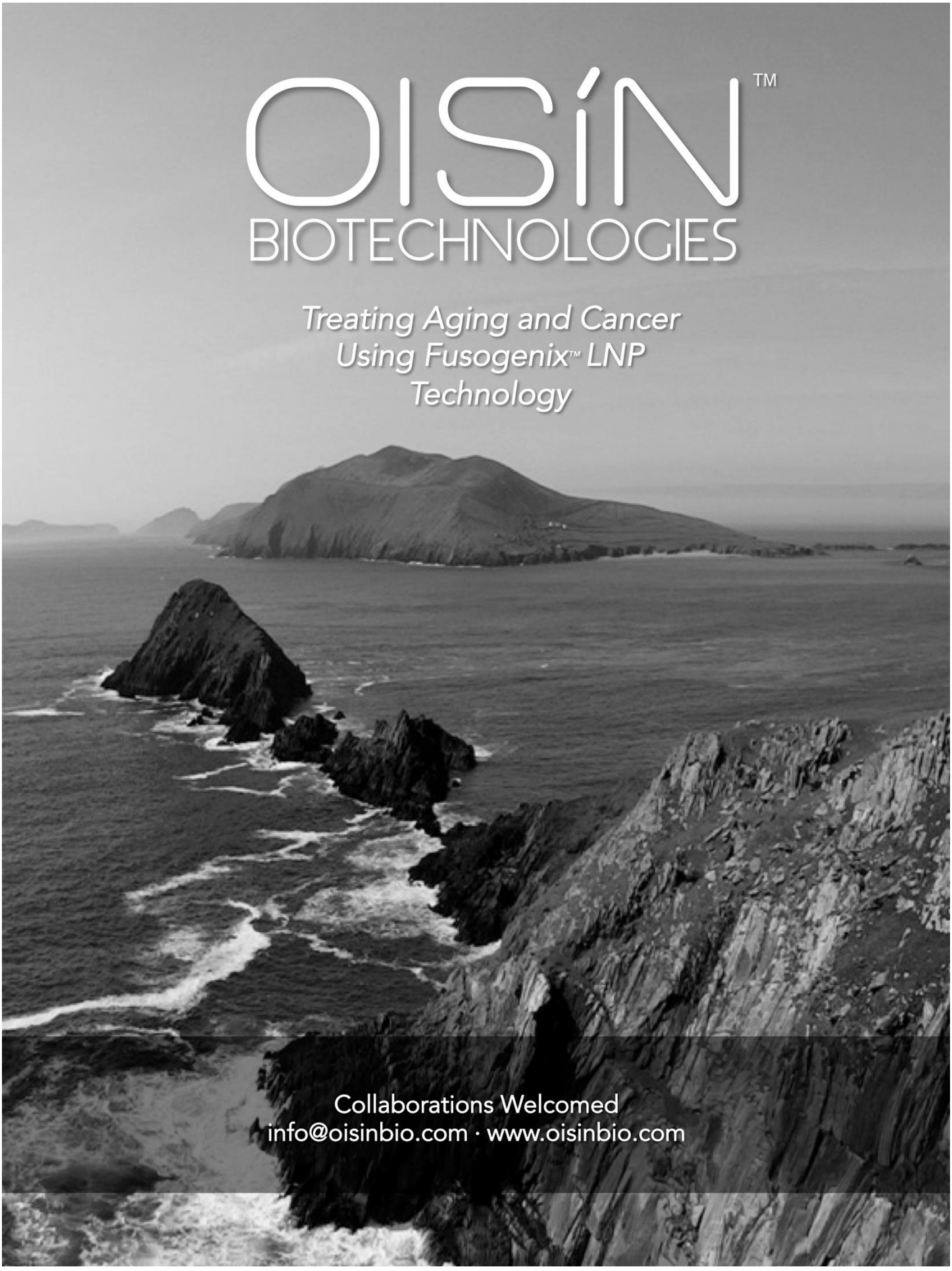
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International Cell Senescence Association (ICSA)

Conference 2018

Montreal, July 8-11th 2018

CRCHUM, Montreal, Canada

ORGANIZERS

Gerardo FERBEYRE	University of Montreal & CRCHUM (Canada)
Francis RODIER	CRCHUM (Canada)
Daohong ZHOU	University of Florida, Health Cancer Center (United States)

SPEAKERS

KEYNOTE SPEAKERS

Jiri Bartek	Danish Cancer Society Research Center (Denmark)
Norman E. Sharpless	National Cancer Institute (United States)
Clemens Schmitt	Charité - University Medical Center (Germany))

INVITED SPEAKERS

Darren Baker	Mayo Clinic (United States)
Christian Beauséjour	Université de Montréal (Canada)
Judith Campisi	Buck Institute for Research on aging (United States)
Irina Conboy	University of California at Berkeley (United States)
Frederick Dick	Western Canadian University (Canada)
Jennifer Elisseeff	Johns Hopkins Biomedical Engineering (United States)
Myriam Gorospe	National Institutes of Health (United States)
Konstantinos Evangelou	University of Athens (Greece)
Andrei Gudkov	Roswell Park Cancer Institute (United States)
Eiji Hara	Osaka University (Japan)
James L. Kirkland	Mayo Clinic (United States)
Valery Krizhanovsky	Weizmann Institute of Science (Israel)
Claude Le Saux	University of California at San Francisco (United States)
Scott Lowe	Memorial Sloan Kettering Cancer Center (United States)
Frédérick A. Mallette	Université de Montréal/Maisonneuve-Rosemont H. (Canada)
Karl Riabowol	University of Calgary (Canada)
Francis Rodier	CHUM Research Center (Canada)
Manuel Serrano	Institute for Research in Biomedicine (IRB), (Spain)
Jan van Deursen	Mayo Clinic (United States)
Xiaolu Yang	University of Pennsylvania (United States)
Daohong Zhou	University of Florida, Health Cancer Center (United States)

International Cell Senescence Association (ICSA)

Conference 2018

Montreal, July 8-11th 2018

CRCHUM, Montreal, Canada

THEME OF THE CONFERENCE

We welcome you to discuss the latest results in the field of cellular senescence at the Research Center of the CHUM (University Hospital) located in the Montreal downtown area. Senescent cells have become an attractive target to be exploitable for therapeutic intervention to reduce or delay age-related diseases including atherosclerosis, idiopathic pulmonary fibrosis, osteoarthritis, and osteoporosis and to extend healthy lifespan. Cellular senescence is also relevant for tissue regeneration and tumor suppression and their modulation may lead to innovative anticancer treatments.

Topics to be covered during the conference include:

1. RNA biology of senescent cells
2. Metabolism of senescent cells
3. Tumor suppression and cancer therapeutics
4. Effects of senescent cells on their microenvironment
5. Aging and anti-senescence drug discovery

Scientific Advisory Board

Dorothy Bennett
Judith Campisi
Scott Lowe
Manuel Serrano
Norman E. Sharpless

Scientific correspondence and abstracts

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Elaine Meunier : elaine.meunier@umontreal.ca

Sponsorship and exhibitor coordinator

Philipe Lampron : p.lampron@umontreal.ca
Véronique Bourdeau : veronique.bourdeau@umontreal.ca

Local organizing committee

(accommodations, disabilities, reception, posters, catering, dinner night, farewell party)

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TABLE OF CONTENTS

GENERAL INFORMATION

WELCOME DESK – OPENING HOURS

The registration desk opens at 3:00 pm on July 8th, 2018. To receive your registration package at any other time, please head to the welcome desk during coffee breaks or contact: emmanuelle.saint-germain@umontreal.ca

ORAL SESSION

Scientific sessions are taking place in the auditorium on the 5th floor of the CRCHUM.
Information for presenters: Please give your presentation before your session in a USB key to Nicolas Malaquin: nico.malaquin@gmail.com or Véronique Tu : veronique.tu.1@ulaval.ca in the Agora

SPEED TALKS

2 minutes per presentation – 2 slides maximum
Presentations are to be sent by email to Veronique Bourdeau before July 8th: veronique.bourdeau@umontreal.ca.

Monday, July 9th	4:10 – 4:20 PM
Tuesday, July 10th	3:50 – 4:00 PM

POSTER SESSIONS

Two poster sessions will take place in the Agora on the 5th floor of the CRCHUM, just outside the conference theater as follow:

- **Poster session I** will start on Monday, July 9th at 5 PM. Posters should be installed after the group photo session taking place at around 4:30 PM. Posters with **odd** numbers will present during this session.
- **Poster session II** will start on Tuesday, July 10th at 4:30 PM. Posters should be installed after the speed talk session at around 4:15 PM. Posters with **even** numbers will present during this session.

IMPORTANT: All posters should be removed at the end of each session.
NB: Poster numbers are in the program book. Check the matching number on the board to display your poster at the right place. Tacks will be available to mount your poster.

COFFEE BREAKS & LUNCHES

Coffee breaks and lunch buffets will be served in the Agora on the 5th floor of the CRCHUM just outside of the conference theater. Access is strictly limited to registered participants.

WIFI

A free public WiFi connection is available in the agora and the auditorium of the CRCHUM (network provider: ZAP.coop network name: ile-sans-fil).

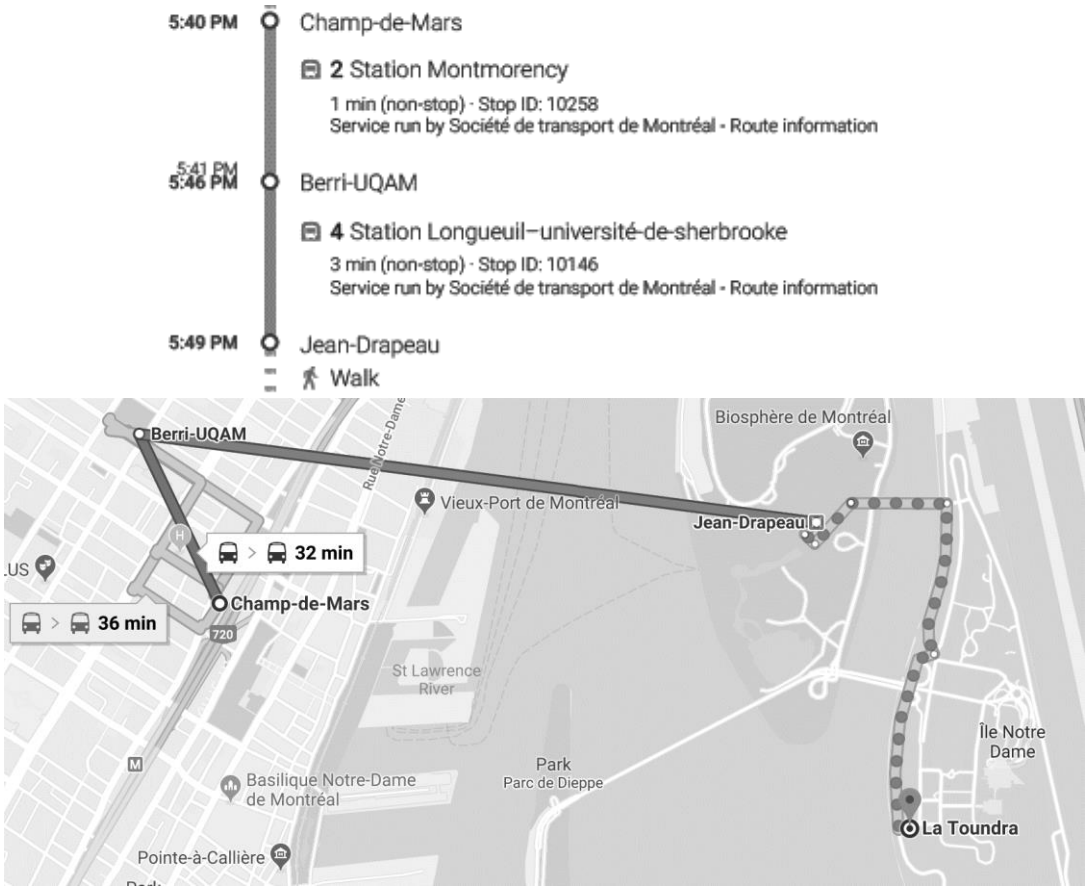
SOCIAL EVENTS

Cocktails

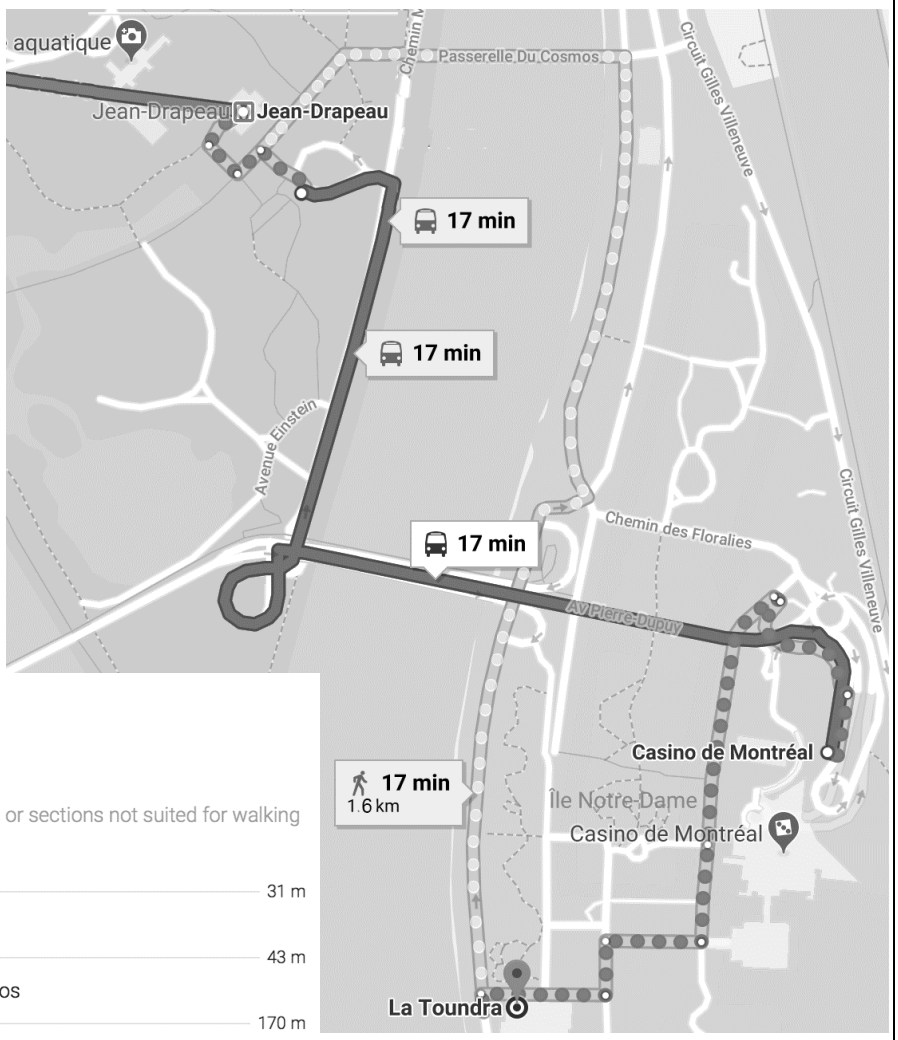
- A reception and dinner cocktail will be served in the Agora on the 5th floor of the CRCHUM on Sunday 8th at 8:15 pm
- Wine and snacks will be available during Poster Sessions

FAREWELL DINNER (LA TOUNDRA HALL) – WEDNESDAY 11TH FROM 6:00 PM

La Toundra (Pavillon du Canada), located on Notre-Dame Island, is accessible via the Montreal Métro subway system (in total a 45-minute trip). We invite participants to gather at the end of the conference session at 4:30pm. Groups of 20, each with a local guide, will depart from the CRCHUM towards the Champ-de-Mars Metro Station (3 min walk). Going in the Montmorency direction on the orange line, we will change trains at the Berri-UQAM station. We will then take the yellow line to Parc Jean-Drapeau Station, followed by a 20 minute walk to La Toundra. Limited car service from the Parc Jean Drapeau Station to La Toundra will be provided upon request. **Please contact Gerardo by email**: g.ferbeyre@umontreal.ca ***or text message (514 299 2992)***.



We will provide a metro pass valid for both way trips. The fare of a Taxi to La Toundra Hall from the CRCHUM is around 27 CAN$. You can call a Taxi to return or take the METRO back to Montreal. Please ask for assistance if you need it! A shorter walking alternative is via the Casino. The Montreal Casino has a shuttle service (bus # 777) to Parc Jean-Drapeau Station and La Toundra Hall is close by (10 min-walk).



5:47 PM **Jean-Drapeau**

Walk 1.6 km

Use caution - may involve errors or sections not suited for walking

Take exit Station Jean-Drapeau — 31 m

Head southeast — 43 m

Turn left toward Passerelle Du Cosmos — 170 m

Turn right onto Passerelle Du Cosmos — 290 m

Turn right at Chemin du Chenal le Moyne — 450 m

Turn right onto Circuit Gilles Villeneuve

Destination will be on the left — 600 m

6:07 PM **La Toundra**

1 Circuit Gilles Villeneuve, Montreal, QC H3C 6A1

The reception will begin with a cocktail. Dinner will be served at 6:45 PM. We will host an after-dinner talk by UNITY Biotechnology president Nathaniel David. DJ entertainment will follow for the remainder of the evening. Please note that the last subway train from Jean-Drapeau Station leaves at 1 AM.

SCIENTIFIC PROGRAM

DAY 1 - Opening Session

July 8th, 2018
3:00-10:00 PM

Registration 3:00-5:15 PM

3:00 PM | Registration Desk opens

Welcome from Organizers and ICSA

5:00 PM | **Gerardo FERBEYRE**, Université de Montréal, Canada
Manuel SERRANO, ICSA President, Institute for Research Biomedicine (IRB), Spain

Keynote Presentation

5:15 PM | **Clemens SCHMITT**, Charité - University Medical Center, Hematology/Oncology (Germany)
Restore, induce, eliminate – cancer cell senescence as treatment effector and driver of failure

6:00 PM – Coffee Break

Session 1 – RNA biology in senescence 6:15-7:55 PM

Chair: Myriam GOROSPE

6:15 PM | **Myriam GOROSPE**, NIH, USA
Senescence Noncoding RNPs

6:45 PM | **Frédéric LESSARD**, Université de Montréal, Canada
Senescence-associated ribosome biogenesis defects contributes to cell cycle arrest through the Rb pathway

7:15 PM | **Jacqueline SALOTTI**, National Cancer Institute, NIH, USA
A Novel mRNA localization mechanism contributes to senescence bypass in RAS tumor cells

7:35 PM | **Mathieu DESCHÊNES**, Université de Sherbrooke, Canada
Alternative splicing alterations potentially contribute to apoptotic resistance associated with senescence

7:55 PM | **Guadalupe Elizabeth JIMENEZ-GUTIERREZ**, Center for Research Advanced Studies of the National Polytechnic Institute (CINVESTAV), Mexico
A role for β-Dystroglycan in cell senescence

8:15 PM – Reception and Dinner Cocktail

DAY 2

July 9th, 2018
8:30 AM-7:00 PM

Session 2 – Senescence and Tumor Suppression 8:30-10:30 AM

Chair : Gerardo FERBEYRE

EMBO LECTURE

8:30 AM | **Jiri BARTEK**, Danish Cancer Society Research Center, Copenhagen, Denmark
Stress-support pathways in cellular senescence and cancer: mechanisms and opportunities for intervention

Chair : Scott LOWE

9:15 AM | **Scott LOWE**, Memorial Sloan Kettering, USA
Cellular senescence and the tumor microenvironment

9:50 AM | **Frederick A. DICK**, Western University, Canada
Regulation of heterochromatin by the RB protein during proliferation and senescence

10:10 AM | **Karl RIABOWOL**, University of Calgary, Canada
A disorderly way to induce senescence

10:30 AM – Coffee Break

Session 3 – Metabolism of Senescent Cells 11:00 AM – 1:00 PM

Chair : Xiaolu YANG

11:00 AM | **Xiaolu YANG**, University of Pennsylvania, USA
p53 and senescence: the NADPH connection

11:30 AM | **Eiji HARA** (Sponsord by Senolytic Therapeutics Inc.), Osaka University, Japan
Obesity and cellular senescence: a gut microbial connection

12:00 PM | **Maria Grazia VIZIOLI**, Beatson Institute for Cancer Research, Bearsden, Glasgow, UK
Targeting a mitochondrial-cytoplasmic chromatin signalling axis to suppress senescence associated inflammation

12:20 PM | **Raquel BUJ**, Pennsylvania State Univ., USA
Loss of p16 mediates senescence bypass through metabolic reprogramming induced by the DNA damage response and mTORC1 pathways

12:40 PM | **Mikolaj OGRODNIK**, Newcastle University Institute for Ageing, UK
Obesity-Induced cellular senescence drives neural stem cell dysfunction and anxiety

1:00 PM – Lunch Break

Session 4 – Senescence and Cancer Therapy 2:00-4:00 PM

Chair : Clemens SCHMITT

2:00 PM **Francis RODIER**, CRCHUM, Canada
From the clinic: Cancer therapy-induced senescence, good or bad?

2:30 PM **Konstantinos EVANGELOU**, University of Athens, Greece
Escaping from oncogene-induced senescence

3:00 PM **Corinne ABBADIE**, Université de Lille, France
Ionizing radiations scattering at the margin of the treated volume during radiation therapy induce DNA single-strand breaks, senescence and neoplastic escape of normal fibroblasts

3:20 PM **Olivier COQUERET**, Université d'Angers, France
Regulation of Senescence Escape by the TSP1-CD47 Pathway Following Chemotherapy Treatment

3:40 PM **Masashi NARITA**, CRUK, United Kingdom
Autophagy in ageing and cancer

2 min Speed Talks 4:10-4:15 PM

Lior ROITMAN, Weizmann Institute of Science, Israel
The role of cellular senescence in the development of pancreatic ductal adenocarcinoma

Maximina YUN, TUD CRTD/DFG-Center for Regenerative Therapies Dresden, Germany
Telomere length is exclusively maintained by the ALT mechanism in a vertebrate, the newt Pleurodeles waltl

Alessandra ZONARI, OneSkin Technologies, USA
Identification of a novel senotherapeutic molecule: comparison with retinoic acid in human aged 2D and 3D skin models

Wesam BAZZAR, Karolinska Institute, Stockholm, Sweden
Loss of CDK2 Delays Onset and Progression of BRAFV600E/MYC-driven Mouse Lung Tumors via Induction of Senescence

Matej DURIK, IGBMC, France
Investigating the dynamic program of single cell senescence

Ana O'LOGHLEN, *Queen Mary University, UK*
The bystander effect of exosomes in senescence

4:30 PM – Group Photo

Poster Session I 5:00-7:00 PM

Posters should be installed after the group photo session.

Posters with **odd** numbers will be presented during this session.

Drinks will be served upon presentation of your drink coupons.

*Les jeux de ficelles (cat's cradles) refers to an Inuit string game (*ayarak *in Inuktitut),*

*Pierre **Bourgault** 2013*

DAY 3

July 10th, 2018
8:30 AM-6:30 PM

Session 5 – Senescence Microenvironment and Age-linked Diseases

8:30 AM-1:00 PM

Chair : Manuel SERRANO

8:30 AM	**Jan VAN DEURSEN**, Mayo Clinic, USA *Senolysis addresses an unmet clinical need in atherosclerosis therapy*
9:00 AM	**Andrei GUDKOV**, Roswell Park Cancer Institute, USA *Cellular senescence is a combination of distinct phenotypes*
9:30 AM	**Jennifer ELISSEEFF**, John Hopkins, USA *Senescent cells in tissue trauma and repair: a bridge to the immune system*
10:00 AM	**Brian DIEKMAN**, University of North Carolina, USA *The Role Of p16INK4a expression in cartilage aging and osteoarthritis development*

10:20 AM – Coffee Break

Chair : Jan VAN DEURSEN

10:40 AM	**Manuel SERRANO**, IRB, Spain *The two faces of cellular senescence in tissue repair and in multiple diseases*
11:10 AM	**Darren BAKER**, Mayo Clinic, USA *Implicating senescent cells to neurodegenerative disease*
11:40 AM	**Irina CONBOY**, UC Berkeley, USA *Systemic influences on tissue senescence and effect of senescent cell ablation on regeneration of muscle, liver and brain*
12:10 PM	**Mei WAN**, John Hopkins University, USA *Cellular Senescence in Childhood Bone Homeostasis*
12:40 PM	**Ha-Neui KIM**, University of Arkansas, USA *Upregulation of RANKL due to osteocyte senescence is a critical mechanism of skeletal aging*

1:00 PM – Lunch Break

Session 6 – The SASP and the Immune System 2:00-4:00 PM

Chair : Judith CAMPISI

2:00 PM **Judith CAMPISI**, Buck Institute for Research on Aging, USA
The shifting landscape of cellular senescence

2:30 PM **Christian BEAUSÉJOUR**, Hôpital Ste-Justine, Canada
Humanized mouse models as a tool to study cellular senescence

2:50 PM **Frédérick A. MALLETTE**, Centre de Recherche HMR, Canada
A potential role for cholesterol metabolism in regulating cellular senescence

3:10 PM **Jesús GIL**, MRC, United Kingdom
Targeting alternative splicing to regulate the SASP

3:30 PM **Albert DAVALOS**, Buck Institute for Research on Aging, USA
High Mobility Group Box 1 protein's effect in paracrine-induced senescence

2 min Speed Talks 3:50-4:00 PM

Xiang LI, Memorial Sloan Kettering, USA
Exosomes transmit the signals of senescence-associated secretory phenotype

David DANKORT, McGill University, Canada
p53 loss does not permit escape from BrafV600E-induced senescence in a mouse model of lung cancer

Marco DEMARIA, European Research Institute for the Biology of Ageing, Netherlands
CDK4/6 Inhibitors Induce Cellular Senescence in Normal Cells without Deleterious Associated Secretory Phenotypes

Lucas ROBINSON, Institut Pasteur, France
PARsing the function of PARP1 in senescence-associated gene regulation

Han LI, Institut Pasteur, France
Cellular senescence occurs during mammary gland involution

Poster Session II 4:30-6:30 PM

Posters should be installed after the 2 min Speed Talks.

Posters with **even** numbers will be presented during this session.

Drinks will be served upon presentation of your drink coupons.

DAY 4

July 11th, 2018
8:30 AM-11:59 PM

Session 7 – Anti-senescence drug discovery (senescence inhibitors, senolytic drugs, and SASP inhibitors) 8:30 AM-1:00 PM

Chair : Valery KRIZHANOVSKY

8:30 AM	**Valery KRIZHANOVSKY**, Weizmann Institute of Science, Israel *Senescent cells incidence: controllers and outcomes*
9:00 AM	**Jim KIRKLAND**, Mayo Clinic, USA *Senolytics: The Path to Translation*
9:30 AM	**John LEWIS**, Oisín Biotechnologies, Inc. Seattle, USA *Selective Ablation of Senescent and Malignant Cells using Apoptotic Gene Therapy*
10:00 AM	**Claude LESAUX**, UCSF, USA *Role of senescent cells in fibrosis: lesson from pulmonary fibrosis*

10:30 AM – Coffee Break

11:00 AM	**Daohong ZHOU**, University of Florida, USA *Senescent cells: an emerging target for aging, cancer, radiation-induced late effect*
11:30 AM	**Andrea ABLASSER**, Swiss Federal Institute of Technology, Switzerland *Targeting STING in senescence with small-molecule inhibitors*
11:50 AM	**Daniel MUÑOZ-ESPÍN**, University of Cambridge, United Kingdom *A versatile drug delivery system targeting senescent cells*
12:10 PM	**Guangrong ZHENG**, University of Florida *Discovery and target identification of piperlongumine-based senolytic agents*
12:30 PM	**Salvador MACIP**, University of Leicester, United Kingdom *Inhibition of BTK prolongs healthspan and lifespan in vivo*

12:50 PM – Lunch Break

Keynote Presentation

2:30 PM | **Norman E. SHARPLESS**, National Cancer Institute, USA
The dynamic interplay between cancer and aging

3:30 PM | Panel Discussion and General Assembly
Panel list: Manuel SERRANO, Gerardo FERBEYRE, Daohong ZHOU and Francis RODIER

5:30 PM – Farewell Dinner and Party – *La Toundra – Parc Jean-Drapeau*

After Dinner Talk

Nathaniel DAVID, UNITY Biotechnology
Senolytic drugs: from mutant mice to human clinical trials

ORAL PRESENTATIONS

Restore, induce, eliminate – cancer cell senescence as treatment effector and driver of failure

Clemens A. Schmitt[1,2] and colleagues

[1]Charité - Universitätsmedizin Berlin, Medical Department of Hematology, Oncology and Tumor Immunology, and Molekulares Krebsforschungszentrum – MKFZ, Berlin, Germany
[2]Max-Delbrück-Center for Molecular Medicine, Berlin, Germany

Oncogenic activation and anticancer therapies are known to evoke – especially if apoptotic cell death is no longer available – cellular senescence as another stress-responsive safeguard and ultimate cell-cycle exit program in (pre-)malignant cells. Hence, oncogene-induced senescence (OIS) and therapy-induced senescence (TIS) are considered to operate as important anti-tumor principles. Accordingly, manifest malignancies may present with specific genetic lesions that mediate senescence reversal – and whose pharmacological inactivation might allow to restore senescence in these post-senescent "escapee" cells, as we just reported for H3K9me3-active demethylases in a large subset of melanomas (Yu et al., Cancer Cell, 2018). And, mice bearing lymphomas that harbor a selective senescence defect in the H3K9 histone methyltransferase Suv39h1 experience an inferior long-term outcome in response to chemotherapy. However, we previously reported (Dörr-JR et al., Nature, 2013) that secondary, "senolytic" elimination of TIS cancer cells improves overall survival, thereby suggesting that lastingly persistent senescent cells might be harmful. Driven by the intriguing overlap of numerous pathway mediators relevant in both stem cell and senescence signaling, we now observed in lymphoma and other cancer types reprogramming of senescent cancer cells into a latent adult tissue stem cell state. Strikingly, these senescent cells exerted their gained stemness upon enforced or spontaneous cell-cycle re-entry out of senescence. As the pivotal underlying mechanism, we identified epigenetic reprogramming into a permissive state for active Wnt signaling, which is maintained in a small but stable fraction of the tumor cells post-senescence. Exploiting a non-stem bulk leukemia model, we found cells incapable of re-initiating the disease to convert into leukemia stem cells via temporarily entering TIS. We hypothesize that nature equips normal cells not only with stress-inducible safeguard mechanisms (such as apoptosis and senescence) that preclude severely damaged cells from further expanding, but also a latent stemness "rescue" program, which comes into play when stresses no longer apply and a cell-depleted tissue compartment needs to be replenished to regain its proper functionality. While such a principle seems to represent an important component of normal tissue homeostasis, it turns into a highly detrimental capability if "hijacked" by cancer cells. Hence, conceptually novel approaches that selectively eliminate senescent cancer cells after senescence-inducing or –restoring therapies appear to be of critical importance for improved long-term tumor control and will be discussed at the conference.

Senescence Noncoding RNPs

Kyoung Mi Kim, Ji Heon Noh, and Myriam Gorospe

Laboratory of Genetics and Genomics (https://www.nia.nih.gov/research/labs/lgg), National Institute on Aging Intramural Research Program, National Institutes of Health, Baltimore, MD 21224, USA

Senescent cells accumulate in aging tissues, and their metabolic and gene expression profiles are linked to cancer and other age-associated pathologies. Our recent studies have focused on the identification of cell surface markers that might be exploited in therapies aimed at senescent cells. In the first of two related studies, we identified dipeptidyl peptidase 4 (DPP4) as a cell surface protein that was drastically elevated in senescent cells compared to proliferating cells. Importantly, DPP4 allowed the detection of of senescent cells in antibody-dependent cellular cytotoxicity (ADCC) assays, providing proof-of-principle evidence that membrane markers could be targeted successfully for elimination of senescent cells [1]. In the second study, we identified Secretory Carrier Membrane Protein 4 (SCAMP4) as another protein selectively and highly expressed on the plasma membrane of senescent cells [2]. Interestingly, SCAMP4 was found to be critical for the senescence-associated secretory phenotype (SASP), a major trait of senescent cells whereby they trigger local inflammation, compromise the extracellular matrix, and elicit angiogenesis. I will discuss the roles of SCAMP4 and DPP4 in the senescent phenotype and further directions in our laboratory.

[1] Kim et al., Genes & Development 2017
[2] Kim et al., Genes & Development 2018 (in press)

Senescence-associated ribosome biogenesis defects contributes to cell cycle arrest through the Rb pathway

F. Lessard[1], S. Igelmann[1], C. Trahan[2], G. Huot[1], E. Saint-Germain[1], L. Mignacca[1], N. Del Toro[1], S. Lopes-Paciencia[1], B. Le Calvé[3], M. Montero[1], X. Deschênes-Simard[1], M. Bury[4], O. Moiseeva[1], M-C Rowell[1], C. E. Zorca[1], D. Zenklusen[1], L. Brakier-Gingras[1], V. Bourdeau[1], M. Oeffinger[1,2] and G. Ferbeyre[1*].

[1]Department of Biochemistry and Molecular Medicine; Université de Montréal; C.P. 6128, Succ. Centre-Ville, Montréal, Québec, H3C 3J7; Canada. [2]Institut de Recherches Cliniques de Montréal, 110 Avenue des Pins Ouest, Montréal, Québec, H2W 1R7; Canada. [3]4URBC-NARILIS, University of Namur, Namur, Belgium. [4]Lady Davis Institute for Medical Research, McGill University, Montreal, QC, Canada.

Cellular senescence triggered by a variety of stimuli leads to diminished ribosome biogenesis and the accumulation of both rRNA precursors and ribosomal proteins. These defects were associated with reduced expression of several ribosome biogenesis factors, the knockdown of which was also sufficient to induce senescence. Genetic analysis revealed that RB but not p53 was required for the senescence response to altered ribosome biogenesis. Mechanistically, the ribosomal protein S14 (RPS14 or uS11) accumulates in the soluble non-ribosomal fraction of senescent cells, where it can bind and inhibits the cyclin-dependent kinase CDK4. Overexpression of RPS14 is sufficient to inhibit RB phosphorylation, inducing cell cycle arrest and senescence. We thus describe a mechanism for maintaining the senescent cell cycle arrest that is relevant for cancer therapy, as well as, biomarkers to identify senescent cells.

A Novel mRNA localization mechanism contributes to senescence bypass in RAS tumor cells

Salotti J. and Johnson P.F.

Mouse Cancer Genetics Program, Center for Cancer Research, National Cancer Institute, Frederick, MD, USA

In normal cells, the transcription factor C/EBPβ contributes to oncogenic RAS-induced senescence and is required for expression of "senescence associated secretory phenotype" (SASP) genes. C/EBPβ is post-translationally activated by oncogenic RAS signaling through phosphorylation by the effector kinases ERK1/2 and CK2. This activated form of C/EBPb is required cell cycle arrest and SASP induction. Senescence bypass is a hallmark of tumor cells, raising the question of how the pro-senescence activity of C/EBPβ is circumvented in RAS-dependent cancers. In RAS-transformed cells, p-ERK1/2 and CK2α are localized to a perinuclear endosomal compartment, whereas Cebpb transcripts are restricted to a separate peripheral region by a 3'UTR-dependent mechanism. Thus, the newly-synthesized C/EBPβ protein is excluded from its kinases, which prevents activation by RAS signaling. This mechanism (termed 3'UTR regulation of protein activity or UPA), requires a GU-rich element (GRE) in the 3'UTR and its binding protein, HuR, and inhibits the pro-senescence functions of C/EBPβ in cancer cells (Basu et al., EMBO J 2011 30:3714-28). We recently showed that oncogenic RAS promotes HuR eviction from the cytoplasm in primary MEFs through a Ca++-CaMKKb-AMPKa2 pathway that suppresses UPA (Basu et al., Oncogene 2018). Here we present evidence that loss of the ARF tumor suppressor activates UPA. C/EBPβ activation and SASP induction by RAS is abrogated in p19ARF-/- MEFs compared to WT cells, coinciding with neoplastic transformation. Moreover, ARF-depleted MEFs derived from mice carrying a homozygous deletion of the Cebpb GRE (ΔGRE) are resistant to RAS transformation. Thus, ARF loss appears to regulate senescence bypass in part by activating UPA and suppressing C/EBPβ activity. To identify additional UPA components, we used an affinity purification/mass spectrometry approach to isolate proteins that specifically associate with the Cebpb GRE. Analysis of several candidates indicates that Upf1 (a key RNA helicase in nonsense-mediated mRNA decay) and Staufen (a dsRNA-binding protein implicated in mRNA localization and decay) promote perinuclear degradation of Cebpb transcripts. Overall, our findings suggest that C/EBPb UPA involves localized (perinuclear) mRNA decay, which prevents C/EBPb activation and facilitates senescence bypass in tumor cells.

Alternative splicing alterations potentially contribute to apoptotic resistance associated with senescence

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Senescence is a cellular state of permanent growth arrest with functions in development and anti-mutagenesis defense. It is partly characterized by flattened morphology with changes in gene expression, proteomic and RNomic profile. The accumulation of senescent cells in tissues is believed to contribute to aging and approaches to clear them out may prolong global homeostasis. Senescent cells are also distinguishable by their acute resistance to programmed cell death which raises additional challenge to senescence clearance. Given that alternative splicing is also altered during senescence and that it can produce pro- or anti-apoptotic variants, it may functionally contribute to the apoptosis resistance phenotype. Our study is conducted with the BJ line with cells ranging between 14 to 62 population doubling (PD). Senescence exponentially correlates to PD using the senescence-associated ß-galactosidase staining assay and crystal violet staining assay. Flow cytometry with Annexin-V/propidium iodide along with detection of cleaved CASP3 and PARP protein supports the view that UVC treatment specifically triggers apoptosis in younger populations. Cells were also examined for the alternative splicing profiles of 74 events occurring in genes with roles in apoptosis, DNA repair and cell cycle. Our aim is to identify functional contributors to apoptosis resistance associated with senescence by ectopically modifying alternative splicing events either by specific variant knockdown or overexpression to re-establish apoptosis sensitivity in senescent cells. These splicing alterations may also be regulated by a narrowed group of splice factors and how this regulation can be control will be asked. Ultimately, an investigation will be conduct on how these splicing events are differentially regulated in senescent cells and whether the expression of the splicing regulators is altered by telomere positioning effect (TPE).

A role for β-Dystroglycan in cell senescence

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ß-Dystroglycan (ß-DG) is a plasma membrane (PM) protein involved in cell adhesion, cell signaling and cytoskeleton remodeling. Interestingly, ß-DG undergoes retrograde trafficking from the plasma membrane to the nucleus to interact with nuclear envelope proteins (emerin and lamin B1) to regulate nuclear architecture and function. Owing the critical role of lamin B1 in senescence, we were prompted to analyze whether ß-DG is implicated in this aging-related cellular process.

In this study, we analyzed the expression and subcellular localization of ß-DG in primary fibroblasts induced to senescence by both sodium butyrate treatment and UVB irradiation. Senescence state was confirmed by different senescence biomarkers, including low lamin B1 levels, ß-galactosidase activity, flattered cell morphology and arrest at the cell cycle phase G0. Induction of premature senescence resulted in increased protein levels of full length/43 kDa ß-DG protein levels. In addition, we found a 26 kDa band that may correspond to the proteolytic fragment of ß-DG generated by ?-secretase cleavage. Recently our lab describes the function of the 26 kDa fragment of ß-DG in nucleolar function. At cellular level, senescent cells exhibited enlarged nucleoli with higher nucleolar immunostaining of ß-DG, compared with control cells, which suggests that the ß-DG 26 kDa fragment is involved in nucleolar plasticity during senescence. To ascertain whether ß-DG function is biological relevant for senescence, we isolated C2C12 muscle cells expressing depleted of ß-DG, using and small RNA interference (siRNA) against DAG1 gene. Remarkable, ß-DG-depleted cells showed decreased lamin B1 protein levels and spontaneous senescence cells. Collectively our data suggest a role for ß-DG in cell senescence through its functional association with lamin B1. Further experiments are required to deeply evaluate this hypothesis.

EMBO LECTURE

Stress-support pathways in cellular senescence and cancer: mechanisms and opportunities for intervention

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Cellular senescence, one of the fundamental cell fates, has been implicated in organismal development, aging (both timely and premature) and diverse pathologies including cancer. Mechanistically, the characteristic features of senescence including cell cycle arrest, are commonly associated with activation of the p53-p21, p16-RB and/or arf tumor suppressor pathways triggered by diverse stress signalling cascades. In this presentation, our recently published and unpublished data on triggers and mechanisms of cellular senescence, as well as their biological relevance and emerging possibilities to target such mechanisms for the benefit of our rapidly aging human populations with ever increasing frequency of chronic diseases, will be discussed. Emphasis will be on mechanistic insights into stress signalling pathways upstream of, as well as independent of, p53. Cellular responses to replication stress (and more generally genotoxic stress), ribosomal biogenesis stress, energy metabolism/oxidative stress and proteotoxic stress, as well as their emerging cross-talks and relevance for senescence will be discussed. Another major topic will be the links between senescence and cancer, particularly in terms of cellular senescence as one of the biological anti-cancer barriers, evidence for escape from the senescence during tumorigenesis, and biological significance of these phenomena, including impact on genomic instability and the underlying molecular causes. Last but not least, the roles of stress-support pathways as both, forces promoting tumorigenesis, and emerging cancer cell vulnerabilities targetable in cancer, will be considered. Our recent results on efforts to identify new compounds and ways to target senescence (senolytics) and modulate cancer-associated stress-support pathways as innovative approaches to cancer treatment will conclude the presentation.

Senescence and the tumor microenvironment

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Cellular senescence can limit the proliferation of damaged cells and act as a potent tumor suppressive mechanism. The program consists of two interacting gene expression modules: a program involving RB and p53 tumor suppressors that potently suppresses proliferation genes, and a NF-□B directed gene activation program that mediates communication between senescent cells and the tissue microenvironment. This latter transcription modulate includes a variety of transcripts that encode secretory proteins and thus is often referred to as the senescence associated secretory phenotype (SASP). While SASP can have pro- or anti-tumor effects depending on context, it can contribute to the elimination of premalignant cells by provoking immune surveillance of cells undergoing oncogene induced senescence. We recently identified a drug combination that induces cellular senescence in established lung and pancreas tumor cells harboring activating mutations in KRAS. This program is RB dependent but p53 independent. The combination also produces SASP and, in lung cancer cells and tumors, leads to their enhanced surveillance and targeting by attack of natural killer (NK) cells. As a consequence, this drug combination, which is cytostatic in vivo, causes tumor regressions and prolonged survival in mice harboring lung tumors with Kras and p53 mutations. These studies identify a means and method of invoking a unique form of NK cell mediated immune surveillance in lung tumors through molecularly targeted therapies that induce cellular senescence

Regulation of heterochromatin by the RB protein during proliferation and senescence

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The retinoblastoma (RB) tumor suppressor protein is a key regulator of the transition from proliferation to arrest and entry into senescence. It functions to enact both short cell cycle arrest, as well as organize changes in heterochromatin patterns to ensure long term arrest. We have undertaken a structure function approach to RB in cell cycle control and heterochromatin formation in which we have engineered discrete mutations into the murine Rb1 gene such that its encoded RB protein is unable to form particular protein interactions, but is otherwise expressed normally. We have previously reported that mutations in Rb1 that support short term cell cycle arrest, but prevent the formation of senescent heterochromatin leave cells in an incomplete state of senescence in which they are prone to re-enter the cell cycle. Surprisingly, when examined in a K-RasG12D mouse model of lung cancer this mutant allele didn't enhance cancer progression, but instead suppressed it as Rb1 mutant cells that bypassed senescence experienced high levels of DNA damage and were prone to apoptosis. This paradoxical result motivated us to develop a broader understanding of RB's roles in chromatin regulation could explain how defective senescence and DNA damage could be linked.

In order to understand RB's many roles in chromosome structure, we have used ChIP-seq and chromosome conformation capture approaches. This work has allowed us to create a comprehensive map of RB's genome locations, and through the use of our structurally defined mutant alleles of Rb1 we are gaining insight into its functions at these different locations. We have determined that RB's association with chromatin is cell cycle responsive at some locations, but invariant at others. Among cell cycle independent genome locations, RB associates with repetitive elements and divergently transcribed promoters with high frequency. At these locations it organizes H3K27me3 to silence repeat expression, and at satellite repeats and divergent promoters it recruits the Condensin II complex to organize higher order chromosome structure. Reduced Condensin II recruitment is most closely correlated with DNA damage events suggesting loss of RB in chromosome compaction is mechanistically linked to DNA damage.

A disorderly way to induce senescence

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The majority of human genes are alternatively spliced, with an average of 6.3 transcripts identified per gene, of which an average of 3.9 transcripts/gene encode protein. Alternative isoforms of both the p53 and p16 tumor suppressors appear to increase during cell aging (replicative senescence) of normal diploid cells, but their biological functions are unclear despite being able to effect senescence when overexpressed. We have found that levels of the ING1a isoform of the INhibitor of Growth epigenetic regulator and type II tumour suppressor increase during replicative senescence and can induce senescence in otherwise growth-competent cells when expressed at levels similar to those seen during senescence. ING1a contains a relatively unique disordered region that may serve as a target for multiple kinases. We find ING1a induces senescence by inhibiting endocytosis and activating the retinoblastoma (Rb) tumor suppressor pathway by inducing Rb transcription and blocking its inactivation by phosphorylation. Our study has established a link between senescence and endocytosis, and suggests that multiple mechanisms that induce cellular senescence may do so through inhibiting normal endocytic processes, affecting normal signal transduction pathways including those mitogenic pathways required for cell growth.

p53 and senescence: the NADPH connection

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Sponsord by Senolytic Therapeutics Inc.

Obesity and cellular senescence: a gut microbial connection

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Multiple epidemiological studies have revealed that obesity is a major risk factor for not only diabetes and cardiovascular diseases but also cancer. Therefore, effective strategies for obesity prevention are needed for cancer prevention. However, since the prevalence of excess bodyweight in most developed countries has been increasing markedly over the past several decades, alternative approaches are also required to conquer obesity-associated cancer. Although several phenomena have been proposed to explain how obesity increases cancer risk, the exact molecular mechanisms underlying obesity-associated cancer have remained largely obscure. Recently, we have traced the association between obesity and increased risk of hepatocellular carcinoma (HCC) development to gut microbiota communities that provoke cellular senescence in hepatic stellate cells (HSCs) through increasing the levels of deoxycholic acid (DCA), a gut bacterial metabolite known to cause DNA damage. The enterohepatic circulation of DCA provokes SASP in hepatic stellate cells (HSCs), which in turn secretes various inflammatory and tumor-promoting factors in the liver, thus facilitating HCC development in mice after exposure to chemical carcinogen. However, it remains unclear exactly how DCA provokes SASP in HSCs in obese mice and which bacteria are involved in DCA production in obese mice. Here, I report recent progress on the link between cellular senescence and obesity-associated HCC. I believe that a better understanding of the molecular mechanisms involved will lead to new strategies for the prevention of obesity-associated cancer.

Targeting a mitochondrial-cytoplasmic chromatin signalling axis to suppress senescence associated inflammation

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Cellular senescence is a highly stable cell cycle arrest elicited by replicative exhaustion or stresses such as DNA damage, oxidative stress and aberrant oncogenic activation. The senescence response is now considered a potent barrier to tumorigenesis but is paradoxically also implicated in aging. Senescent cells secrete a group of factors known as the senescence-associated secretory phenotype (SASP). The SASP reinforces senescence and promotes immune-mediated clearance, but it can also alter the tissue microenvironment contributing to age-related pathologies including cancer. Non-cytotoxic inhibitors of SASP might have value in suppressing the pro-aging effects of senescent cells, without the toxicity of senolytics. In previous surprising findings we discovered that senescent cells extrude fragments of YH2AX-positive chromatin from the nucleus into the cytoplasm, so-called cytoplasmic chromatin fragments (CCFs) dependent on a nuclear lamin B1-LC3 interaction (Ivanov et al., 2013, JCB; Dou et al., 2015, Nature). We also showed that CCFs activate the innate immunocytosolic DNA sensing cGAS-STING pathway, triggering SASP (Dou et al., 2017, Nature). Here we define the molecular mechanisms of CCF formation. We show that a mitochondria-ROS-JNK signalling pathway drives CCF and hence SASP. Importantly, we show that low doses of HDAC inhibitors, well known anti-inflammatory agents, are able to suppress the mitochondria-to nucleus retrograde signal that triggers CCF and SASP. These results delineate an extended mitochondria-to-nucleus retrograde signalling pathway that initiates formation of CCF and is a target for drug-based interventions to inhibit the SASP.

Loss of p16 mediates senescence bypass through metabolic reprogramming induced by the DNA damage response and mTORC1 pathways

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Oncogene-induced senescence (OIS) is a bona-fide tumor suppressor mechanism characterized by replication stress leading to a sustained DNA damage response (DDR) and proliferative arrest. Our previous studies showed that the replication stress and DDR during OIS are in part caused by Dntp depletion due to suppression of ribonucleotide reductase M2 (RRM2, the rate-limiting enzyme for dNTP synthesis). Knockdown of RRM2 induces senescence, while supplementation with exogenous nucleosides overcomes senescence. Thus, inhibition of dNTP synthesis is crucial for the senescence-associated cell-cycle arrest. Overactivation of the metabolic pathways fueling dNTP synthesis is critical in tumorigenesis. Hence, understanding the endogenous mechanisms by which cells increase dNTPs to bypass senescence will shed light on this early step in tumorigenesis. To determine which genes are important for dNTP synthesis to bypass senescence, we performed an shRNA screen in dNTP depleted cells. We found that knockdown of p16 restored dNTP levels in shRRM2 cells and bypassed senescence. Interestingly, loss of p16 is concomitant with RAS/BRAF activation in multiple cancers. Together, these data suggest that p16 suppresses dNTP levels in senescent cells to limit DNA replication and proliferation.

Given the role of the p16-RB-E2F pathway in transcription, we performed an RNA-Seq analysis between senescent (shRRM2) and senescent-bypassed (shRRM2/shp16) cells. Gene-ontology showed an enrichment in DNA damage response and terms associated with dNTP synthesis through the mTORC1 pathway. Consistently, senescence-bypassed cells showed an increased activation of ATR and mTORC1 via p-Chk1 and p-S6K, respectively. ATR inhibition impaired senescence-bypass, which correlated with decreased mTORC1 activity. Likewise, mTORC1 inhibition also suppressed senescence-bypass. Finally, p16 knockdown in p16wt cancer cell lines promoted mTORC1 activation and cell proliferation, while mTORC1 inhibition reversed this phenotype. These data suggest that loss of p16 promotes mTORC1 activation though the ATR pathway, allowing for increased dNTP synthesis to fuel cell proliferation and bypass senescence. Together, our results indicate that loss of p16 not only affects the cycle cycle, but also induces a pro-tumorigenic metabolic reprogramming. Additionally, combinatorial mTORC1/ATR inhibitor treatment may open a therapeutic window for patients with concomitant oncogene activation and p16 loss.

Obesity-Induced cellular senescence drives neural stem cell dysfunction and anxiety

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Cellular senescence entails a stable cell-cycle arrest and frequently a powerful pro-inflammatory senescence-associated secretory phenotype (SASP), which is thought to contribute to aging and age-related diseases. Obesity is associated with low-grade inflammation, increased senescent cell burden, and neurological disorders, including anxiety and depression. To investigate the role of cellular senescence in anxiety, we used INK-ATTAC mice, from which highly p16Ink4a-expressing cells can be cleared, and senolytic drugs, which induce apoptosis in senescent cells. We found that high fat diet-induced obesity results in accumulation of glial cells exhibiting increased levels of markers of senescence in proximity to the lateral ventricle (LV), a region in which adult neurogenesis occurs. Clearing senescent cells from high fat-fed and leptin receptor-deficient (db/db) obese mice restored neurogenesis, and alleviated anxiety-related behavior.

From the clinic: Cancer therapy-induced senescence, good or bad?

Francis Rodier
CRCHU

Cellular senescence is an anticancer program that link stress responses to tissue remodeling. The impact of senescence on tissue homeostasis is due to context-dependent beneficial and detrimental effects accompanying senescent cells. Although we know that therapy-induced senescence (TIS) and other cell fate decisions like apoptosis (cell death) must occur during cancer treatment, whether they differentially alter the biology of damaged human tissues (and tumors), or impact clinical treatment outcomes for patients remains unknown. To explore this question, we use cancer biobank-derived human tissues and evaluate the relationship between clinical data and key senescence-associated (SA) hallmarks including persistent DNA damage responses (DDR), SA proliferation arrest (SAPA) and SA secretory programs (SASPs). Our data on two major subtypes of human ovarian cancer imply for the first time that a state of “senescence-competence” in cancer cells may have a beneficial impact on treatment outcome for patients, suggesting that senescence-competence should be evaluated contextually in the clinic for other cancers. Despite this positive side, we challenge the notion that cancer TIS is irreversible under current treatment modalities and propose pharmaceutical strategies to manipulate TIS to circumvent this problem and further improve treatment outcome.

Escaping from oncogene-induced senescence

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Oncogene induced senescence (OIS) is activated by the coordinated action of the DNA damage response (DDR) pathway and ARF, alternatively to apoptosis, in early stages of cancer, preventing transformation of incipient cancer cells. Progression to cancer requires antitumor barrier bypass and occurs when critical DDR and ARF pathway components like p53 are impaired, fueling genomic instability. This explains the frequent p53 mutations in cancer and how apoptosis results in "clearance" of incipient cancer cells while escape from OIS, which is a viable state, remains an uncharted territory.

Detection of senescence is of paramount importance, especially in vivo, as it plays a bimodal role in cancer and seems to be related to prognosis. Moreover, estimations on the outcome of Senotherapeutics that target senescent cells require a reliable senescence biomarker. Until recently, available methods failed to accurately recognize senescent cells in vivo. This conundrum was lately addressed by the development of an innovative biotinylated Sudan Black-B (SBB) analogue (SenTraGorTM) and hybrid histochemical/immunohistochemical method, that allows detection of senescent cells in any biological material (including archival one).

As shown here for the first time in vivo, using the SenTraGorTM methodology, senescence occurs in primary human malignancies and is related to adverse clinical outcome. This might be attributed either to the pro-tumorigenic effect of SASP or to the fact that neoplastic cells "trapped" in senescence exhibit tolerance against classical antitumor strategies and can subsequently escape from senescence. In this context, tumor relapses and a worse clinical outcome may occur rendering their elimination in primary lesions, as a complementary strategy, an attractive perspective.

To examine these issues and to recapitulate the in vivo findings in vitro, we developed prototypical cellular OIS models. Various manipulations that resulted in aberrant chronic stabilization of the replication licensing factors Cdc6 and/or Cdt1 led to an evolutionary recapitulation of cancer development. Initially, a senescence-like state was observed, characterized by replication stress, DNA-damage and an error-prone DNA repair process that eventually altered the genome. Following, a subpopulation of cells emerged that re-entered the cell cycle. Interestingly, these "escaped" cells exhibited aggressive features and increased chemo-resistance, while epithelial derived ones underwent epithelial to mesenchymal transition.

These findings have uncovered an unprecedented mode of how oncogenes drive cancer development, through escape from senescence, providing also new opportunities for cancer treatment.

Ionizing radiations scattering at the margin of the treated volume during radiation therapy induce DNA single-strand breaks, senescence and neoplastic escape of normal fibroblasts

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The persistence of unrepaired DNA damages (shortened telomeres, DNA double strand-breaks (DSBs) or hyper-replication stress) inducing a persistent DNA Damage Response (DDR) is the major cause of the irreversibility of the senescent cell cycle arrest. However, we have recently shown that epithelial cells (normal human keratinocytes and mammary epithelial cells) undergo in vitro and in vivo a senescence program which is DDR-independent. Instead, it is oxidative-stress dependent, associated with persistent DNA single-strand breaks (SSBs). Importantly, some of these senescent epithelial cells systematically escape the cell cycle arrest to give rise to transformed, mutated and tumorigenic cells (Nassour et al, Nature Commun, 2016).

A severe complication of radiotherapy is the induction of a second primary cancer (SPC) in 1% to 2% of cases. SPCs are not a recurrence of the initial cancer, but are generated from normal cells affected by the radiations. Amazingly, SPCs preferentially develop at the margin of the treated volume, where there is only some diffusion of low energy ionizing particles (electrons).

The ionizing radiations used in radiotherapy produce DSBs which are assumed to be primarily responsible for inducing cancer cell death. However, ionizing radiations also produce reactive oxygen species and SSBs and can induce senescence. Therefore, we have characterized the DNA damages encountered by normal fibroblasts positioned at the margin of a field irradiated at 2Gy per day (i.e. mimicking a standard radiotherapeutic protocol) and analyzed their outcome at long term. Our results indicate that these cells do not undergo DSBs and cell death, but SSBs and senescence after 3 weeks of treatment. Moreover, 7 to 10 days after the end of the treatment, some cells escaped the senescent cell cycle arrest to give rise to a progeny of mutated cells. Taken together, these results suggest that the ionizing particles which diffuse from the border of an irradiated field could induce an oncogenic premature senescence associated to an accumulation of SSBs.

Regulation of Senescence Escape by the TSP1-CD47 Pathway Following Chemotherapy Treatment

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Senescence is a tumor suppressive mechanism induced by telomere shortening, oncogenes or chemotherapy treatment. Although it is clear that this suppressive pathway leads to a permanent arrest in primary cells, this might not be the case in cancer cells that have inactivated their suppressive pathways. We have recently shown that subpopulations of cells can escape chemotherapy-mediated senescence and emerge as more transformed cells that induce tumor formation, resist anoikis and are more invasive. In this study, we characterized this emergence and showed that senescent cells favor tumor growth and metastasis, in vitro and in vivo. Senescence escape was regulated by secreted proteins produced during emergence. Among these, we identified thrombospondin-1 (TSP1), a protein produced by senescent cells that prevented senescence escape. Using SWATH quantitative proteomic analysis, we found that TSP1 can be detected in the serum of patients suffering from triple-negative breast cancer and that its low expression was associated with treatment failure. Results also indicate that senescence escape is explained by the emergence of CD47low cells that express a reduced level of CD47, the TSP1 receptor. Results show that CD47 expression is regulated by p21waf1. The cell cycle inhibitor was sufficient to maintain senescence since its downregulation in senescent cells increased cell emergence. p21waf1 inhibition reduced CD47 expression and allowed the generation of CD47low cells that escape the suppressive arrest. Altogether, these results uncovered a new function for the TSP1-CD47 pathway in the control of chemotherapy-mediated senescence.

Autophagy in ageing and cancer

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Autophagy is a bulk cellular degradation system, playing a critical role in the quality control of macromolecules and metabolic homeostasis. Autophagy activity declines with age and, at least in lower eukaryotes, an autophagy defect promotes ageing. While autophagy is anti-ageing machinery, the precise role of autophagy in cancer, a major age-related disorder, is not entirely clear: it can be both tumour suppressive and pro-tumorigenic depending on the context. Here, we have generated a mouse with a doxycycline (dox) inducible knockdown of a key autophagy gene, Atg5 (called Atg5i mice), enabling temporal control of autophagy levels in vivo. In contrast to typical knockout mouse models for autophagy genes, due to the limited permeability of dox through the blood-brain-barrier, dox-fed Atg5i mice do not show the rapid lethality associated with neurotoxicity. They instead reveal accelerated age-associated phenotypes with no evidence of tumour development. Autophagy restoration by removing dox after a prolonged period of autophagy inhibition alleviates the otherwise premature death of the Atg5i mice and some their age-related phenotypes, implying a segmental reversibility to ageing. Strikingly, however, these mice often develop malignant tumours. This suggests that, while a chronic period of autophagy deficiency, which leads to reduced cellular integrity, is not sufficient for tumour development but subsequent restoration of 'basal' autophagy promotes malignant transformation, recapitulating the dual role of autophagy in cancer.

Senolysis addresses an unmet clinical need in atherosclerosis therapy

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Our work on a mouse model for Mosaic Variegated Aneuploidy (MVA), a rare progeroid human disorder caused by deficiencies in the mitotic checkpoint protein BubR1, led to the discovery of a causal link between the accumulation of senescent cells and the development of age-related phenotypes. These findings raised the question as to whether the clearance of senescent cells from tissues and organs, now commonly referred to as senolysis, can delay aging and prevent or attenuate age-related diseases. Using several transgenic mouse models that we designed to selectively eliminate senescent cells upon the administration of various drugs, we established that senescent cells drive aging and age-related diseases. With regard to atherosclerosis, a major disease that is the primary cause of myocardial infarction, we found that senescent cells drive atherogenic lesion initiation, growth, and rupture, and that senescent cell clearance by transgenic or pharmacological approaches had a dramatic therapeutic impact without causing any detectable side effects. Here will present recent insights into the role of senescent cells in the development of unstable and thrombogenic plaques that result in heart attack, stroke or other severe ischemic injuries. We provide evidence that senolysis induces disease regression, thereby addressing an unmet clinical need in atherosclerosis therapy.

Cellular senescence is a combination of distinct phenotypes

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Aging is characterized by increasing severity of chronic, sterile, systemic inflammation ("inflammaging") that is believed to drive multiple aging-related frailty and other pathologies. "Inflammaging" has been attributed to the accumulation of senescent cells (SC) as a putative cause of systemic inflammation. The term "senescent" is commonly applied to the cells that underwent an irreversible proliferation arrest as a consequence of DNA damage and acquired a series of specific properties including the secretion of proinflammatory factors (senescence-associated secretory phenotype or SASP) and expression of senescence-associated β-gal (SA□GAL). Senescence is not an immediate result of DNA damage and requires several days for its establishment. Molecular events underlying development of senescent phenotype and their relationship with DNA damage are poorly understood. Biomarkers of SC were historically identified based on the comparison of cells at different time points following DNA damage-induced growth arrest with untreated cells capable of proliferation. Potential contribution of a long-term growth arrest in a medium rich in nutrients and growth factors to the phenotype of SC has not been addressed. To dissect the impacts of DNA damage response and long-term incubation in arrested state, we compared transcriptomes of intact diploid human fibroblasts (strain WI38) arrested by contact inhibition and cultivated under the same conditions as cells following variety of DNA damaging treatments that were collected at different times (2, 12 and 22 days after treatment). Principal component analysis (PCA) was applied to the analysis of deep RNA sequencing data to reveal major tendencies occurring among the transcriptomes. We found clear clusterization of the transcriptomes along two distinct directions reflecting the time of cultivation in arrested state (PC1) and DNA damaging treatment (PC2). The major differences (PC1 axis) do not depend on the senescence-inducing treatments and reflect common transcriptional reprogramming that occur in arrested cells following long-term cultivation in rich medium regardless of DNA damage. Treatment-associated patterns (PC2 axis) are established early following treatment and do not undergo significant changes at the later time points. These results suggest that the phenotype of SC is a superposition of two phenotypes, one of which depends on the time of cultivation in arrested state and the other one – on the type of treatment. The analysis of gene sets indicative of the PC1 and PC2 processes showed that SASP and SA□GAL are independent of irreversible growth arrest as they are similarly acquired by treated and untreated cells following long-term incubation in arrested state. These results require modification of existing views on SC and DNA damage in aging.

Senescent cells in tissue trauma and repair: a bridge to the immune system

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Tissue engineering or regenerative medicine evolved as a field 20 years ago to address the challenge of providing replacements for tissue lost due to trauma, disease or congenital abnormalities. The discovery of stem cells infused great excitement into the field but clinical impact has thus far been limited, suggesting that there are other key factors that are important for their efficacy and tissue repair. While the involvement of the innate immune system has been recognized in tissue repair, we recently demonstrated that the adaptive immune system and Th2 T cells in particular are also involved and help to create a pro-regenerative environment in response to biological scaffolds. Senescence cells (SnCs) and their associated senescence associated phenotype (SASP) can promote tissue repair in the early phases but can be detrimental in the long term as demonstrated with injury in the articular joint. SnCs develop and remain in the local tissue chronically after articular joint injury, leading to osteoarthritis and tissue degradation. Clearance of these SnCs reduces OA development and actually supports new tissue development in young mice. SnCs secrete many cytokines and chemokines the attract and impact the immune response. A Th17 immune profile is generated after articular joint trauma which is significantly reduced after local senolytic clearance in young and aged animals. However, systemic SnC clearance promotes a interleukin (IL)-4 and Th2 pro-regenerative immune response even in aged animals. SnCs in the tissue stroma may be a critical link with the immune system that can regulate tissue specific effector profiles, repair and regeneration.

The Role Of p16INK4a expression in cartilage aging and osteoarthritis development

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INTRODUCTION: Aging is the greatest risk factor for the development of osteoarthritis (OA), and the increased presence of senescent cells with aging may drive OA through the production of matrix-degrading and pro-inflammatory factors known as the senescence associated secretory phenotype (SASP)1. Using transgenic and senolytic approaches, the targeted elimination of senescent cells from the joint was effective in reducing post-traumatic OA2. To investigate senescence in aged chondrocytes, we evaluated the gene expression and functional role of the senescence biomarker p16INK4a (hereafter p16). We hypothesized that p16 expression increases with age in primary human chondrocytes and that in vivo genetic deletion of p16 in murine chondrocytes would limit the development of age-related OA.

METHODS: Primary human chondrocytes were isolated from normal cadaveric ankle tissue for gene expression analysis. For OA studies, cohorts of male mice were injected with tamoxifen at skeletal maturity to induce cartilage-specific loss of p16INK4a (p16 loss, AggrecanCreERT2:p16flox/flox) alongside controls (p16 intact, AggrecanCreERT2:p16wt/wt). Age-related OA was assessed at 18 months using an established histological scoring system.

RESULTS and DISCUSSION: Gene expression of p16 was increased in murine cartilage at 18 months and 22-27 months of age as compared to 4 month old mice ($p<0.05$). p16 also showed a strong correlation to age in primary human chondrocytes from 57 donors aged 17 to 72 ($r2 = 0.2682$, $p<0.0001$). The expression of SASP factors such as matrix metalloproteinase (MMP-1) was higher in donors with high p16 expression but did not independently correlate with age. OA developed to varying degrees in 18-month-old mice and the chondrocyte-specific loss of p16 was insufficient to alter the rate of age-related OA. Taken together, these findings suggest that p16 is a biomarker of chondrocyte dysfunction but that p16 expression is not functionally required to mediate the catabolic features of senescent cells. Current work is investigating the mechanism of senescence induction in cartilage explant tissue for applications in senolytic screening.

REFERENCES: This work is in press at Aging Cell (doi: 10.1111/acel.12771). 1) Loeser RF, Collins JA, Diekman BO, 2016, Nat Rev Rheumatol. 12, 412-420. 2) Jeon OH et al, 2017, Nat Med. 23, 775-781.

The two faces of cellular senescence in tissue repair and in multiple diseases

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Upon tissue damage or stress, a substantial fraction of cells respond by adopting a cellular state known as “senescence”. Regardless of their initial cell identity, senescent cells share key properties; namely, global chromatin remodelling, robust proliferation blockade, and a massive pro-inflammatory secretome. Major advances in recent years indicate that the biologic purpose of senescent cells is to orchestrate tissue repair, ultimately leading to their own disposal by the immune system and to their replacement by new, functional cells. This is the favorable, beneficial, face of cellular senescence. However, in certain contexts that are generally associated with chronic damage, degenerative processes, or organismal ageing, tissue repair is inefficient and senescent cells are not cleared. Indeed, senescent cells accumulate in many human pathologies including various fibrotic diseases, atherosclerosis, and neurodegenerative diseases. This is the detrimental, pathological, face of cellular senescence. Importantly, the last few years have witnessed the identification of pharmacologic interventions that preferentially kill senescent cells, termed senolytics. Such senolytic treatments in mice show an unprecedented therapeutic effect on animal models of the aforementioned diseases including lung fibrosis, atherosclerosis, and neurodegenerative diseases. I will present our contributions to the understanding of cellular senescence both in tissue repair and in pathological contexts.

Implicating senescent cells to neurodegenerative disease

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The single greatest risk factor for the development of diseases and pathologies in people is advancing age. With increased life expectancies, the economic ramifications of this correlation are astounding. A potential mechanistic explanation of this association is that the fundamental processes of aging actively promote tissue dysfunction and age-associated diseases. Several groups have recently identified cellular senescence as a fundamental process of aging that associates with many of these diseases. Interestingly, cells with features reminiscent of senescence have been found in a variety of neurodegenerative diseases, including Alzheimer's disease and Parkinson's disease. This research suggests that senescent cells may contribute to both the initiation and progression of neurodegenerative diseases. Data supporting this hypothesis and potential therapeutic opportunities will be highlighted.

Systemic influences on tissue senescence and effect of senescent cell ablation on regeneration of muscle, liver and brain

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Heterochronic parabiosis and blood exchange studies provided a proof of principle that tissue health and regenerative responses are influenced by the age of circulatory milieu. The molecular and functional connection between the aging of solid tissues and the circulatory milieu is not well understood, and here we will discuss the idea that one key local mechanism that can be influenced by systemic changes is cellular senescence. The work in progress using the p16-3MR mouse model demonstrates that high p16 levels, a hallmark of cellular senescence become induced in adult mice through parabiosis to old animals, and that depletion of senescent cells in aged mice quickly enhances regeneration of muscle and reduces liver adiposity, but does not enhance hippocampal neurogenesis or hepatogenesis. These results suggest the causes of cellular senescence are not entirely intrinsic cellular changes but involve extrinsic, systemic regulation. These data also expand on the positive outcomes of depleting senescent cells and pave the way for to identify and inhibit age-imposed physiologic systemic molecules, to reverse tissue senescence.

Cellular Senescence in Childhood Bone Homeostasis

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Childhood and adolescence are critical periods for optimizing bone growth and mineral accrual. Specifically, bone growth and apposition are characterized by a sharp increase during early puberty, and deceleration and eventual cessation during late puberty and young adulthood. However, little is known about changes in bone cell fate and the regulatory mechanisms in postnatal skeleton. Using mouse models, we found that mesenchymal stem/progenitor cells (MSPCs) in primary spongiosa of long bone during late puberty undergo a normal programed senescence, which was defined by the presence of a senescence marker SA-ßGal and common senescence effector genes p16INK4a, p15INK4b, and p21CIP1 as well as the reduced proliferation rate. Moreover, MSPC senescence is epigenetically controlled by the polycomb histone methyltransferase Ezh2 and its H3K27me3 mark. Ezh2 maintains the repression of the senescence effector genes through H3K27me3, and deletion of Ezh2 in early pubertal mice results in premature cellular senescence, depleted MSPCs pool, and impaired osteogenesis as well as osteoporosis in later life. Therefore, cellular senescence in primary spongioa is an important signature for the transition from fast to slow growing phase in long bones during childhood. For children with genetic skeletal disorders or chronic disease, bone growth and mineral accrual are often compromised, leading to osteoporosis and high bone fracture rate. Glucocorticoid (GC)-induced osteoporosis is the most common form of secondary pediatric osteoporosis, with up to 34% prevalence of vertebral fractures in children and youth with long-term GC therapy. We examined the effect of glucocorticoid (GC) on bone cell senescence, and found that young mice treated with prednisolone developed early onset cellular senescence in primary spongiosa of long bone, followed by impaired angiogenesis and osteogenesis. The senescent cells exhibited much lower expression of Ezh2 and its H3K27me3 mark. Histone demethylase UTX mediates removal of repressive H3K27me3. Dramatically reduced senescent cells were detected in femoral primary spongiosa of the UTX iKO mice relative to WT mice. Importantly, elevating H3K27me3 by UTX deletion maintained angiogenesis and osteogenesis and rescued the bone loss phenotype caused by prednisolone. Thus, antagonizing cellular senescence by manipulating epigenetic factors may be a potential approach to treat pediatric or juvenile osteoporosis.

Upregulation of RANKL due to osteocyte senescence is a critical mechanism of skeletal aging

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Like humans, mice lose bone mass with advancing age. Loss of cortical bone with age is associated with increased osteoclast number and bone resorption at the endocortical surface. Osteocytes – formed when osteoblasts become buried in the bone matrix – are an essential source of RANKL, the critical cytokine for osteoclast formation. Old mice exhibit increased markers of DNA damage, elevated p16 and expression of the senescence associated secretory phenotype (SASP), accumulation of GATA4, as well as increased expression of RANKL in osteocytes. Elimination of p16-expressing cells in old mice using the INK-ATTAK model increases bone mass. However, the cellular and molecular mechanisms mediating these effects remain unknown. Here, we examined whether cellular senescence in osteocytes caused by DNA damage and GATA4 activation could be responsible for the increase in RANKL with old age. Exposure of ex-vivo cultures of osteocyte enriched cortical shafts or bone marrow-derived stromal cells from young C57BL/6 mice to γ-radiation (IR) caused an increase in γH2AX, GATA4 and RANKL. Overexpression of GATA4, using a retroviral vector, in primary osteoblastic cells or osteocytic cell line increased the production (or expression) of RANKL and other elements of the SASP. To test whether elimination of senescent cells in old mice altered RANKL levels, we administered the senolytics ABT263, or Bcl-PROTAC that selectively degrades Bcl-xl for 30 days to 24 months female mice. Both stromal cell cultures and osteocyte-enriched shafts from mice treated with the senolytics had decreased markers of senescence and lower transcript levels of RANKL compared to mice treated with vehicle. To determine if osteocyte-derived RANKL plays a role in age-associated bone loss, we deleted the RANKL gene using a Dmp1-Cre transgene and compared bones of conditional knockout (CKO) and control (f/f) female littermates at 6 and 24 months of age. MicroCT analysis revealed that control mice lost a significant amount of femoral cortical thickness between 6 and 24 months of age. In contrast, CKO mice exhibited no loss of cortical bone mass with age. Our findings indicate that RANKL is a novel component of the SASP in osteocytes and that osteocyte senescence represents a critical mechanism of skeletal aging.

The shifting landscape of cellular senescence

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Cellular senescence was first described in two classic papers by Hayflick and colleagues that were published in the 1960s. At that time, cellular senescence was proposed to contribute to mammalian aging by virtue of the stringent growth arrest that was, and remains, an integral part of the senescence response. We now know that senescent cells adopt a much more complex set of traits, and that their role in aging phenotypes and pathologies is not due solely to the failure of senescent cells to proliferate. These traits include a robust but variable senescence-associated secretory phenotype (SASP), limited but important bystander effects, and the ability to stimulate or inhibit the immune system, all depending on the physiological context. Accordingly, we now know that senescent cells can have either beneficial or deleterious effects on tissues and organisms, again, depending on the physiological context. I will discuss the intricacies of the SASP, particularly with regard to its cell type specificity, dynamics, inducer specificity and the complexity and variability of its composition. I will also discuss new phenotypes that might comprise the senescence response, largely through activities of the SASP, and their implications for aging phenotypes and age-related pathologies. Finally, I will discuss the importance of understanding when and where it might be beneficial to harness the power of senolytic agents to selectively target senescent cells for elimination in order to treat a host of age-related diseases.

Humanized mouse models as a tool to study cellular senescence

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Increased expression of the p16INK4a tumor suppressor gene is frequently observed in senescent cells independently of the senescence inducer. In particular, we and other previously showed that exposure to ionizing radiation (IR) leads to a deferred (several weeks) p16INK4a expression in mice and human tissues. The reason for this delay is unclear but we showed is necessary to protect mice against cancer progression. Yet, in most tissues, the accumulation of senescent cells is detrimental. Why do senescent cells accumulate in vivo is not clear but has been associated to a decline in immune functions with age. Indeed, we recently observed that IR-induced p16INK4a expression contributes to loss of immune cell functions in the spleen, an effect that was reversible upon the genetic clearance of senescent cells. Nonetheless, oncogene-induced senescent cells were shown to be eliminated by immune cells in the liver of mice. However, whether human senescent cells are also immunologically cleared in vivo is unknown. To answer this question, we developed two distinct humanized mouse models (hu-BLT and hu-AT) generated respectively following the injection of foetal liver cells and thymus or by the adoptive transfer of adult peripheral blood mononuclear cells. Results showing human senescent cells clearance in presence of a competent human immune system will be presented.

A potential role for cholesterol metabolism in regulating cellular senescence

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Neoplastic transformation is a complex multi-step process during which activation of oncogenes and inhibition of tumor suppressor genes drive unfettered cellular proliferation. In response to aberrant oncogenic signaling, normal cells engage intrinsic anti-tumor responses such as apoptosis or senescence. Cellular senescence is a distinct state of stable growth arrest characterized by profound changes in chromatin structure, gene expression, and metabolism. Oncogene-induced senescence (OIS) is often observed in premalignant tumors eg., lung adenomas, neurofibromas, and dysplastic naevi. Moreover, recent studies indicate that OIS constitutes a powerful tumor suppressive mechanism in vivo, and pro-senescent therapies per se can inhibit cancer progression. In addition, senescence has also been documented in tumors treated with genotoxic chemotherapeutics often defining its contribution to positive treatment outcome. On the other hand, the vast majority of age-associated diseases display accumulation of senescent cells within the affected tissue, which might contribute to the aging phenotype by affecting tissue homeostasis. In addition, age-dependent accumulation of senescent cells occurring in multiple tissues such as skin, lung, spleen, and liver may play a role in tissue degeneration. Interestingly, clearance of senescent cells delays the onset of age-related pathologies and extends health span.

Senescent cells secrete numerous inflammatory cytokines, which trigger cellular senescence in surrounding cells, stimulate immune-mediated clearance of senescent cells and promote stemness and pluripotency. Secretion of cytokines contributes to the clearance of pre-cancerous senescent cells carrying activated oncogenes. However, the different molecular mechanisms underlying the establishment of senescence and the regulation of the SASP are complex and remain to be further determined. Here we discuss a novel link between cholesterol metabolism and regulation of cellular senescence in response to oncogene activation but also in a mouse model of retinopathy, a condition associated with the accumulation of senescent cells.

Targeting alternative splicing to regulate the SASP

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Oncogene-induced senescence is a potent tumor-suppressive response. Paradoxically, senescence also induces an inflammatory secretome that promotes carcinogenesis and age-related pathologies. Consequently, the senescence-associated secretory phenotype (SASP) is a potential therapeutic target. Here, we describe an RNAi screen for SASP regulators. We identified 50 druggable targets whose knockdown speficically suppresses the inflammatory secretome without reverting the senescence growth arrest. Interestingly, the identified candidates differentially regulate other components of the senescent secretome, therefore providing a toolbox to sample SASP function. One of the identified candidates is PTBP1, a regulator of alternative splicing previously shown to promote cancer proliferation and metastasis. We show that PTBP1 controls the SASP by regulating an alternative splicing program that includes genes involved in intracellular trafficking, such as the exocyst component EXOC7. Knockdown of PTBP1 in vivo reduced the pro-tumorigenic effects of senescence and impaired senescence immune surveillance. Interestingly, the impaired clearance of preneopastic hepatocytes did not translate in an augmented risk of tumorigenesis. These findings suggest that targeting the pro-inflammatory SASP is a safe and effective therapeutic strategy that can be employed against inflammation-driven cancers such as advanced liver tumors.

High Mobility Group Box 1 protein's effect in paracrine-induced senescence

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Increasing evidence indicate that senescence cells exhibit a robust secretory phenotype which contribute to aging pathologies. In addition to the Senescent Associated Secretory Phenotype (SASP), senescent cells display a unique cellular signature which includes, chromatin reorganization, loss of nuclear membrane protein and secretion of Damage Associated Molecular pattern (DAMP), High Mobility Group Box 1 protein (HMGB1). Of interest, some studies suggest secreted factor(s) induce senescence in neighboring non-senescent cells. This paracrine or bystander effect caused us to focus on senescence secreted factors which may drive senescence. We initially cultured non-senescent primary cells with conditioned medium taken from irradiation-induced senescence cells. We measured markers of senescence (SA-β-Galactosidase, proliferation, DNA Damage Foci (DDF), SASP factors). Media from cultured senescent cells promoted a 3-8 fold increase in senescent markers compared to media from non-senescent cells. We previously reported that senescent cells actively secrete HMGB1, a founding member of the DAMP family, which prompted us to cultured non-senescent cells with recombinant HMGB1 (rHMGB1) and measure the appearance of senescence markers. Similar to results with condition media taken from irradiated senescent cells, rHMGB1 induced senescence in approximately 30% of the cell population. While rHMGB1 failed to induce secretion of prototypical SASP factors, cells cultured with rHMGB1 exhibited an increase in DDF, MMP-3, p53 and p21 protein expression. Importantly, cultured cells pre-incubated with an HMGB1 blocking antibody or in cells depleted of p53, but not p16, blunted the senescence-inducing effect. Biotin-conjugated rHMGB1 remained at the cell membrane periphery which suggested senescence induction stemmed from receptor mediated signaling. Our initial studies discounted RAGE (Receptor Advanced Glycation End products) as driving senescence induction. Mouse embryo fibroblasts obtained from a senescence mouse model (3MR-mice) exhibited elevated luminescence (senescence marker) when incubated with rHMGB1. Mouse cells cultured with old mice sera (32 month) exhibited elevated levels of senescence markers compared to sera from young mice (4 month). Pre-culturing cells with a HMGB1 blocking antibody significantly attenuated senescence-inducing effect of factors contained in old sera. Our studies expand the role of HMGB1 in senescence and identify it as a possible target for therapeutic intervention in select aging pathologies.

Senescent cells incidence: controllers and outcomes

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Multiple senolytic approaches were suggested in order to target senescent cells in aging and age-related diseases. I'll review these approaches and their possible effects from the evolutionary perspective. Indeed, aging is multifaceted process and there are several theories that aim to explain its evolutionary basis. One of the theories, antagonistic pleiotropy, states that traits beneficial in young age become deleterious in old age. There are studies suggesting that cellular senescence, one of the hallmarks of aging, is an example of antagonistic pleiotropy. I would like to discuss this theory using an example of p53 driven senescence in bronchial epithelial cells. p53 is tumor suppressor that limits tumorigenesis by inducing apoptosis, cell cycle arrest, and senescence. Although p53 is known to limit inflammation during tumor development, its role in regulating chronic lung inflammation is less well understood. To elucidate the function of airway epithelial p53 in such inflammation, we subjected genetically modified mice, whose bronchial epithelial club cells lack p53, to repetitive inhalations of lipopolysaccharide (LPS), an exposure that leads to severe chronic bronchitis and airway senescence in wild-type mice. Surprisingly, the club cell p53 knockout mice exhibited reduced airway senescence and bronchitis in response to chronic LPS exposure and were significantly protected from global lung destruction. Furthermore, pharmacological elimination of senescent cells also protected wild-type mice from chronic LPS-induced bronchitis. Our results implicate p53 in induction of club-cell senescence and chronic airway inflammation. These results indicate that both p53 expression and induction of senescence are not simply follow the theory of antagonistic pleiotropy, but rather provide an example of increased cost over benefit with age. Thus, senescence limits tumorigenesis and tissue damage in cell-autonomous manner in both young and old organisms. However, in the old organisms the cell non-autonomous cost exceeds this benefit.

Senolytics: The Path to Translation

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Selective Ablation of Senescent and Malignant Cells using Apoptotic Gene Therapy

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Therapeutic approaches to eliminate senescent cells (SCs) in vivo using transgenic mouse models have demonstrated significant improvements in lifespan, reduction of cancer and amelioration of age-related degeneration. Unfortunately, this approach requires that the organism be genetically engineered from the embryo and thus cannot be implemented in humans. We describe a clinically viable gene therapy consisting of a suicide gene under a senescent cell promoter delivered in vivo with fusogenic lipid nanoparticles (LNPs). These LNPs employ fusion-associated small transmembrane (FAST) proteins that can efficiently transduce a wide range of cells in vivo without observed toxicity or off-target effects. Selective ablation of target cells is then achieved through the expression of a potent pro-apoptotic transgene driven by a senescence-associated promoter such as p16Ink4A or p53.

Here, we describe targeting of p16Ink4A-positive cells in vitro and in vivo using this method and the in vivo clearance of SCs in a dose-dependent manner. Additionally, we present data on the targeting and ablation of human p53-positive prostate cancer and melanoma in subcutaneous and metastatic tumor models, where we have observed tumor mass reductions of as high as 90% from a single treatment. Metastatic burden is reduced by as much as 20-fold after three closely spaced treatments. Results of repeated dosing using constructs targeting various promoters are presented, including interim results of a lifespan/healthspan study in a cohort of naturally aged B6 mice (105 week-old at start of trial) along with results of biodistribution and toxicity of LNPs in non-human primates.

In summary, this approach represents a first-in-class therapeutic that targets cells based on transcriptional activity, rather than surface markers or metabolism

Role of senescent cells in fibrosis: lesson from pulmonary fibrosis

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Cellular senescence is a multifaceted response to stress, damage and certain physiological signals, resulting in a permanent mitotic arrest and the secretion of numerous proteins with potent biological activities. This senescence-associated secretory phenotype (SASP) is known to promote embryonic development and wound healing but can also drive many aspects of aging and age-related pathology such as fibrosis. We have clear evidence that the removal of senescent cells using genetically engineering mouse models or senolytic drugs protect from the development of fibrosis. But the question remains: How? This study demonstrates that senescent cells secrete lipids with novel autocrine and paracrine activities. In response to senescence-inducing stress signals, human fibroblasts increased mRNA levels of genes encoding eicosanoid biosynthetic enzymes, resulting in the production of several leukotrienes and prostaglandins. The leukotrienes have a direct effect on fibroblasts resulting in activation of the cells and secretion of collagen, the main extracellular matrix protein in fibrosis. In a mouse model of damaged-induced lung fibrosis, the elimination of senescent cells lowered the levels of specific leukotrienes and attenuated damage-induced fibrosis. These findings identify a new biologically important aspect of the SASP, and a novel mechanism that controls senescent phenotypes. They also enforce the potential of eliminating senescent cells to treat certain fibrotic conditions.

Senescent cells: an emerging target for aging, cancer, radiation-induced late effects

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Cellular senescence is an important tumor-suppressive mechanism because it permanently arrests the proliferation of damaged and genetically deranged cells and promotes their removal by the immune system. However, if senescent cell (SC) production exceeds the immune clearance capacity or the immune system cannot efficiently remove SCs, SCs can accumulate in tissues; this occurs during aging and after exposure to IR. Accumulation of SCs can contribute to many age-related diseases including cancer and IR-induced normal tissue damage by disrupting tissue structures and functions and accelerating tissue stem and progenitor cell exhaustion directly and indirectly by secreting inflammatory cytokines and many other factors, termed the senescence-associated secretory phenotype (SASP). In addition, SCs create a tumor promoting microenvironment that can facilitate tumor resistance, recurrence and metastasis also in part via SASP after chemotherapy and radiation. Therefore, SC production and clearance have to be tightly regulated in order to prevent SC accumulation to extend the healthspan, improve tumor response to therapy, and reduce radiation-induced late effects. New strategies and potential therapeutics that can effectively clear senescent cells and suppressing SASP and their applications will be discussed in this talk.

Targeting STING in senescence with small-molecule inhibitors

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Senescence, a cellular program triggered by various distinct stresses, has emerged as an important contributor to aging-associated diseases. One critical feature, which underlies some of the maladaptive effects of senescent cells, is their inflammatory secretome, collectively referred to as the senescence-associated secretory phenotype (SASP). Recently, we have defined a critical role for the innate DNA sensing pathway comprising cyclic GMP-AMP synthase (cGAS) and Stimulator of interferon genes (STING) in the regulation of the SASP. Briefly, we found that cGAS recognizes aberrant cytosolic chromatin fragments (CCFs) in senescent cells and, in turn, triggers the production of SASP factors through STING. Our finding of aberrant activation of innate immune signalling in senescence raises the possibility that targeting this pathway may provide beneficial effects in senescence-associated pathologies. However, the development of pharmacological inhibitors that specifically act on molecules of the innate DNA sensing pathway has remained a major challenge. In this talk, we report the discovery of highly potent and selective small molecule antagonists of stimulator of interferon genes (STING). In depth characterization of the compounds uncovered an entirely unexpected mechanism to pharmacologically antagonize STING signalling. We show that the discovered compounds reduce STING-mediated inflammatory cytokine production in various contexts in vitro and, moreover, we demonstrate their therapeutic utility in autoinflammatory disease in mice. Finally, we discuss the effect of acute inhibition of STING in contexts of cellular senescence. In sum, our work describes the first ever reported STING antagonists and provide a proof-of-concept of the realization of anti-STING therapies. We propose targeting STING with small molecules may be benefical for diseases caused by chronic inflammation, potentially also diseases driven by the SASP.

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A versatile drug delivery system targeting senescent cells

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Senescent cells accumulate in multiple ageing-associated diseases and eliminating these cells has recently emerged as a promising therapeutic approach. Here, we take advantage of the high lysosomal β-galactosidase activity of senescent cells to design a targeted drug delivery system based on the encapsulation of drugs with galacto-oligosaccharides. We show that gal-encapsulated fluorophores are preferentially released within senescent cells in mice. In a model of chemotherapy-induced senescence, gal-encapsulated cytotoxic drugs target senescent tumor cells and improve tumor xenograft regression in combination with palbociclib. Moreover, in a model of pulmonary fibrosis in mice, gal-encapsulated cytotoxics target senescent cells, reducing collagen deposition and restoring pulmonary function. Finally, gal-encapsulation reduces the toxic side effects of the cytotoxic drugs. Drug delivery into senescent cells opens new diagnostic and therapeutic applications for senescence-associated disorders.

Discovery and target identification of piperlongumine-based senolytic agents

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Senolytic agents, defined as small molecules that can selectively kill senescent cells, have the potential to be developed into "anti-aging" drugs that can extend human healthspan by delaying or treating age-related diseases. We recently identified a dietary natural product, piperlongumine, as a novel senolytic agent. Piperlongumine has good pharmacokinetic properties and appears to be very safe in mouse studies. However, compared with ABT-263, a senolytic agent we identified earlier, piperlongumine has lower potency and selectivity. In addition, the underlying molecular mechanism of action of piperlongumine in inducing senescent cell death is undefined. Thus, our goal is to discover piperlongumine analogue with improved senolytic activity and identify the senolytic target(s) of piperlongumine. An extensive structure-senolytic activity relationship study on the basis of piperlongumine has been carried out. To date, over 100 analogues have been synthesized in our lab and we have identified analogues with senolytic profile (potency and selectivity) comparable to or better than that of ABT-263. We have also designed piperlongumine-based probe molecules to identify protein targets through mass spectrometry-based chemical proteomics approaches. Oxidation resistance 1 (OXR1), an important oxidative stress sensor that regulates the expression of a variety of antioxidant enzymes, has been identified as a valid senolytic target of piperlongumine. These finding may lead to the development of better senolytic agents.

Inhibition of BTK prolongs healthspan and lifespan in vivo

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We have previously shown that Bruton's Tyrosine Kinase (BTK) is a p53 target gene and modulator of p53 activity1. BTK phosphorylates p53 at the N terminal region, which stabilizes p53 protein levels and enhances the transactivation of its target genes in response to stress. Moreover, BTK also phosphorylates MDM2 to block its inhibitory effects on p532. Because of all this, we found that inhibition of BTK impairs p53-induced senescence in human cell culture models. To determine the relevance of these findings in vivo, we treated Drosophila melanogaster, which have a homolog of BTK, with ibrutinib, a clinically approved chemical inhibitor of BTK. Flies showed an increase in average and maximum lifespans compared to control, with a reduction of accumulation of senescent cells in tissues. However, there were no changes in p53-/- flies, suggesting that the anti-ageing effects of BTK inhibition were dependent on p53. Next, we dosed fast ageing Zmpste24-/- mice with ibrutinib for prolonged periods of time. We observed an increase in maximum lifespan in treated mice. Also, we found that they had a longer healthspan, showing preserved cognitive functions (using a Barnes maze, which measures spatial learning and memory) and muscle strength (as measured by the Kondziela test), among other signs. Of note, there was no increase in tumors in these mice. We concluded that BTK inhibition has an impact on ageing in vivo, probably by preventing the accumulation of p53-induced senescent cells. We propose that BTK inhibition can be a strategy to ameliorate certain symptoms of ageing and perhaps prolong lifespan in humans.

References

1 Althubiti, M. et al. BTK Modulates p53 Activity to Enhance Apoptotic and Senescent Responses. Cancer research 76, 5405-5414, doi:10.1158/0008-5472.CAN-16-0690 (2016).

2 Rada, M. et al. BTK blocks the inhibitory effects of MDM2 on p53 activity. Oncotarget 8, 106639-106647, doi:10.18632/oncotarget.22543 (2017).

The dynamic interplay between cancer and aging

Norman E. Sharpless

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Human aging has been considered inexorable, but this may be about to change. Recent advances in our understanding of the molecular underpinnings of cellular aging may allow for new diagnostics and therapeutics to measure, retard and even reverse some aspects of physiological aging. Using the experimentally tractable paradigm of 'iatrogenic' (or therapy-induced) aging in patients receiving cytotoxic therapy for cancer, I will describe two bodies of work aiming to measure, treat and/or prevent molecular aging.

First, I will focus on the use of p16INK4a analysis to measure senescence in vivo, and thereby quantify an important mediator of physiological age which is useful in predicting age-associated toxicities. Second, I will discuss the use of small-molecule inhibitors of cyclin-dependent kinases 4 and 6 (CDK4/6) contemporaneously with DNA damaging stimuli such as cytotoxic chemotherapy to protect hematopoietic stem and progenitor cells (HSPC) from treatment-induced exhaustion. I will show this approach leads to enhanced long-term HSC function resulting in enhanced serial transplantation and reduced myeloid skewing, and translates into measurable benefits for human patients.

Senolytic drugs: from mutant mice to human clinical trials

Nathaniel David

UNITY Biotechnology

2 MIN SPEED TALKS

The role of cellular senescence in the development of pancreatic ductal adenocarcinoma

Dror Gal-Kolodkin[1,2*], Lior Roitman[3*], Yossi Ovadya[3*], Rachel Kalifa[1,2], Shaul Horwitz[1,2], Eli Pikarsky[4], Karen Meir[4], Karin Atlan[4], Agnieszka Witikiewicz[5], Yuval Dor[1†], Gideon Zamir[2†], Ittai Ben-Porath[1†] and Valery Krizhanovsky[3†]

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Pancreatic Ductal Adenocarcinoma (PDAC) is the third-most common cause of cancer-related deaths in the U.S. and eighth worldwide. PDAC arises through the progression of precursor lesions known as pancreatic intraepithelial neoplasia (PanIN). Senescent cells are abundant at sites of early stage PanINs. Cellular senescence, a stable form of cell cycle arrest, is a mechanism, which limits the proliferative potential of cells and imposes a potent barrier of tumorigenesis. Senescent cells trigger immune surveillance through secretion of senescence associated secretory phenotype (SASP), an array of pro-inflammatory cytokines. Recent studies indicate that in contradiction to its tumor suppressive role, SASP secretion by senescent cells could lead to a chronic inflammatory environment which is a fertile ground for cancer development. Senescent cells were shown to have an effect on tumor progression through SASP, although their role and necessity in the progression of PanINs to a full blown PDAC is not fully understood.

In order to address this question, we studied PDAC development using mouse models that recapitulates the pathophysiology of human PDAC patients. We found that the PanINs in the mouse model harbor a substantial subpopulation of senescent cells which are non-dividing, and are intermixed with dividing premalignant cells. Isolation of these senescent PanIN cells from the *kras*-driven mouse model revealed that they express a strong inflammatory signature. This signature is consistent with the senescence-associated secretory phenotype and NFkB activity. In particular, Cox2 levels were dramatically elevated in the senescent but not in the PanIN dividing cells. Cox2 inhibition by NSAID treatment led to a dramatic inhibition of PanIN growth, indicating that the pro-inflammatory action of senescent cells provides critical support to the lesions. Specific pharmacologic elimination of the senescent PanIN cells through the bcl2-family inhibitor, ABT-737 reversed this inflammatory response and blocked PanIN formation as well as progression to carcinoma.

These findings indicate that senescent cells provide essential paracrine support to the development of premalignant pancreatic lesions and their progression to carcinoma. This is partly attributed to Cox2 activity within the pancreas. Senolytic therapy targeting senescent cells may thus be an effective treatment for preventing PDAC formation.

Telomere length is exclusively maintained by the ALT mechanism in a vertebrate, the newt Pleurodeles waltl

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Telomere shortening places a key limitation on the lifespan of a cell. In all known vertebrates, this limitation is overcome by a telomerase--dependent telomere extension mechanism, whose failure results in premature ageing and functional impairments in highly replicative cell populations as telomeres erode. An alternative mechanism for lengthening telomeres (ALT), dependent on homologous recombination, has recently been shown to compensate for telomerase loss in a limited proportion of cancer cell lines. Here, we show that the newt Pleurodeles waltl controls telomere length through the ALT mechanism throughout lifespan. Telomerase activity is absent from larval and replicative adult tissues, tracks of vertebrate telomere consensus sequence are absent from its DNA, and its chromosomes lack binding of shelterin components at their ends. By mining the newt genome, we show that the telomeric sequences of P. waltl are comprised of a series of interspersed, highly recombined telomere consensus variants, characteristic of ALT activity. Furthermore, we show that newt tissues contain extra chromosomal telomeric DNA circles, sub--products of the ALT mechanism. Importantly, we show that this mechanism leads to active telomere recombination during development and regeneration. Finally, our data suggests that ALT operates throughout the Salamandridae family of Urodele vertebrates. Thus, we demonstrate that the ALT mechanism can operate at the whole organism level, a finding which has important implications for regenerative and cancer biology

Identification of a novel senotherapeutic molecule: comparison with retinoic acid in human aged 2D and 3D skin models

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Senescent cells are not only a product of tissue aging, they also actively contribute to further cellular/tissue senescence induction. Therefore, the focus on senescence prevention or reversal might prove to be an effective strategy for novel anti-aging compound discovery. The gold-standard treatment for skin aging, Vitamin A, is known to promote deposition of new collagen and to prevent its degradation. Nevertheless, no correlation with senescence reduction has been demonstrated. In this work, we established a screening platform for anti-aging compounds based on the analysis of senescence-associated features. Additionally, we compared the hits from a proprietary molecule library to the retinoic acid treatment and assessed the senescence profile of 2D and 3D aged human skin models. In vitro analysis demonstrated that retinoic acid is not able to reduce the level of senescence in a primary human fibroblast population initially composed of 25% senescent cells. Conversely, treatment with a novel senotherapeutic molecule, a product of our library screening, reduced B-gal positive cells approximately 25% ($p<0.05$). Moreover, aged 3D human skin models were treated with retinoic acid or the senotherapeutic molecule for 5 days and morphological analysis was performed after H&E staining. Both treatments promoted an overall increase in the quality of treated skins compared to non-treated controls. Enhanced features included better epidermal stratification and nucleation of the basal layer. Importantly, only the senotherapeutic approach reduced the expression of genes associated with senescence and aging, including P16, FOXO-4 and IL-8. Taken together, these results suggest that targeting skin senescence is a promising strategy applicable to dermocosmetic purposes with impact at the morphological and molecular levels.

Loss of CDK2 Delays Onset and Progression of BRAFV600E/MYC-driven Mouse Lung Tumors via Induction of Senescence

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Activated RAS and BRAF are important oncogenic drivers in cancer, but are also potent inducers of premature senescence. MYC plays a role in suppression of RAS/BRAF-induced senescence during malignant transformation. This MYC activity requires the function of cyclin-dependent kinase 2 (CDK2) in cell cultures. Here we utilized a conditional transgenic BRAFV600E/MycER lung tumor model to investigate the role of CDK2 for senescence regulation in vivo by generating BRAFV600E/MycER/CDK2flox/flox mice. Inhalation of Ad-CRE into the lungs of these mice resulted in simultaneous activation of BRAFV600E, expression of MycER and deletion of CDK2. We observed a significantly enhanced overall survival and reduced tumor burden in CDK2 knockout compared with CDK2 wt mice. A total of 30% of the mice were still alive and hade either no, few or small tumors at day 249 (termination) (correct?). A significant decrease in proliferating (Ki67 positive) tumor cells, as well as upregulation of the CDK inhibitor p21CIP1 and histone H3 lysine 9 trimethylation (H3K9me3), all consistent with induction of senescence. Apoptosis was negligible. Kinetic analysis demonstrated a delay in tumor onset, and at later time points a significant reduction in tumor burden, manifested both as reduced tumor number and size in mice lacking CDK2 compared to CDK2 wt mice. Analysis of proliferation/senescence at 3-4 weeks after start showed a significant decrease in Ki67 positive cells and upregulation of p21 and H3K9me3 staining in the tumor area in response to CDK2 depletion, with no apparent induction of the apoptotic markers. Treatment of tumor-bearing BRAFV600E/MycER (CDK2 wt) mice with the pharmacological CDK2 inhibitor CYC065 resulted in a diminished tumor growth, reduced Ki67 expression and upregulation of p21, indicative of restoration of the senescence program, similar to the CDK2 knockout mice. Our results show that CDK2 activity plays an important role in BRAFV600E/MYC-driven tumor development and is an essential part of the suppression of BRAFV600E-induced senescence in vivo. Taken together, our results suggest that inhibition of CDK2 potentially has clinical relevance for combating lung cancer and other tumors driven by cooperating oncogenes such as MYC and BRAFV600E.

Investigating the dynamic program of single cell senescence

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Cellular senescence is a potent tumor suppressive mechanism, whose aberrant accumulation contributes to aging and disease. At the cellular level, senescence is a complex process with many characteristics and associated features, including, in different conditions, an enlarged size and flat shape, heterochromatin foci, lysosomal enlargement, vacuole formation and chromatin fragmentation. However, to date, a universal marker or defining feature of senescence is lacking. Interestingly, much of our understanding of cell senescence was discovered by analyzing total populations of cells in vitro after exposure to senescence inducing stimuli. Such an approach leaves gaps regarding the dynamics and intercellular variability of senescence and potentially masks features of a core senescence program. Additionally, such synchronous induction of senescence is unlikely to occur initially in (patho)physiological conditions in vivo.

We aim to alleviate these gaps by analyzing the dynamic process of single cell senescence, from a cell-biological and molecular view. To achieve this, we are using time lapse microscopy, together with immuno-fluorescent staining and gene expression analysis of single senescent cells over time, focusing on individual cells in the context of either undamaged or damaged environments.

Interestingly, our initial observations have uncovered features of senescence that have not been previously described. We observed dramatic alterations in the shape and movement of cells after the senescence-inducing stimulus, which progressively changes over time as other features of senescence become apparent. Interestingly, the timing of such gradual change is affected by the cellular context in which the cells undergo senescence (proliferating vs. senescent environment). Additionally, we observed striking changes in the adherence of senescing cells to the culture surface and to neighboring cells. This is accompanied by a progressive increase in fragmentation of the cells on the outer edges, which precede the characteristic flattening of the senescing cell. Importantly, this is not associated with apoptosis or compromised integrity of the plasma membrane, and can also be observed in an in vivo model of single cell senescence-induction. We believe such an approach at studying single senescing cell dynamics over time offers the potential to identify new features of the cellular senescence program.

Exosomes transmit the signals of senescence-associated secretory phenotype

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Senescence-associated secretory phenotype (SASP) is a critical element of the tumor suppressive mechanism of oncogene-induced senescence. Previous studies have demonstrated that SASP factors not only reinforce cell cycle arrest, but also contribute to immune surveillance via inflammatory cytokines and other immune modulators, leading to the clearance of senescent pre-malignant cells. In addition to the variety of soluble factors as the conventional components of SASP, extracellular vesicles (EVs) have emerged as an important mode of delivering signals that acts both locally and systemically to affect the microenvironment of senescent cells. However, the complex biological effect of senescence-associated extracellular vesicles and its regulatory mechanism remain largely unknown. In order to unveil the features of this unique form of intercellular communication in senescent cells, we focused on the secretion and regulation of exosomes, a subtype of secreted vesicles that originates in the endosomal compartments called multivesicular bodies (MVBs). We demonstrate that exosome secretion is significantly increased upon oncogene (HRas)-induced senescence in human fibroblast cells. These senescence-associated exosomes contain SASP cytokines as well as growth factors and membrane-signaling proteins. Consistent with the possibility that these extracellular vesicles mediate communication between senescent cells and the microenvironment, senescence-associated exosomes can alter immune cell function in vitro. In summary, our observations suggested that exosomes are responsible for key consequences of the SASP.

p53 loss does not permit escape from BrafV600E -induced senescence in a mouse model of lung cancer

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McGill Biology

Lung cancer arises through the acquisition of a number of genetic lesions, with a preponderance of activating mutations in the canonical MAPK cascade (RTK-RAS-RAF-MEK). BrafV600E expression induces benign lung adenomas that fail to progress to adenocarcinoma due to oncogene-induced senescence (OIS). BrafV600E expression, coupled with simultaneous p53 ablation, permits bypass of senescence and progression to lung adenocarcinoma. However, spontaneous human tumors sustain mutations in a temporally separated fashion. Here, we use a mouse lung cancer model where oncogene activation (BrafV600E expression) and tumor suppressor loss (p53 ablation) are independently controlled through the actions of Flp and Cre recombinase respectively. We show that p53 loss prior to OIS, is permissive for the transition from lung adenoma to adenocarcinoma. In contrast, p53 loss after senescence is established fails to enable escape from senescence and disease progression. This study demonstrates that BrafV600E induced senescence is irreversible in vivo and suggests that therapy-induced senescence would halt further tumor progression.

CDK4/6 Inhibitors Induce Cellular Senescence in Normal Cells without Deleterious Associated Secretory Phenotypes

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Most used anti-cancer therapeutic approaches are based on impairing mitosis and targeting highly proliferative cells. The non-specificity of these interventions often leads to side effects, including immunosuppression, fatigue, organ damage, cognitive impairment and secondary neoplasms.

Cellular senescence - a complex stress response whereby cells lose irreversibly their capacity to proliferate – is potent tumor suppressive mechanism and a desired outcome of anti-cancer therapies. However, a subset of senescent cells is characterized by the Senescence-Associated Secretory Phenotype (SASP), a collection of inflammatory cytokines, chemokines, growth factors and proteases.

We have previously shown that mouse and human primary fibroblasts and cells in vivo are induced to senescence upon treatment with genotoxic chemotherapy agents. Chemotherapy-induced senescent cells develop a strong SASP, promote local and systemic inflammation, and contribute to chemotoxicity in mice including bone marrow suppression, cardiac decline, decreased physical activity and strength and cancer relapse.

Here, we show that a novel class of oncological drugs directly inhibiting cell cycle progression -- the inhibitors of Cyclin-Dependent Kinases (CDK)-4/6 – promotes primary cells into senescence both in cell culture and in vivo. Interestingly, using RNAseq, cytokine arrays and in-tissue analyses we demonstrate that CDKi-induced senescent cells are characterized by a strongly reduced SASP. CDKi-induced senescent cells fail to promote paracrine detrimental effects, and do not lead to adverse effects in mice. However, despite the low SASP, endogenous and transplanted CDKi-induced senescent cells are efficiently eliminated in immunocompetent mice. Importantly, CDK4/6 inhibitors appear to promote senescence via activation of p53. In accordance, both primary and tumor cells without functional p53 do not irreversibly arrest after treatment.

Together, our data suggest that senescence can be triggered by CDK4/6 inhibitors in both primary and tumor cells via p53 activation. However, in contrast to chemotherapy-induced senescence, CDKi-induced senescent cells do not develop a strong senescence-associated secretory phenotype. Importantly, the phenotypical characterization of these different senescent cells could predict toxicity and side effects associated to standard oncological drugs.

PARsing the function of PARP1 in senescence-associated gene regulation

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Cellular senescence is a complex stress response that arrests cell proliferation and is accompanied by widespread changes in chromatin structure, metabolism and gene expression including the production and secretion of a plethora of inflammatory factors. Cellular senescence plays beneficial roles during embryonic development, tissue regeneration and tumour suppression. Paradoxically, it is also considered a major contributor to ageing and age-related diseases, the latter, mostly through its inflammatory phenotype, the so-called SASP (senescence-associated secretory phenotype). Ample evidence supports a role of PARP1 in the transcriptional regulation of inflammatory processes. However, whether PARP1 regulates these processes through its enzymatic activity and/or an architectural function is unclear. Here, we set out to define the functional role of PARP1 in gene regulation and chromatin structure in cells undergoing oncogene-induced senescence (OIS). Performing protein-protein interaction studies and charting the genome-wide locations of PARP-1 using ChIP-seq and ADP-ribosylated (ADP-r) chromatin using a newly developed technique allowed us to 1) distinguish between global PARP-1 binding (mostly on nucleosomes) and its enzymatic activity on chromatin and 2) identify gene-regulatory regions that are important for SASP-expression and the timely execution of senescence. In line with this, silencing of PARP1 expression and pharmacologically inhibiting its enzymatic activity strongly impact both gene expression and chromatin accessibility (as measured by ATAC-seq) of many genes important for senescence establishment and maintenance. Together, we define a novel and global role for PARP1 in senescence-associated gene-regulation and chromatin structure changes both through its prevalent and direct interaction with nucleosomes and its enzymatic modification of chromatin. The potential role of PARP-inhibitors for senescence targeting and the treatment of age-related pathologies will be discussed.

Cellular senescence occurs during mammary gland involution

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Cellular senescence is a stable cell-cycle arrest that is induced by damage and is involved in the embryonic development, tissue repair, regeneration and many human diseases. However, it is unknown whether cellular senescence is involved in the post-natal physiological processes. We set to address this question in the context of mammary gland involution. The primary function of the mammary gland is to provide nutrition with milk to the newborns. The morphogenesis of the mammary gland is very limited during embryonic development and occurs mainly after birth. There are three successive stages in the post-natal development of the mammary gland: 1) ductal growth and branching in pubertal mice, 2) lobuloalveolar development and lactogenic differentiation during gestation, and 3) involution of the gland at the end of lactation following weaning of the pups. Mammary gland involution is an essential process that removes the milk-producing epithelial cells upon weaning, which requires apoptosis and tissue remodeling.

Here, we find that cellular senescence occurs specifically in the irreversible stage of mammary gland involution. Interestingly, involution induced senescence is largely dependent on p16, which is in sharp contrast with the embryonic development, where p21 is strictly required. Moreover, perturbation of key players of the senescence program impacts the progression of involution. Taken together, we present evidence, for the first time, that senescence occurs during normal physiological processes, which might play an important role in promoting cellular plasticity and tissue remodeling.

POSTER PRESENTATIONS

Session 1 : Day 2, July 9th, 2018, 5:00-7:00 PM, Posters with **ODD** numbers.
Session 2 : Day 3, July 10th, 2018, 4:30-6:30 PM, Posters with **EVEN** numbers

Poster list with numbers:

1 **Astrocyte senescence in Alzheimer's disease mouse model leads to a neurotoxic profile**
Amram S.[1,2] and Frenkel D.[1,2]
Sagol School of neuroscience, Tel-Aviv University 2 Tel-Aviv University 2 Department of Neurobiology, George S. Wise Faculty of Life Sciences

2 **Chromosome instability (CIN) is an inducer and a marker of cellular senescence**
Andriani GA[1], Pique D[2], Campisi J[3], Vijg J[1], Mar J[2] Montagna M[1]
[1]Dept Genetics, Albert Einstein College of Medicine; [2]Dept Systems Biology, Albert Einstein College of Medicine 3 Buck Institute for Research on Aging

3 **Study of normal human keratinocytes in replicative senescence and in UVB-induced premature senescence**
E.Bauwens, S. Hellin, L. Ernst, N. Ninane, C. Demazy and F. Debacq-Chainiaux
URBC-Narilis, University of Namur, Belgium

4 **Ate1 is a master regulator of stress response and mutagenesis with a prominent role in prostate cancer metastasis**
Michael D. Birnbaum, Ning Zhao, Akhilesh Kumar, Kerry L. Burnstein, Fangliang Zhang
Molecular and Cellular Pharmacology Department, University of Miami

5 **Different susceptibility to undergo therapy induced senescence of human cancer cell lines**
Agnieszka Bojko, Joanna Czarnecka, Piotr Sunderland, Ewa Sikora
Laboratory of Molecular Bases of Aging, Nencki Institute of Experimental Biology, Polish Academy of Sciences, 3 Pasteur Street, 02-093 Warszawa, Poland

6 **Exposure to chronic hypoxia is associated with lung cell senescence: consequences on hypoxia-induced pulmonary hypertension**
Breau M, Abid S, Houssaini A, Marcos E, Born E, Adnot S
INSERM U 955, Département de Physiologie, CHU Henri Mondor, AP-HP, 94010 Créteil

7 **Cell cycle arrest in replicative senescence is not an immediate consequence of telomere dysfunction**
M. Shamim Nassrally, Katherine Wise, Noah John, Sanjeev Kotecha, Kar Lai Lee and Robert F. Brooks[1*]
King's College London, Faculty of Life Sciences & Medicine, Department of Anatomy, Guy's Campus, LONDON SE1 1UL, UK
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**correspondence: rbrooks@sgul.ac.uk*

8 **Cellular senescence and cellular plasticity in muscle regeneration**

Coralie Cazin, Aurelie Chiche, Han Li
Cellular Plasticity & Disease Modelling, Department of Developmental & Stem Cell Biology, Institut Pasteur, France

9 **Development of Oncogenic RAS 'Predictive Reporter' System for Investigating Dose Dependency in Oncogene-Induced Senescence**

Adelyne Chan[1], Masako Narita[1], Ioana Olan[1,2] and Masashi Narita[1]
[1]Cancer Research UK Cambridge Institute, University of Cambridge, United Kingdom
[2]MRC Cancer Unit, Hutchison/MRC Research Centre, University of Cambridge, United Kingdom

10 **S100A13 promotes senescence-associated secretory phenotype and cellular senescence via modulation of non-classical secretion of IL-1α**

Yuanyuan Su, Chenzhong Xu, Zhaomeng Sun, Yao Liang, Guodong Li, Tanjun Tong & Jun Chen
Peking University Research Center on Aging, Department of Biochemistry and Molecular Biology, Peking University Health Science Center, Beijing 100191, China

11 **Impact of factors secreted by senescent vascular smooth muscle cells on the immune cells functions**

Agata Ciolko[1], Dominik Cysewski[2], Ewa Kozlowska[4], Paulina Podszywałow-Bartnicka[3], Ewa Sikora[1], Grażyna Mosieniak[1]
[1]Laboratory of Molecular Basis of Aging, Nencki Institute of Experimental Biology, Polish Academy of Sciences, Warsaw, Poland; [2]Mass Spectrometry Laboratory, Institute of Biochemistry and Biophysics, Polish Academy of Sciences, Warsaw, Poland; [3]Laboratory of Cytometry, Nencki Institute of Experimental Biology, Polish Academy of Sciences, Warsaw, Poland; [4]Department of Immunology, Institute of Zoology, Faculty of Biology University of Warsaw, Poland

12 **p16INK4a controls hepatic lipid metabolism through the AMPK-SIRT1-PPARa signalling pathway independently of senescence**

Deleye, Y.[1], Haas, J.[1], Cotte, A.[1], Hannou, S.[1], Caron, S.[1], Vallez, E.[1], Pourtier, A.[2], Abbadie, C.[2], Staels, B.[1], Paumelle, R.[1]
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13 **Chromosomal instability-induced senescence potentiates cell non-autonomous tumourigenic effects**

He Qianqian, Monique Luijten and Karen Crasta
Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore

14 **Characterizing the contributions of dysfunctional epithelium in IPF: developing physiologically relevant in vitro model systems of senescence and ER stress**

Daryle DePianto & Joseph R. Arron
Genentech Inc

15 **Human induced pluripotent stem cells derived fibroblasts efficently undergo cellular senescence in response to DNA damage**

Cynthia Désaulniers-Langevin, Basma Benabdallah, Francis Rodier and Christian Beauséjour
CRCHU-Sainte-Justine, Université de Montréal

16 **Aging impacts immunoregulatory functions of cardiac mesenchymal stromal cells and their vascular differentiation potentials**

Martini H[1,2], Maggiorani D1, Dutaur M[1,3], Marsal D[1], Roncalli J[1,2], Pizzinat N1, Mialet-Perez J[1], Cussac D[1,3], Parini A[1,2,3], Lefevre L[1,3] and Douin-Echinard V[1,3]
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17 **Identifying a role for MOB3A in oncogene induced senescence and Ras/Raf driven cancers**

Kendall Dutchak, Sam Garnett, David Dankort
McGill University, Department of Biology

18 **Uncovering the mechanism of senescence activation in cancer cells**

Ugochim Stefany Eduputa[1], Madeleine Moore[1], Rob Lowe[2] and Cleo L. Bishop[1]
[1]Centre of Cell Biology and Cutaneous Research, Blizard Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, 4 Newark Street, London E1 2AT, UK [2]Centre of Genomics and Child Health, Blizard Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, 4 Newark Street, London E1 2AT, UK

19 **Mutation of a N-terminal tyrosine uncovers a role for Sprouty1 in cellular senescence**

Marta Vaquero[1], Carlos Anerillas[1], Sara Cuesta-Sancho[1], Anna de Bolòs[2], Joaquim Egea[2], Joan Ribera[1], and Mario Encinas[1]
Departments of [1]Experimental Medicine and of [2]Basic Medical Sciences, Universitat de Lleida Lleida, Spain

20 **JMJD2A/KDM4A lysine demethylase regulates heterochromatin maintenance and the stability of oncogene-induced senescence**

Fernández E.[1,2], Germain M.-A.[1], Neault M.[1], Regnier M.[1], Glatz D.[1] and Mallette F. A.[1,2,3]
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21 **A Role for IAPP in Oncogene Induced Senescence**

Sam Garnett & David Dankort
McGill University

22 **Effects of chemotherapy-induced SASP in lung cancer progression**

Estela González-Gualda[1] and Daniel Muñoz-Espín[1]
[1]Cancer Research UK (CRUK) Cambridge Centre Early Detection Programme, Department of Oncology, University of Cambridge, UK

23 **Development of humanized autologous mouse models for senescent myoblasts immunogenicity assessment**

Goyer M-L[1,2], Benabdallah B[1], Desaulniers-Langevin C[1], Li Y[1], Haddad E[1,3], Beauséjour C[1,2].
[1]CHU Sainte-Justine Research Center. [2]Department of Pharmacology and Physiology, Université de Montréal. [3]Department of Pediatrics, Université de Montréal.

24 **Drug screens identify a novel class of senolytic compounds**

Ana Guerrero[1,2], Nicolás Herranz[1,2] and Jesús Gil[1,2]
[1]MRC London Institute of Medical Sciences (LMS) and [2]Institute of Clinical Sciences (ICS), Faculty of Medicine, Imperial College London, London W12 0NN, UK.

25 **Concomitant loss of Atm and Wrn accelerates senescence in mouse fibroblasts**

Majd Haj[1], Ofer Bihari[2], Dong Eun Kim[3], F. Bradley Johnson[4], Ari Barzilai[2], Judith Campisi[3], Yael Ziv[1], and Yosef Shiloh[1].
[1]The David and Inez Myers Laboratory for Cancer Genetics, Department of Human Molecular Genetics and Biochemistry, Sackler School of Medicine, and [2]Department of Neurobiology, George S. Wise Faculty of Life Sciences, Tel-Aviv University, Tel-Aviv 69978, Israel, [3]Buck Institute for Research on Aging, Novato, CA, 94945, and [4]Department of Pathology and Laboratory Medicine, University of Pennsylvania, Philadelphia, PA 19104-6100, USA.

26 **Stem cell senescence drives age-attenuated induction of pituitary tumours in mouse models of paediatric craniopharyngioma**

Scott Haston[1], Jose Mario Gonzalez-Meljem[1], John Apps[1], Jesus Gil[2], Juan Pedro Martinez-Barbera[1]

[1]Developmental Biology and Cancer Programme, Birth Defects Research Centre, UCL Institute of Child Health, London, WC1N 1EH, UK. [2]Cell Proliferation Group, MRC Clinical Sciences Centre, Imperial College London, Hammersmith Campus, Du Cane Road, London, W12 0NN, UK.

27 **Unraveling the 3D structure and dynamics of PML nucleolar interactions during ribosomal stress**

Terezie Imrichova[1], Pavla Vasicova[1], Jan Kosla[1], Blanka Mrazkova[1], Jiri Bartek[1,2,3] and Zdenek Hodny[1]

[1]Department of Genome Integrity, Institute of Molecular Genetics of the ASCR, v. v. i., Prague 142 20, Czech Republic [2]Division of Genome Biology, Department of Medical Biochemistry and Biophysics, Karolinska Institute, Stockholm SE-171 77, Sweden [3]Danish Cancer Society Research Center, Copenhagen DK-2100, Denmark

28 **Upregulation of RANKL due to osteocyte senescence is a critical mechanism of skeletal aging**

Ha-Neui Kim[1], Jinhu Xiong[2], Keisha Cawley[1], Ryan Macleod[1], Srividhya Iyer[2], Jianhui Chang[3], Li Han[1], Aaron Warren[1], Daohong Zhou[3], Charles O'Brien[1], Maria Almeida[1]

[1]Division of Endocrinology and Metabolism, Center for Osteoporosis and Metabolic Bone Diseases; and the Central Arkansas Veterans Healthcare System, Little Rock, Arkansas. [2]Departement of Orthopedic Surgery, University of Arkansas for Medical Sciences, Little Rock, Arkansas. [3]Department of Pharmaceutical Sciences, University of Arkansas for Medical Sciences, Little Rock, Arkansas

29 **Cellular Senescence; A driver of the pro-aging side effects of antiretroviral therapies**

Chisaka Kuehnemann[1], Christopher Wiley[1] & Judith Campisi[1,2]

[1]Buck Institute for Research on Aging, 8001 Redwood Boulevard, Novato, CA 94945, USA

[2]Lawrence Berkeley National Laboratory, 1 Cyclotron Rd., Berkeley, CA 94720, USA

30 **Uncoupling the senescence-associated secretory phenotype from cell-cycle exit to study the pro-tumorigenic properties of the SASP**

Lena Lau, Angelo Porciuncula, Yoichiro Iwakura, Gregory David

Institute of Medical Science, University of Tokyo; New York University School of Medicine

31 **The role of cholesterol metabolism during cellular senescence and in senescence-associated secretory phenotype.**

Paul Lemire[1,4], Marine Regnier[1,4], Agnieszka Dejda[1,2,4], Karine Boulay[1,4], Francis Rodier[3,5], Przemyslaw Sapieha[1,2,4], Frédérick A. Mallette[1,4]

[1]Département de Biochimie et Médecine Moléculaire, Université de Montréal, Montréal, QC, Canada [2]Département d'Ophtalmologie, Université de Montréal, Montréal, QC, Canada [3]Département de radiologie, radio-oncologie et médicine nucléaire, Université de Montréal, Montréal, QC, Canada. [4]Centre de recherche de l'Hôpital Maisonneuve-Rosemont, Montréal, QC, Canada [5]Centre de recherche du Centre hospitalier de l'Université de Montréal and Institut du cancer de Montréal, Montréal, QC, Can

32 **Senescence during gliomagenesis : tumor suppressor or activator ?**

Rana Salam, Franck Bielle[1], Emmanuelle Huillard and Isabelle Le Roux

Brain and Spine Institute (ICM) CNRS UMR 7225 - Inserm U 1127 - UPMC-P6 UMR S 1127 Pitié-Salpêtrière Hospital , 47, Bd de l'Hôpital CS 21414 75646 Paris Cedex 13. [1]Neuropathology Department Raymond-Escourolle, INSERM-UPMC UMRS 975-CRICM, Pitié-Salpêtrière Hospital, Assistance Publique - Hôpitaux de Paris 47, Bd de l'hôpital, 75013, Paris, France

33 **SILAC analysis reveals a role for the senescence-associated secretory phenotype in hemostasis**

Christopher Wiley[1], Su Liu[1], José Alberto López-Domínguez[1], Birgit Schiling[1], Chandani Limbad[1], Anna Zawadzka[1], Jennifer Beck[1], Marco Demaria[1], Robert Artwood[1], Fatouma Alimirah[1], Steven R. Danielson[1], Tal Ronnen Oron[1], Pierre-Yves Desprez[1,2], Sean Mooney[1], Bradford W. Gibson[1], Judith Campisi[1,3], and Pankaj Kapahi[1]

[1]Buck Institute for Research on Aging, Novato, CA 94945, USA. [2]California Pacific Medical Center, Research Institute, San Francisco, CA 94107, USA. [3]Biosciences Division, Lawrence Berkeley National Laboratory, Berkeley, CA 94720, USA

34 **Rap1-mediated chromosome stability during replicative senescence**

Liudmyla Lototska, Aaron Mendez-Bermudez, Sabrina Pisano, Eric Gilson

Institute for Research on Cancer and Aging (IRCAN), Nice CNRS UMR 7284 - INSERM U 1081 - UNS

35 **SASP analysis in rat primary astrocytes treated with anti-inflammatory drugs**

Maciel-Barón Luis Ángel[1,7], Morales-Rosales Sandra Lizbeth[1,7], Silva-Palacios Alejandro[1,7], Rodríguez-Barrera Roxana Haydee, García-Álvarez Jorge Antonio[3], Luna-López Armando[4], Pérez Viviana Isabel[5], Torres Claudio[6], Konigsberg Mina[1]

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36 **Cellular senescence and chronological age in various human tissues: a systematic review and meta-analysis**

M.E.C. Waaijer[1*], C. Tuttle[2*], T. Stijnen[3], R.G.J. Westendorp[4], A.B. Maier[2,5]

[1]Department of Gerontology and Geriatrics, Leiden University Medical Center, the Netherlands. [2]Department of Medicine and Aged Care, @AgeMelbourne, Royal Melbourne Hospital, University of Melbourne, Melbourne, Australia. [3]Department of Statistics, Leiden University Medical Center, The Netherlands. [4]Department of Public health and Center of Healthy Aging, University of Copenhagen, Copenhagen, Denmark. [5]Department of Human Movement Sciences, @AgeAmsterdam, VU University Amsterdam, Amsterdam, The Netherlands

37 **Are skin senescence and immunosenescence associated intra-individually?**

M.E.C. Waaijer[1], R.G.J. Westendorp[2], G. Pawelec[3], A.B. Maier[4,5]

[1]Department of Gerontology and Geriatrics, Leiden University Medical Center, the Netherlands. [2]Department of Public health and Center of Healthy Aging, University of Copenhagen, Copenhagen, Denmark. [3]Department of Internal Medicine II, Centre for Medical Research, University of Tübingen, Germany. [4]Department of Human Movement Sciences, @AgeAmsterdam, MOVE Research Institute Amsterdam, VU University Amsterdam, Amsterdam, The Netherlands. [5]Department of Medicine and Aged Care, @AgeMelbourne, Royal Melbourne Hospital, University of Melbourne, Melbourne, Australia

38 **A non-canonical TIP60/MRN-associated low-level chomatinic DDR activity temporally define senescence-associated secretory programs**

Nicolas Malaquin[1], Audrey Carrier-Leclerc[1], Christina Sawchyn[2], Aurélie Martinez[1], Jean-Philippe Coppé[3], Guillaume Cardin[1], Frédérick A. Malette[2], Judith Campisi[4,5] and Francis Rodier[1,6]

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39 **Human cellular senescence and immunity: functional analysis of the novel histone variant H2A.J**

A. Mangelinck[1], C. Coudereau[1], R. Courbeyrette[1], F. Fenaille[2], J.-Y. Thuret[1], C. Mann[1]

[1]I2BC, CEA, CNRS, Univ. Paris-Saclay, France. [2]SPI, CEA, CNRS, Univ. Paris-Saclay, France.

40 **Genetic and Pharmacological Inhibition of the Phospholipase A2 Receptor (PLA2R1) Protects Against Lung Cell Senescence in Chronic Obstructive Pulmonary Disease (COPD)**

Marcos E[1], Attwe A[1], Huang J[1], Amsellem V[1], Breau M[1], Kebe K[1], Houssaini A[1], Validire P[3], Maitre B[1], Vindrieux D[2], Bernard D[2], Adnot S[1]

[1]INSERM U 955, Département de Physiologie, CHU Henri Mondor, AP-HP, 94010 Créteil, France. [2]INSERM U1052/CNRS 5286, Université de Lyon, France. [3]Institut Mutualiste Montsouris, Département Anatomopathologie, Paris, France

41 **Genetic screens to identify novel liabilities of senescent cells**

Domhnall McHugh[1,2] and Jesús Gil[1,2]

[1]MRC London Institute of Medical Sciences (LMS) and [2]Institute of Clinical Sciences (ICS), Faculty of Medicine, Imperial College London, London W12 0NN, UK.

42 **Abscopal effect of radiation-induced lung cellular senescence and fibrosis on the hematopoietic system in mice**

Junling Zhang[2], Deguan Li[2], Jin Pan[1], Yueying Wang[2], Daohong Zhou[3], Aimin Meng[1*]

[1]Institute of Laboratory Animal Science, Chinese Academy of Medical Science & Comparative Medical Center, Peking Union Medical College, Beijing 100021, China. [2]Institute of radiation medicine, Chinese Academy of Medical Science & Peking Union Medical College, Tianjin 300192, China. [3]Department of Pharmacodynamics, College of Pharmacy, University of Florida, Gainesville, Florida, USA

43 **Development of a 3D living skin equivalent to explore the influence of senescence on the skin ageing phenotype**

Deborah Milligan[1], James Newman[1], Matthew Caley[1], Linda Wainwright[2], Gail Jenkins[2], Mike Philpott[1], Cleo Bishop[1]

[1]The Blizard Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, 4 Newark Street, London, E1 2AT, UK. [2]Unilever R&D, Colworth Science Park, Sharnbrook, Bedfordshire MK44 1LQ, UK

44 **Oncogene-induced senescence in hematopoietic progenitors leads to myeloid restricted hematopoiesis, chronic inflammation and aggressive histiocytosis**

Riccardo Biavasco, Emanuele Lettera, Margherita Norelli, Barbara Camisa, Daniela Cesana, Pierangela Gallina, Maurilio Ponzoni, Lorenzo Dagna, Attilio Bondanza, Raffaella Di Micco§ and Eugenio Montini

San Raffaele Telethon Institute for Gene Therapy, Italy

45 **Effect of primary rat senescent astrocytes on the functionality of cortical neurons in a co-culture model**

Morales-Rosales SL, Maciel-Barón LA, Gerónimo-Olvera C, Rincon-Heredia R, Torres C, Massieu Trigo L, Konigsberg Fainstein M

Posgrado en Biología Experimental, UAM-Iztapalapa, Mexico City; Instituto de Fisiología Celular, Universidad. Nacional Autónoma de México (UNAM), Mexico City; Department of Pathology and Laboratory Medicine, Drexel University College of Medicine, Philadelphia; Laboratorio de Bioenergética y Envejecimiento Celular, Departamento de Ciencias Biológicas y de la Salud, Universidad Autónoma Metropolitana, Iztapalapa (UAM-I), Mexico City

46 **Comparison of senescent cells derived from atherosclerotic plaques, arteriovenous fistulas stenosis and aneurysms**

Dorota Janiszewska[1], Krzysztof Bojakowski[2], Agata Ciołko[1], Dorota Przybylska[1], Małgorzata Piechota[3], Ewa Sikora[1], Grazyna Mosieniak[1]

[1]Laboratory of Molecular Bases of Aging, Nencki Institute of Experimental Biology, Warsaw, Poland; [2]2nd Vascular Department, Center of Postgraduate Medical Education, Warsaw, Poland; [3]Laboratory of Molecular Basis of Behavior, Nencki Institute of Experimental Biology, Warsaw, Poland

47 **Search for specific markers of cellular senescence: induction, regulation and roles of neural adhesion molecule L1CAM**

B. Mrazkova[1], R. Dzijak[1], T. Imrichova[1], L. Kyjacova[1], P. Barath[2], P. Dzubak[3], D. Holub[3], M. Hajduch[3], Z. Nahacka[4], L. Andera[4], P. Holicek[4], P. Vasicova[1], O. Sapega[5], J. Bartek[1,6,7], Z. Hodny[1]

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48 **Down-regulation of inflammatory network in senescent fibroblasts of wild long-lived and cancer-resistant subterranean rodent Spalax**

Amani Odeh[2], Maria Dronina[1], Imad Shams[1,2], and Irena Manov[1]

[1]Institute of Evolution; and [2]Department of Evolutionary and Environmental Biology, Faculty of Natural Sciences, University of Haifa, Haifa, Israel

49 **Complex co-regulation reflected by changes in enhancer-promoter network during RAS-induced Senescence**

Ioana Olan[1], Aled Parry[1,2], Stefan Schoenfelder[2], Guy Slater[1], Adelyne Chan[1], Shamith Samarajiwa[3], Peter Fraser[2], Masashi Narita[1]

[1]Cancer Research UK CI, University of Cambridge, UK. [2]Babraham Institute, University of Cambridge, UK. [3]MRC Cancer Unit, University of Cambridge, UK

50 **Telomere-initiated senescence requires homologous recombination-mediated sister chromatid fusions and genomic instability**

Marc-Alexandre Olivier[1], Sabrina Ghadaouia[1], Aurélie Martinez[1], Guillaume B Cardin[1], Nicolas Malaquin[1] and Francis Rodier[1,2]

[1]CRCHUM and Institut du cancer de Montréal, Montreal, QC, Canada. [2]Université de Montréal, Département de radiologie, radio-oncologie et médecine nucléaire, Montreal, QC, Canada

51 **Stress granules counteract senescence by sequestration of PAI-1**

Amr Omer, Devang Patel, Xian Jin Lian, Jason Sadek, Sergio Di Marco, Arnim Pause, Myriam Gorospe & Imed Eddine Gallouzi

McGill University

52 **Labelling human senescent cells in breast cancer models to study OIS and TIS**

Veronica Rodilla, Irene Garces, Cristina Bernado and Joaquin Arribas

Vall d'Hebron Institute of Oncology. Growth Factors Laboratory, Barcelona (Spain)

53 **Versatile diagnostic and therapeutic strategies to target senescence**

M. Rovira[1,2], D. Munoz-Espin[1,3], Beatriz Lozano-Torres[4], Irene Galiana, C[4]. Giménez, S[4]. Llanos[1], S. Chaib[1-2], A. Bernardos[4], J.R. Murgía[4], R. Martínez-Máñez[4], M. Serrano[1,2].

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54 **mTOR activation with dysregulated mitochondrial integrity associated with lamin B1 reduction is involved in cellular senescence in COPD pathogenesis**

Nayuta Saito, Jun Araya, Saburo Ito, Yusuke Hosaka, Masahiro Yoshida, Akihiro Ichikawa, Yusuke Kurita, Kenji Kobayashi, Shunsuke Minagawa, Hiromichi Hara and Kazuyoshi Kuwano

Division of Respiratory Diseases, Department of Internal Medicine, The Jikei University, Tokyo, Japan

55 **Exploring the role of the KDM4A Jumonji-C demethylase in pediatric acute myeloid leukemia**

Christina Sawchyn[1,2], Florence Couteau[1], Marie-Ève Lalonde[1], Alena Motorina[1], Erlinda Fernandez-Diaz[1], Nazar Mashtalir[1], El Bachir Affar[1,2,6], Julie A. Lessard[3], Johannes Zuber[4], Sonia Cellot[5], Frédérick A. Mallette[1,2,6]

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56 **Genome-wide CRISPR-Cas9 mediated identification of gene targets that induce growth arrest, with or without a senescence-associated secretory phenotype**

Arnout Schepers, René Bernards

Division of Molecular Carcinogenesis, Cancer Genomics Centre, Netherlands Cancer Institute, Plesmanlaan 121, 1066 CX Amsterdam, the Netherlands

57 **DNA damage response and NF-kB pathways in induced senescence of cancer cells**

Anna Strzeszewska, Olga Alster, Grazyna Mosieniak and Ewa Sikora

Laboratory of Molecular Bases of Ageing, Nencki Institute of Experimental Biology, Polish Academy of Sciences, 3 Pasteura St., 02-093 Warsaw, Poland

58 **Downregulation of nuclear DNases plays key roles in the onset of SASP in senescent cells**

Akiko Takahashi, Ryo Okada, Tze Mun Loo, Eiji Hara

Project for Cellular Senescence, Cancer Institute of Japanese Foundation for Cancer Research, PRESTO

59 **Are human ovarian cancer avatar models useful to probe therapy-induced senescence?**

Véronique Tu[1], Michael Skulimowski[1], Pavel Chrobak[1], Loise Gilbert[1], Daméhan Tchelougou[1], Euridice Carmona[1], Anne-Marie Mes-Masson[1], Diane Provencher[1,2], John Stagg[1,2] and Francis Rodier[1,2]

[1]CRCHUM and Institut du cancer de Montréal, Montreal, QC, Canada. [2]Université de Montréal, Montreal, QC, Canada

60 **Early growth response 2 (EGR2) is a novel transcriptional regulator of the senescence programme**

Eleanor Tyler, Rob Lowe, Vardhman Rakyan, Mike Philpott, Cleo L. Bishop

The Blizard Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London, United Kingdom

61 **Gut microbiota-derived metabolite and cell wall component promote obesity-associated liver cancer through PGE2-mediated suppression of antitumor immunity**

Tze Mun Loo, Fumitaka Kamachi, Naoko Ohtani
Project for Cellular Senescence, The Cancer Institute, Japanese Foundation for Cancer Research

62 **Exosomes Can Be Isolated From the Conditioned Media of Senescent Human Mammary Fibroblasts**

Ryan J Wallis, Eleanor J Tyler, Pavel Novak, Cleo L Bishop
The Blizard Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London, UK

63 **Impact of histone deacetylases (HDACs) on the senescent phenotype**

Warnon C.[1], Verhoyen M.[1], Piel G.[2], Mottet D.[3] and Debacq-Chainiaux F.[1]
[1]URBC-Narilis, University of Namur (UNamur), Namur [2]Laboratory of Pharmaceutical Technology and Biopharmacy (LTPB)−Center for Interdisciplinary Research on Medicines (CIRM),University of Liege [3]Protein Signalisation and Interaction (PSI)−GIGA, University of Liege, Liege

64 **Bmi-1 controls cancer cell motility and invasion through the glycosyltransferase C2GnT2**

Kimi Yamakoshi[1], Mayu Iida[1], Risa Nishijima[1], Akihiko Kameyama[2], Mitsuo Maruyama[1]
[1]Dep. of Mech. of Aging, Res. Inst. of NCGG, [2]Biotech. Res. Inst. for Drug Discovery, AIST

65 **The CDK 4/6 inhibitor Palbociclib can modulate DNA damage-induced senescence in human ovarian cancer cells**

Y. Zhan[1], S. Cheng[1], J. Lafontaine[1], L. Gonzalez[1], F. Rodier[1,2]
[1]Centre de recherche du CHUM. [2]Département de radiologie, radio-oncologie et médicine nucléaire, Université de Montréal, Montreal, Canada

66 **MYC and RAS are not able cooperate in overcoming oncogene-induced senescence and apoptosis in normal human fibroblasts**

Fan Zhang[1,a], Siti Mariam Zakaria[1,a], Vedrana Tabor[1,2], Madhurendra Singh[1], Susanna Tronnersjö [1,3], Jacob Goodwin[1], Galina Selivanova[1], Alina Castell[1], Lars-Gunnar Larsson[1,b]
[1]Department of Microbiology, Tumor and Cell Biology, Karolinska Institutet, Stockholm, Sweden
[3]Present address: GE Healthcare, Uppsala, Sweden

67 **Immunological Effects of Senescent Cell Clearance in The Articular Joint Traumatic Wound**

Hong Zhang[1], Heather J. Faust[1], Liam Chung[1,2], Matthew Wolf[1, 2], Ada J. Tam[2], Frank Housseau[2], Jennifer H. Elisseeff[1,2]
[1]Translational Tissue Engineering Center, Johns Hopkins University, Baltimore, MD, USA
[2]Bloomberg~Kimmel Institute for Center Immunotherapy, Johns Hopkins University, Baltimore, MD, USA

68 **Cellular senescence elicited by PRMT5 depletion is required for the sensitization of osteosarcoma cells to DNA damage of cisplatin**

Huan-Tian Zhang [1,2,*], Yu-Hang Li[1], Jie Yang[1], Tao Gui[1], Yuan Sang[1], Zhen-Yan Li[1], Qing-Yu He[2], Zhen-Gang Zha[1,*]

[1]Institute of Orthopedic Diseases and Center for Joint Surgery and Sports Medicine, the First Affiliated Hospital, Jinan University, Guangzhou 520630, PR China. [2]Key Laboratory of Functional Protein Research of Guangdong Higher Education Institutes, College of Life Science and Technology, Jinan University, Guangzhou 510632, PR China

69 **Sequential targeting the YAP1 and miR-93-regulated p21 expression enhances the elimination of senescent cells elicited by BET inhibitor JQ1**

Huan-Tian Zhang[1,2,*], Tao Gui [1], Yuan Sang[1], Jie Yang[1], Zhen-Yan Li[1], Yu-Hang Li[1], Qing-Yu He[2], Zhen-Gang Zha[1,*]

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2-min Speed Talk Posters and numbers:

70 **p53 loss does not permit escape from BrafV600E -induced senescence in a mouse model of lung cancer**

Sam Garnett, Kendall L. Dutchak, Rosalie V. McDonough, and David Dankort

McGill Biology

71 **Identification of a novel senotherapeutic molecule: comparison with retinoic acid in human aged 2D and 3D skin models**

Daniel A. Foyt[1], Mylieneth Guiang[1]; Carolina Reis de Oliveira[1]; Edgar Andres Ochoa[1]; Mariana Boroni[1,3]; Juliana Lott de Carvalho[1,2]; Alessandra Zonari[1]

[1]OneSkin Technologies, San Francisco - California, USA; [2]Catholic University of Brasília, Brasília, Brasil; [3]National Cancer Institute (INCA), Rio de Janeiro, Brasil

72 **Cellular senescence occurs during mammary gland involution**

Aurelie Chiche, Elsa Charifou, Han Li

Cellular Plasticity and Disease Modelling group, Department of Developmental & Stem Cell Biology, CNRS UMR 3738, Institut Pasteur, Paris, France

73 **The role of cellular senescence in the development of pancreatic ductal adenocarcinoma**

Lior Roitman*, Dror Gal*, Yossi Ovadya, Valery Krizhanovsky[1], Itay Ben-Porath[2]
[1]Department of Molecular Cell Biology, the Weizmann Institute of Science, Rehovot 76100, Israel
[2]Department of Developmental Biology and Cancer Research, Institute for Medical Research-Israel-Canada, Hebrew University-Hadassah Medical School, Jerusalem, Israel.

74 **PARsing the function of PARP1 in senescence-associated gene regulation**

Lucas Robinson[1], Ricardo I Martinez Zamudio[2], Pierre-François Roux[1], Gregory Doré, and Oliver Bischof[1]
[1]Institut Pasteur, Senescence and Age-Related Pathologies Group (SAPS); Oncogenesis and Nuclear Organization Unit (ONO); Dept. of Cell Biology and Infection (BCI); Paris, France; [2]Cancer Institute of New Jersey at University Hospital, Microbiology, Biochemistry & Molecular Genetics, Newark, NJ.

75 **Investigating the dynamic program of single cell senescence**

Matej Durik, Jean-Luc Plassat and Bill Keyes
IGBMC, 1 Rue Laurent Fries, Illkirch, 67404, France

76 **CDK4/6 Inhibitors Induce Cellular Senescence in Normal Cells without Deleterious Associated Secretory Phenotypes**

Boshi Wang, Simone Brandenburg, Alejandra Hernandez-Segura, Thijmen van Vliet, Britt Sterken, Cornelis F. Calkhoven and Marco Demaria
European Research Institute for the Biology of Ageing (ERIBA), University Medical Center Groningen (UMCG), University of Groningen. Groningen, Netherlands

77 **Telomere length is exclusively maintained by the ALT mechanism in a vertebrate, the newt Pleurodeles waltl**

Phillip Gates[1], Qinghao Yu[2], Ivan Mikicic[2], Florian Salomon[2], Ahmed Elewa[3], Andras Simon[3] & Maximina Yun[2,4*]
[1]Institute of Structural and Molecular Biology, University College London, UK
[2]Technische Universität Dresden, DFG/Center for Regenerative Therapies Dresden, Germany
[3]Karolinska Institute, Stockholm, Sweden
[4]Max Planck Institute for Molecular Cell Biology and Genetics, Dresden, Germany

78 **Exosomes transmit the signals of senescence-associated secretory phenotype**

Xiang Li[1,2], Ana Banito[1], Direna Alonso Curbelo[1], Darjus Tschaharganeh[1], Scott Lowe[1]
[1]Cancer Biology and Genetics Program, Memorial Sloan-Kettering Cancer Center, New York, USA; [2]Weill Cornell Graduate School of Medical Sciences, Cornell University, New York, New York, USA

79 **Loss of CDK2 Delays Onset and Progression of BRAFV600E/MYC-driven Mouse Lung Tumors via Induction of Senescence**

Wesam Bazzar, Nyosha Alikhani, Jacob Goodwin, Marcela Franco, Raoul Kuiper and Lars-Gunnar Larsson

[1]Department of Microbiology, Tumor and Cell Biology (MTC), Karolinska Institutet, Stockholm, Sweden; [2]Department of Laboratory Medicine, Karolinska University Hospital Huddinge, Stockholm, Sweden

Late Arrival Posters and numbers:

80 **Autophagy Dysfunction During Neuronal Senescence**

Daniel Moreno-Blas, Elisa G. Gorostieta-Salas, Gabriel Muciño-Hernández, Alexander M. Pommer-Alba & Susana Castro-Obregón

Neurodevelopment and Physiology Department, Institute of Cellular Physiology, UNAM Circuito Exterior SN, Ciudad Universitaria, Coyoacán, Mexico City, Mexico.

81 **2-min Speed Talk**

The bystander effect of exosomes in senescence

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Ageing is a biological and natural process by which an organism starts to degenerate and decline. From a molecular point of view, senescence is a hallmark of ageing. Senescence is a cellular phenotype characterised by an irreversible cell cycle arrest and the secretion of inflammatory proteins, denominated senescence-associated secretory phenotype (SASP). The SASP is important in influencing the behaviour of neighbouring cells, therefore altering the microenvironment. Though so far, this has been exclusively attributed to soluble factors. Here, we report that exosomes (extracellular vesicles of endocytic origin) also alter the environment by transmitting the senescent phenotype to other cells. Thus, blocking exosome biogenesis by the use of small molecular inhibitors or siRNA targeting key proteins regulating the endocytic pathway prevents the activation of paracrine senescence. A comparative analysis of the soluble and the exosome fraction shows that both are responsible for intercellular communication, while microvesicles are not. In fact, the treatment of normal human primary diploid fibroblasts with an equal number of exosomes derived from control and senescent cells induces paracrine senescence in primary and cancer cell lines. By taking advantage of a Cre-loxP reporter system we can confirm at a single-cell level that the cells internalizing exosomes derived from senescent cells activate this program, showing a correlation in functionality. Proteomic analysis of the exosome content from control and senescent exosomes followed by an siRNA functional screen identify the activation of a non-canonical interferon (IFN) pathway mediated by exosomes purified from senescent cells. Therefore, exosomes, as part of the senescent secretome, could be responsible for the local and systemic spreading of cellular and tissue decline during ageing and age-related diseases.

The Science of Maple Syrup

Maple sap was used by the indigenous natives before the arrival of Europeans on the American continent. There exist two kinds of trees that are used to produce maple products: the sugar maple and the red maple. Maple water flows in the spring thanks to freeze-thaw cycles that create the right pressure. To obtain maple syrup and other products from maple water, the sugar content must be concentrated by reverse osmosis and boiled. Maple syrup is defined by a 66% sugar content.

Maple sap composition changes all along the short spring season where it is collected and this will affect the taste of the different products. How?

The proportion of different carbohydrates evolves during the season: the concentration of fructose and glucose increases as the season progresses whereas sucrose concentrations tend to drop. With warming temperatures, bacterial content increases which favors the breakage of sucrose into glucose and fructose. These two sugars are involved in the Maillard reaction, which is responsible for non-enzymatic browning in food, and which releases different flavours. The type of amino acid reacting with the sugar will be responsible for the different flavours. In conclusion, as the season advances, maple syrup will get darker and more strongly flavoured, whereas it is lighter of color and more delicate at the beginning of the season. Quality is the same for these differently flavored syrups, it is simply a matter of taste!

Syrup is the most popular of maple products, but many other products are made with maple water and they are all delicious: they range from taffy to hard sugar loafs without forgetting maple butter. Obtaining these different textures requires either provoking the crystallization of the sugar or preventing it.

Maple syrup and maple taffy, for example, are translucent. These products must be cooled without mixing to prevent crystallization from occurring. Traditionally eaten on snow, taffy is cooled very rapidly, resulting in a glass-like sugar. Maple butter, on the other hand, is obtained by creating a saturated solution at high temperatures (83% sugar) and cooling it down quickly while mixing. This results in a supersaturated solution at a lower temperature and makes it crystallize into a smooth creamy texture.

If you want to taste these different products, you will find them in some grocery stores, but with more certainty in specialized places such as Jean-Talon Market or the Atwater Market. Some gift shops also have a few products on sale. You can use maple syrup in lots of recipes, whether for marinating meat or in desserts. It is great on pancakes or just dip some bread in a mix of maple syrup and cream. Bon appétit!

N.B.: For a better and lasting taste, we suggest to keep your complimentary maple syrup bottle in the fridge.

The History of Smoked Meat

World Famous **Schwartz's smoked meat**, serving smoked meat from the original recipe of spices since 1928.

Imagine walking through the door and taking a step back 80 years into Main Street history in Montreal. A "true" Montreal that has welcomed celebrities and visitors from all over the world.

Schwartz's was founded in 1928 by Reuben Schwartz, a Jewish immigrant from Romania, and our restaurant has been in the same location ever since, on boulevard Saint-Laurent, where it is now ticket in around funky storefronts and trendy boutiques. The restaurant is a single white-tiled room containing several rows of long narrow tables. Come and enjoy a unique experience.

We've protected our tradition for over 80 years by maintaining the standards of old. Unlike other smoked-meat purveyors, who add chemicals to their briskets, Schwartz's prepares smoked meat the old fashioned way using a secret blend of fine herbs and spices marinated for 10 days. Our smoked meat is smoked daily and contains no preservatives; just the award winning taste and freshness that have brought celebrities from all around the world to our tables.

So enjoy!

Organizers and Invited speakers' disclosure Information

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Disclosed no conflict of interest

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Disclosed no conflict of interest

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Disclosed no conflict of interest

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2018
Sirop d'érable
Maple syrup
100 mL
Érablière Camille Bilodeau
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