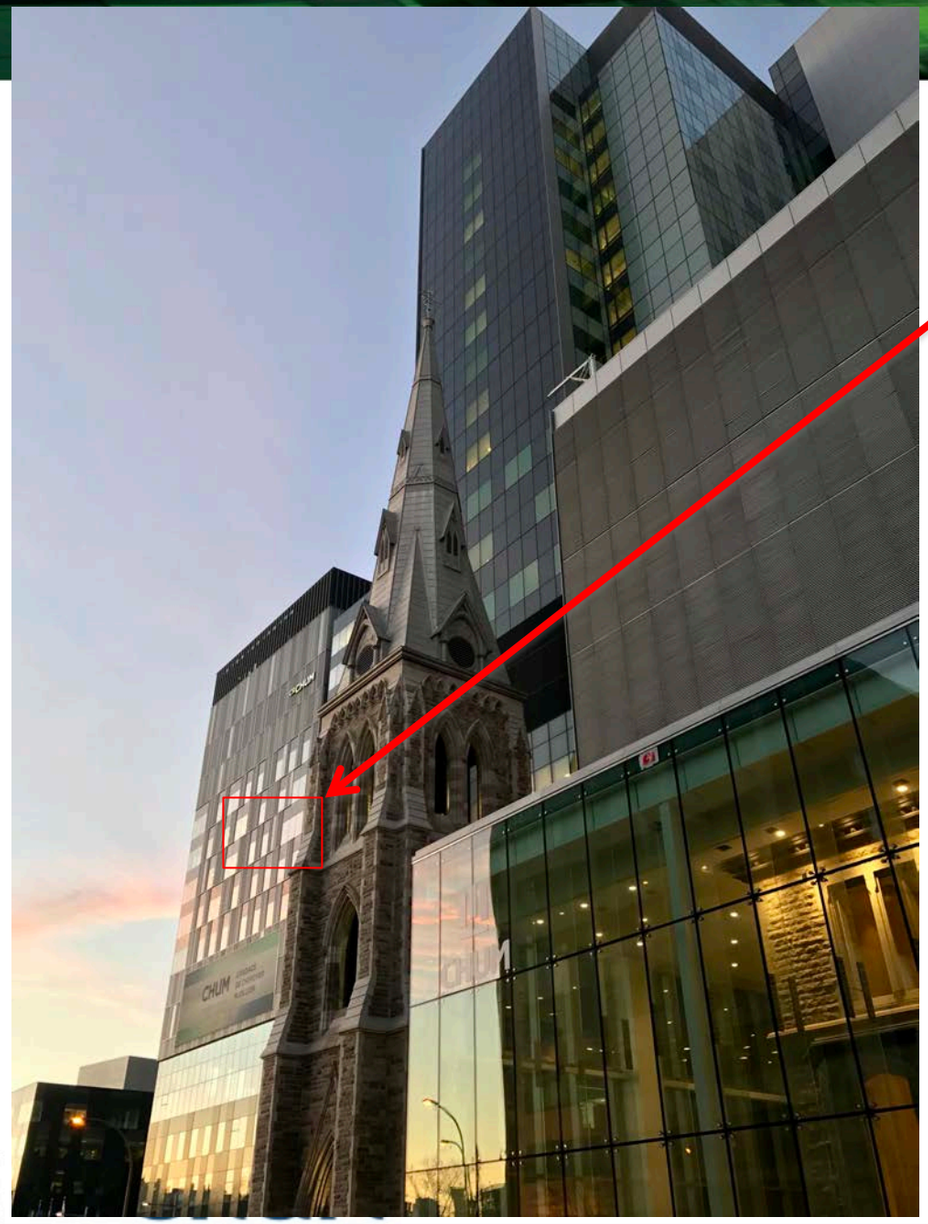
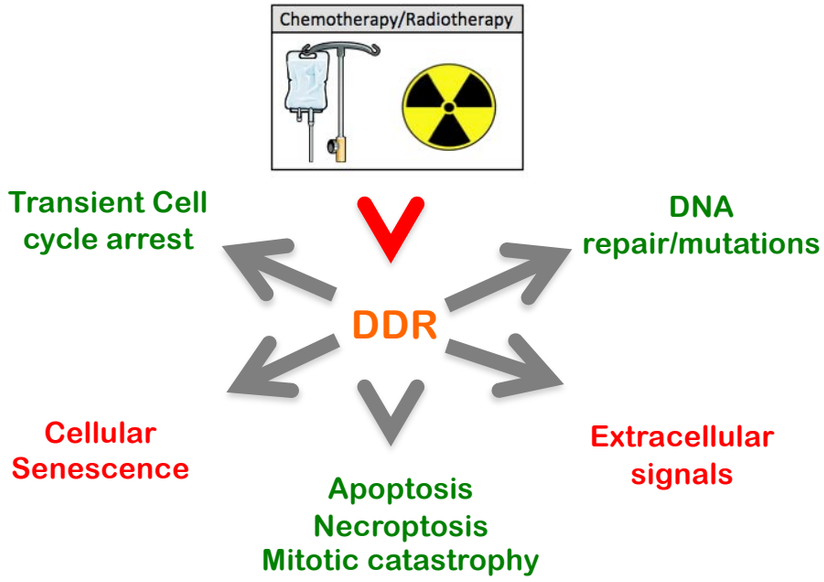
Explorer les biomarqueurs de l'âge biologique associés à la sénescence cellulaire dans l'étude CARTaGENE et la cohorte PETALE

- **Francis Rodier**
- Professeur agrégé, Uiversité de Montréal
- Chercheur CRCHUM et Institut du cancer de Montréal
- **Sophie Marcoux**
- Médecin spécialiste en santé publique et médecine preventive
- Chercheuse post-doctorale au CRCHUM



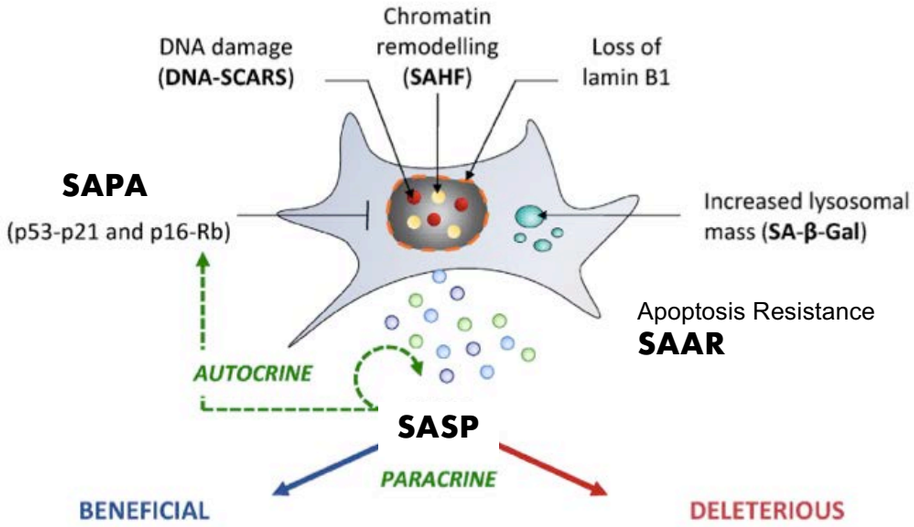
Axe Cancer et Institut du cancer de Montréal

Therapy-induced cell fate decisions laboratory



Gonzalez LC et al. Biogerontology 2016

Cellular senescence: Hallmarks and functions



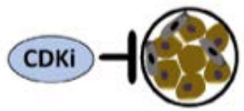
Embryonic development

- *Patterning*
- *Macrophage recruitment (clearance)*

Wound healing

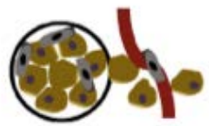
- *Resolution of fibrotic scar*
- *Immune cell attraction*
- *Mobilisation of stem cells*

Cancer suppression



- *Reinforcement of senescence*
- *Immune clearance*

Cancer progression



- *Promotion of cancer cell aggressiveness*
- *Niche of chemo-resistance*
- *Angiogenesis*

Aging

- *Tissue dysfunction*
- *Chronic Inflammation*
- *Age-related diseases (e.g. Alzheimer, osteoarthritis, etc.)*

What is aging?

Webster dictionary:

age
verb
aged; **aging** or **ageing**
Definition of *age*
intransitive verb

1: to become old **:** show the effects or the characteristics of increasing age
2: to acquire a desirable quality (such as mellowness or ripeness) by standing undisturbed for some time: "letting cheese age"

Encyclopedia Britannica:

Aging: progressive physiological changes in an organism that lead to senescence, or a decline of biological functions and of the organism's ability to adapt to metabolic stress.

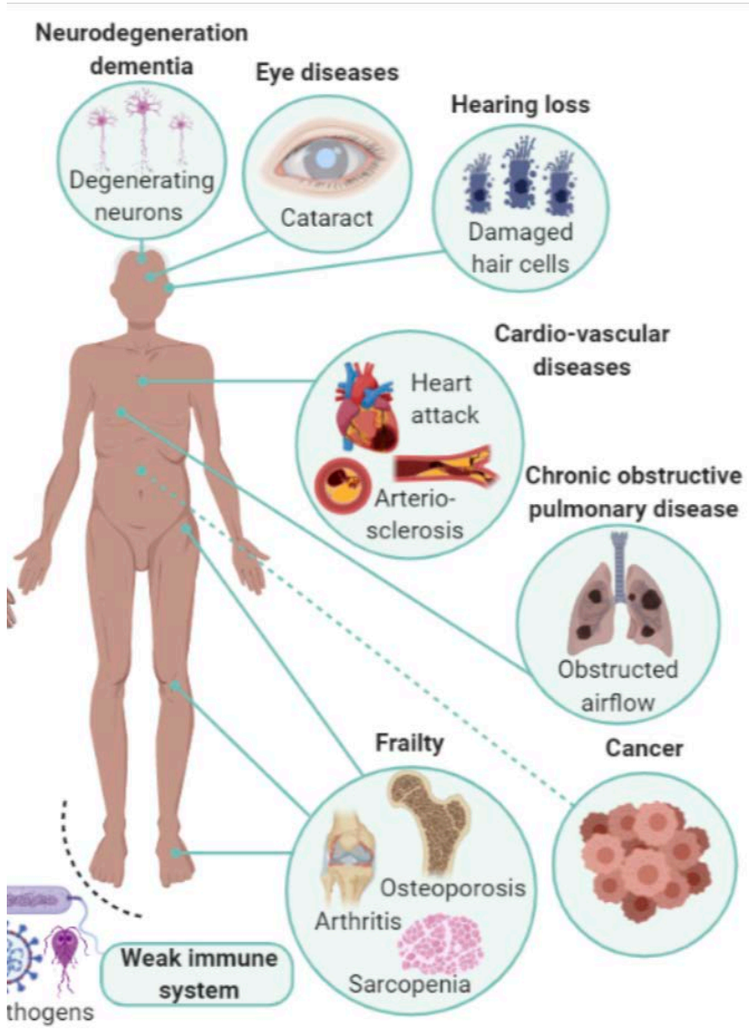
"The viability (survival ability) of a population is characterized in two actuarial functions: the survivorship curve and the age-specific death rate, or Gompertz function"

What is aging?

Why does the probability of death increase in old age?

Because of **Age-associated diseases**

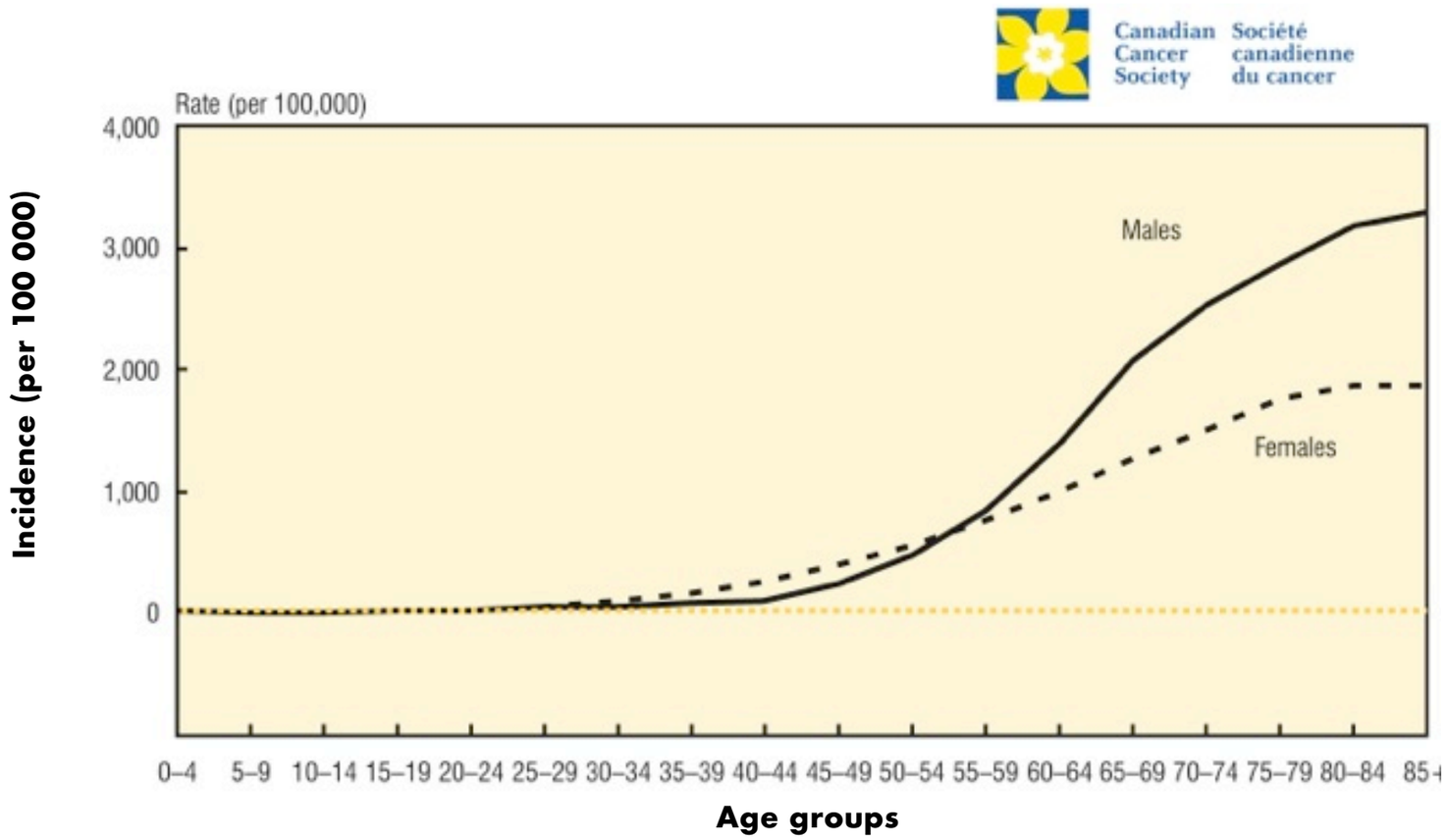
The example of cancer



Larisa Sheloukhova, Biorender
https://app.biorender.com/community/gallery/s-5edf6cec2e012f00aeabacd1-age-associated-diseases-and-conditions

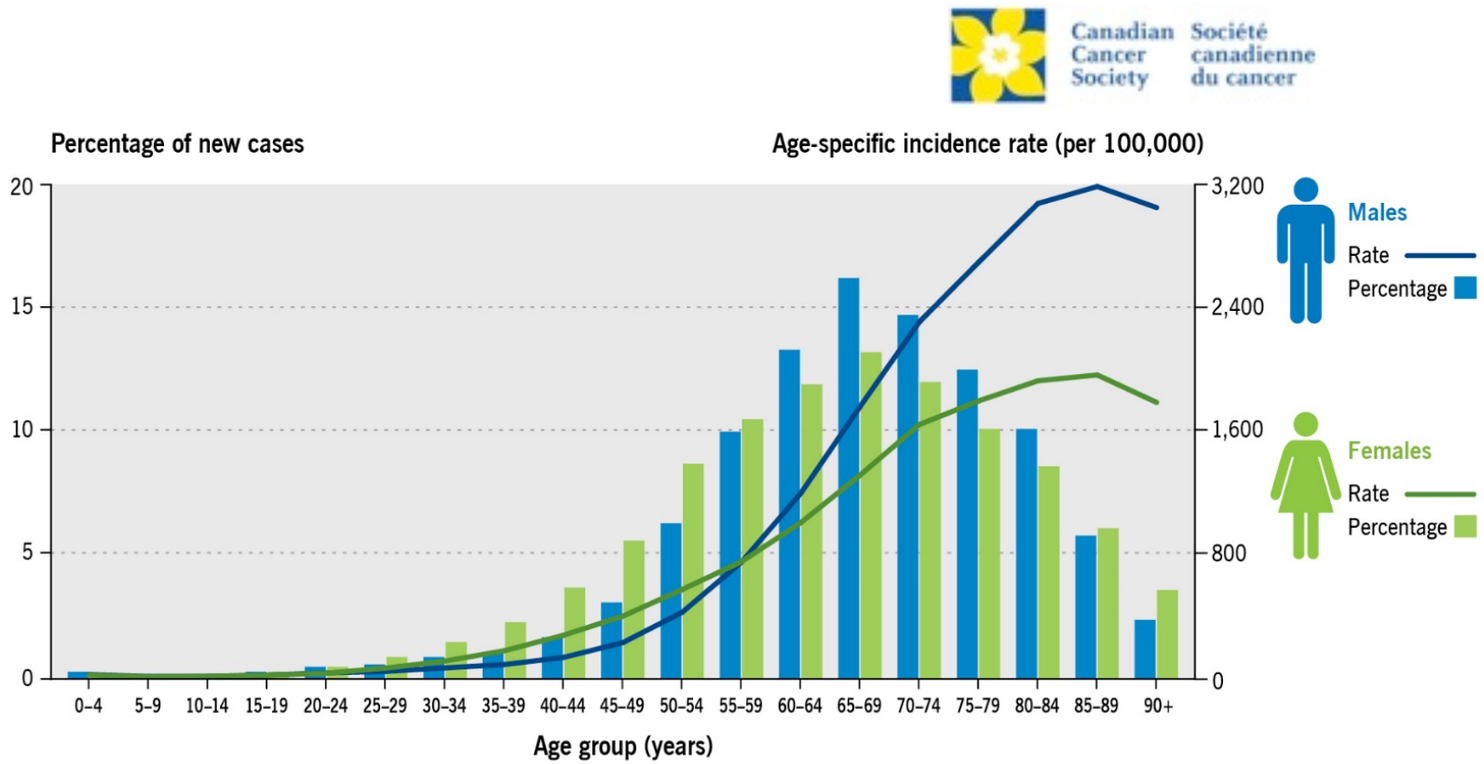
Cancer is an age-associated disease

Cancer incidence by age groups (All cancer, Canada 2006)



Cancer is age-associated

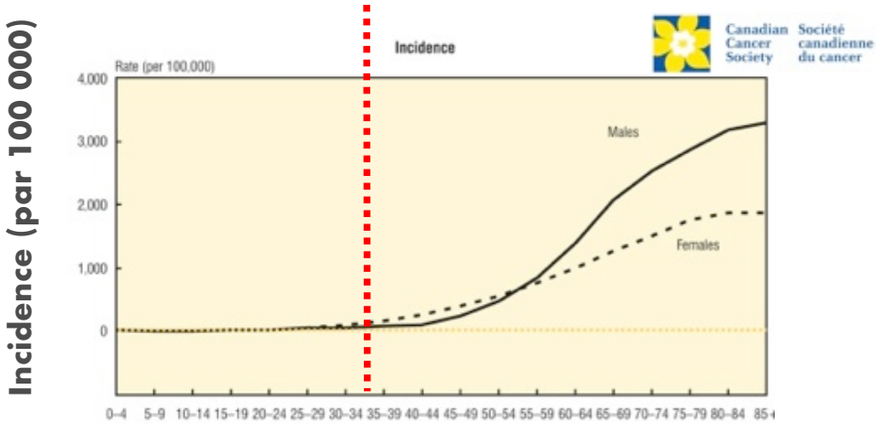
Cancer incidence by age groups (All cancer, Canada 2013-2015)



Age is the risk factor #1

Just like other age-associated diseases

Cancer is an age-associated disease



Canadian Cancer Society / Société canadienne du cancer

LIFE EXPECTANCY THROUGH THE AGES

Early humans did not generally live long enough to develop heart disease, cancer or loss of mental function. A snapshot of how life expectancy has changed, and the big killers of each era:

AVERAGE LIFE EXPECTANCY

30 years

Neanderthals (30,000 years ago): Died of injuries caused by rock falls, hunting accidents and conflicts. Food scarcity led to malnutrition. These hunter-gatherer groups contracted diseases that spread from animals. Rabies, tuberculosis, brucellosis, yellow fever and encephalitis were widespread.

38

Neolithic (8500 BC to 3500 BC): Agriculture, irrigation and urbanization brought problems associated with settled populations, such as fecal contamination of water and diseases such as cholera, smallpox, typhoid, polio and influenza. Malaria and other diseases carried by mosquitoes and insects, which fed on domesticated animals, appeared.

35 **Classical Greece and Rome** (500 BC to 500 AD): Tuberculosis, typhoid fever, smallpox and scarlet fever spread among the denser urban populations. Malnutrition, gastroenteritis and violence were also big killers.

48 EARLY MEDIEVAL **38** LATE MEDIEVAL

Medieval period (500 AD to 1500 AD): Life expectancy grew with urbanization, but famine caused by crop failures and bubonic plague were the big killers. The Black Death (1347-1351) wiped out 25 million people in Europe and 60 million in Asia, returning several times, culminating in the Great Plague of London (1664-1666). By 1500, life expectancy had dropped back to 38.

40

Victorian (1850s to 1900): Typhus, typhoid fever, rickets, diphtheria, tuberculosis, scarlet fever and cholera raged in crowded cities.

MEN **70** WOMEN **75**

1900s: Better health care, sanitation and living conditions boosted life expectancy to 70 for men and 75 for women by 1950.

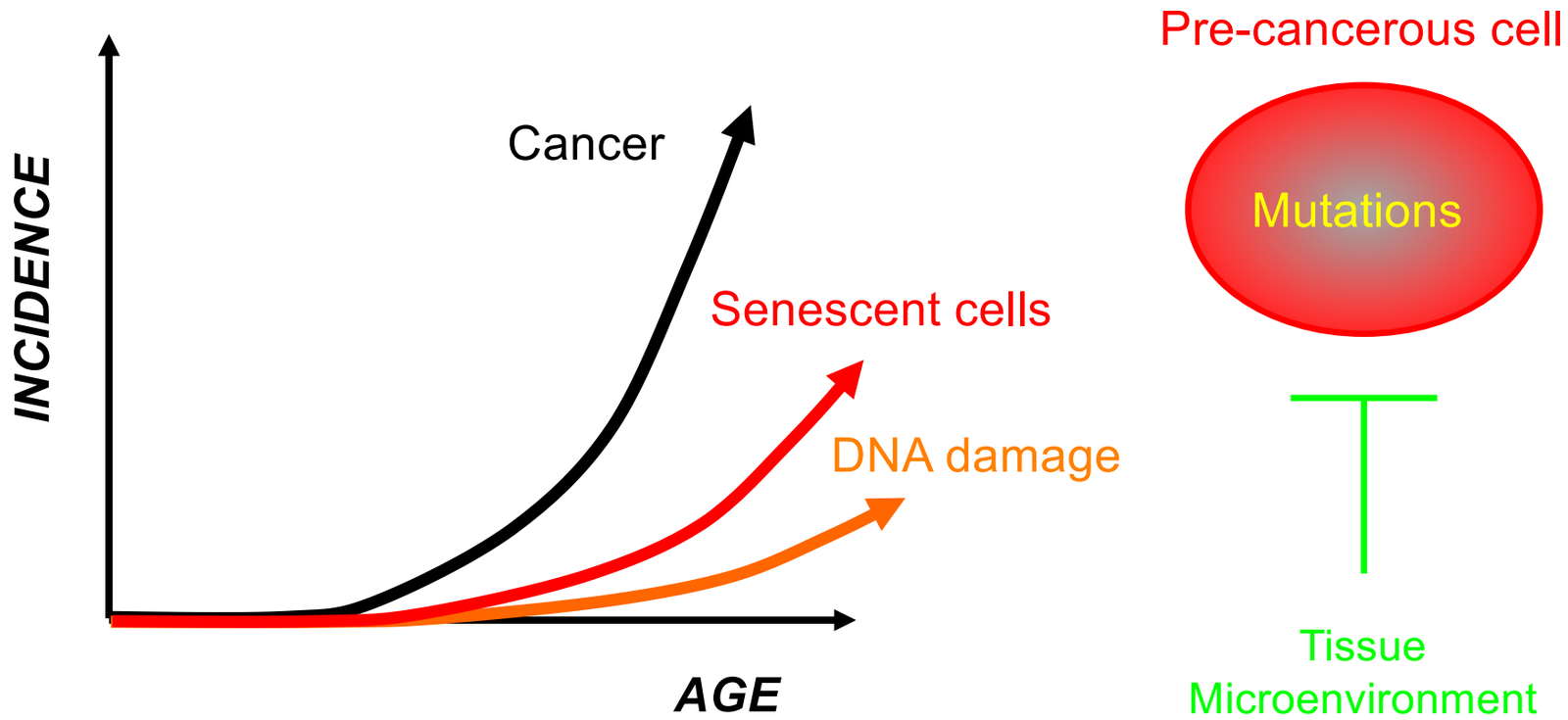
CANADA: MEN **82** WOMEN **85**

Today: Cancer, heart disease and stroke are the biggest killers in the developed world. Our longer lifespan also comes with unprecedented loss of mental function and mobility problems.

RESEARCH BY RICK SZNAJDER/TORONTO STAR LIBRARY SOURCES: JOURNAL OF POPULATION RESEARCH, PRINCETON UNIVERSITY, STANFORD UNIVERSITY, WORLD HEALTH ORGANIZATION

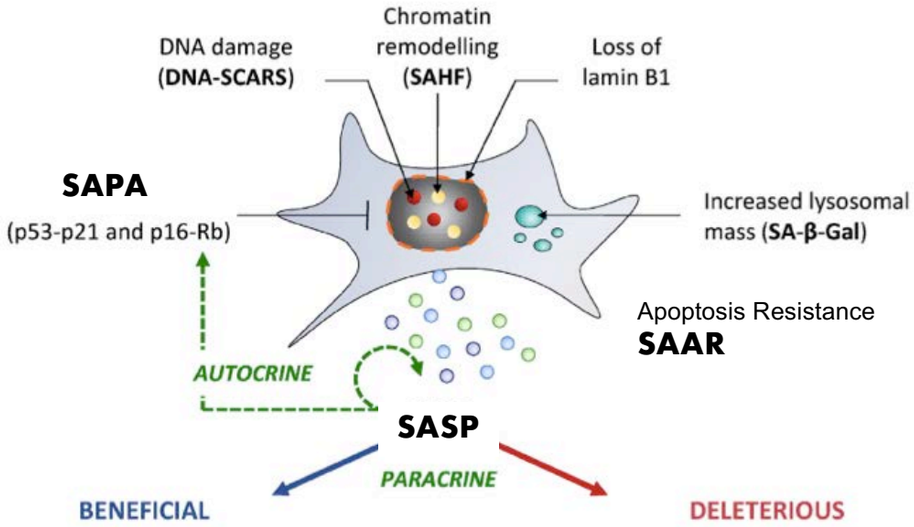
***Antagonistic pleiotropy**: What is good for you when you are young, is not necessarily good when you are old!*

Cancer is an age-associated disease



Current hypothesis: the convergence of accumulated mutations (DNA damage) and dysfunctional aging tissues (senescence) cooperate to promote transformed cell growth

Cellular senescence: Hallmarks and functions



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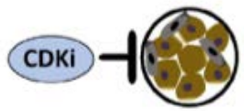

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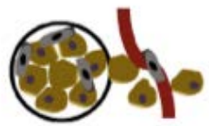
Cancer progression



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Published February 14, 2011

JCB: Review

Four faces of cellular senescence

Francis Rodier[1,2] and Judith Campisi[3,4]

[1]The Research Centre of the University of Montreal Hospital Centre/Institut du Cancer de Montréal, Montreal, Quebec, H2L 4M1 Canada
[2]Department of Radiology, Radio-Oncology and Nuclear Medicine, Université de Montréal, Montreal, Quebec, H3C 3J7 Canada
[3]Buck Institute for Age Research, Novato, CA 94945
[4]Lawrence Berkeley National Laboratory, Berkeley, CA 94720

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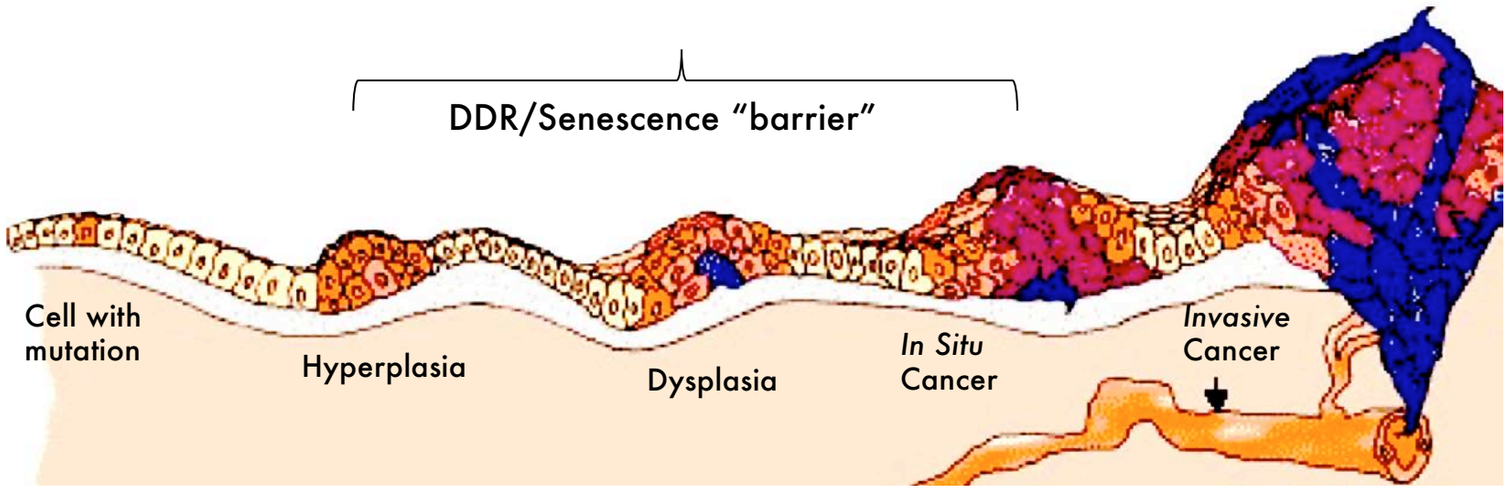
Cellular senescence: Functions

Cancer suppression: Mutations/Oncogene-induced senescence



Cell INTRINSIC

- SA proliferation arrest (SAPA)

- Highly depends on Rb/p53
- Induction - Genotoxic stresses/Hyper-proliferation (DNA DAMAGE)

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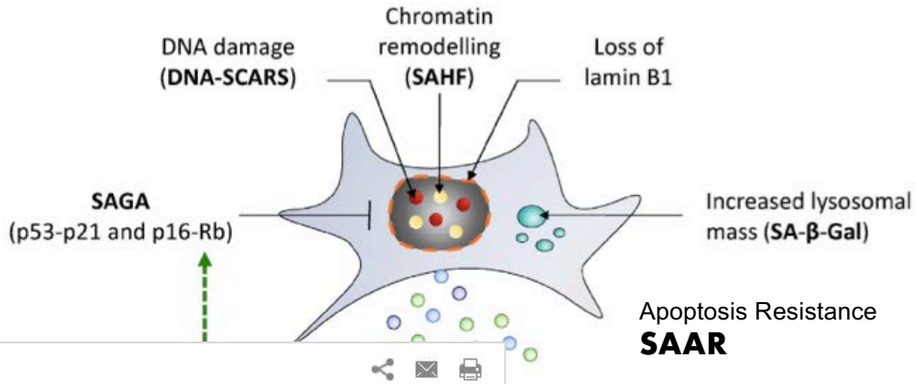
FACE 3-4 - Aging & Cancer 2016



Apoptosis Resistance
SAAR

DELETERIOUS

NATURE | NEWS

Destroying worn-out cells makes mice live longer

Elegant experiment confirms that targeting senescent cells could treat age-related diseases.

Ewen Callaway

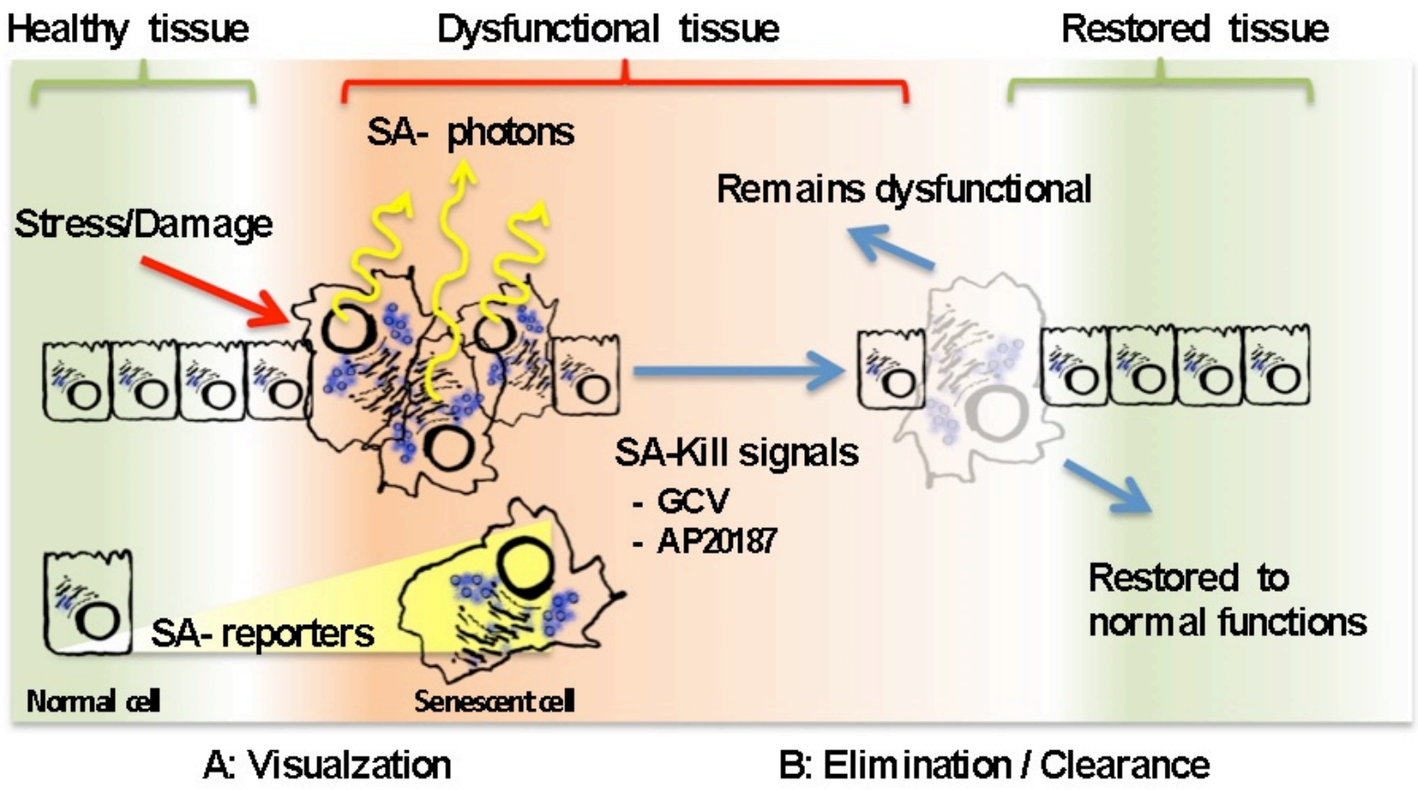
Aging

- *Tissue dysfunction*
- *Chronic Inflammation*
- *Age-related diseases (e.g. Alzheimer, osteoarthritis, etc.)*

Baker et al. Nature 2016

Cell “extrinsic” FACES – emerging tools of 2010s

Senescence-manipulation using genetic mouse models

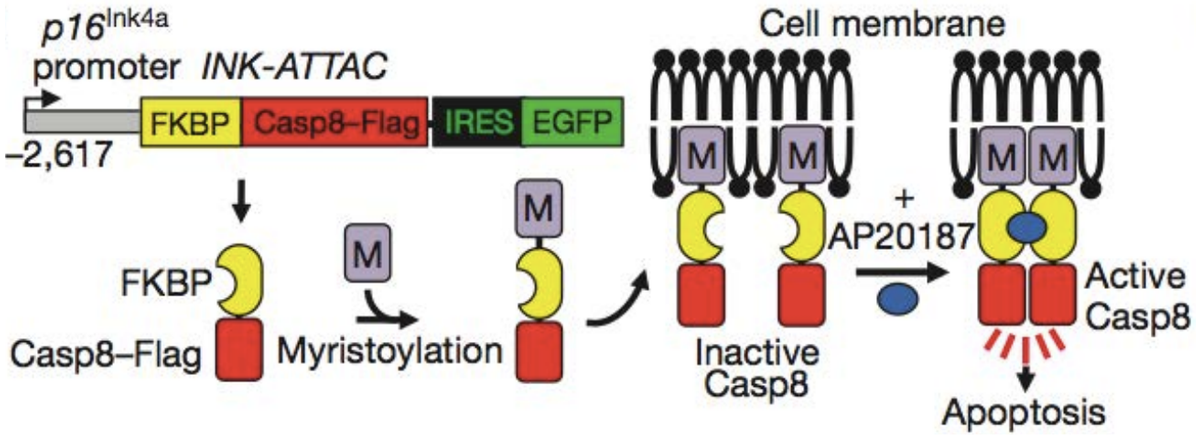


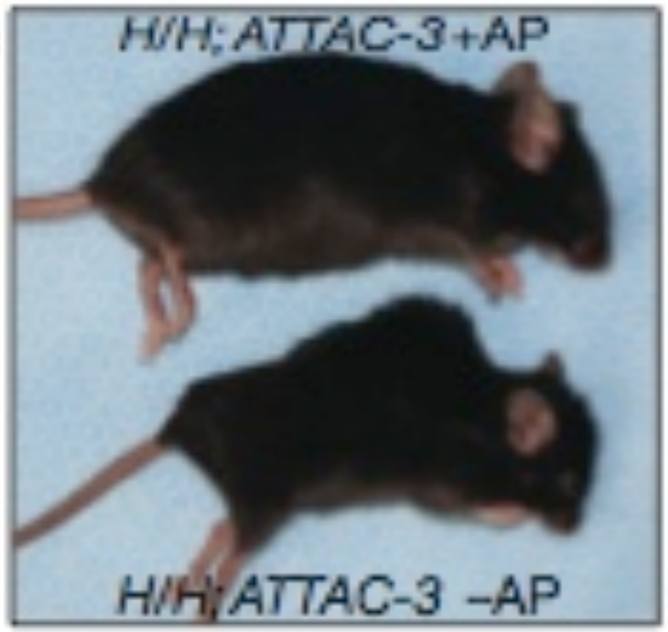
LETTER

doi:10.1038/nature10600

Clearance of p16^{Ink4a}–positive senescent cells delays ageing–associated disorders

Darren J. Baker[1,2,3], Tobias Wijshake[1,4], Tamar Tchkonia[3], Nathan K. LeBrasseur[3,5], Bennett G. Childs[1], Bart van de Sluis[4], James L. Kirkland[3] & Jan M. van Deursen[1,2,3]





Baker, Nature 2011, 479: 232

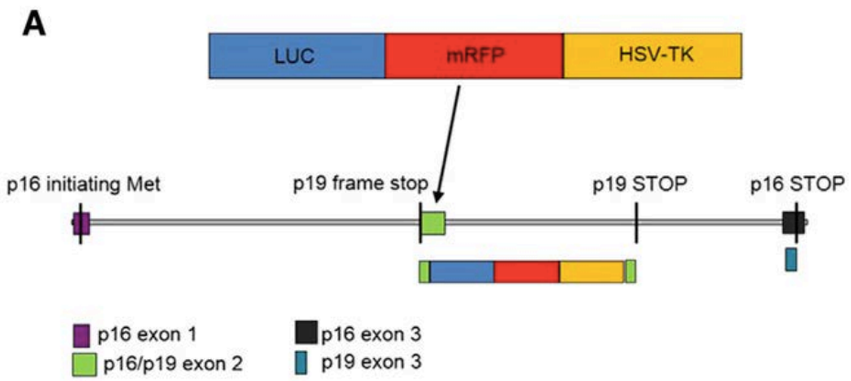
CanPath
Canadian Partnership for Tomorrow's Health

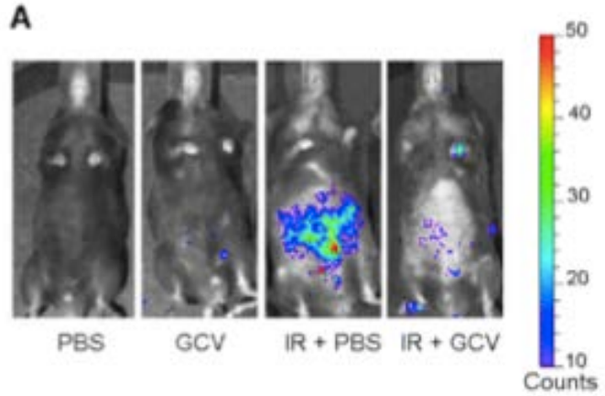
CellPress

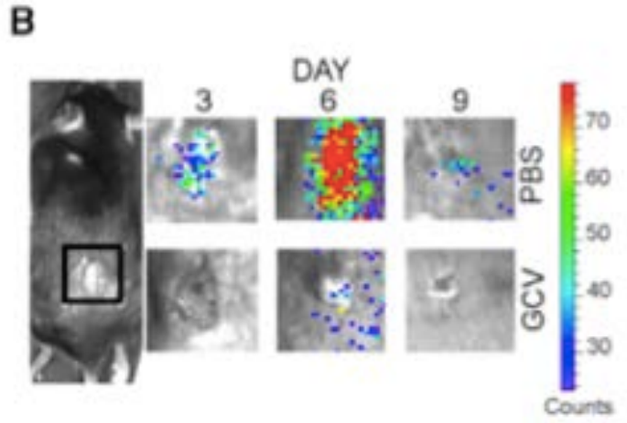
An Essential Role for Senescent Cells in Optimal Wound Healing through Secretion of PDGF-AA

Developmental Cell
Article

Marco Demaria,[1] Naoko Ohtani,[2] Sameh A. Youssef,[3] Francis Rodier,[1,9] Wendy Toussaint,[4,10] James R. Mitchell,[4,11] Remi-Martin Laberge,[1] Jan Vijg,[5] Harry Van Steeg,[6,7] Martijn E.T. Dollé,[7] Jan H.J. Hoeijmakers,[4] Alain de Bruin,[3] Eiji Hara,[2] and Judith Campisi[1,8,*]







CRCHUM

Cellular **senescence: Hallmarks and functions**

Published February 14, 2011

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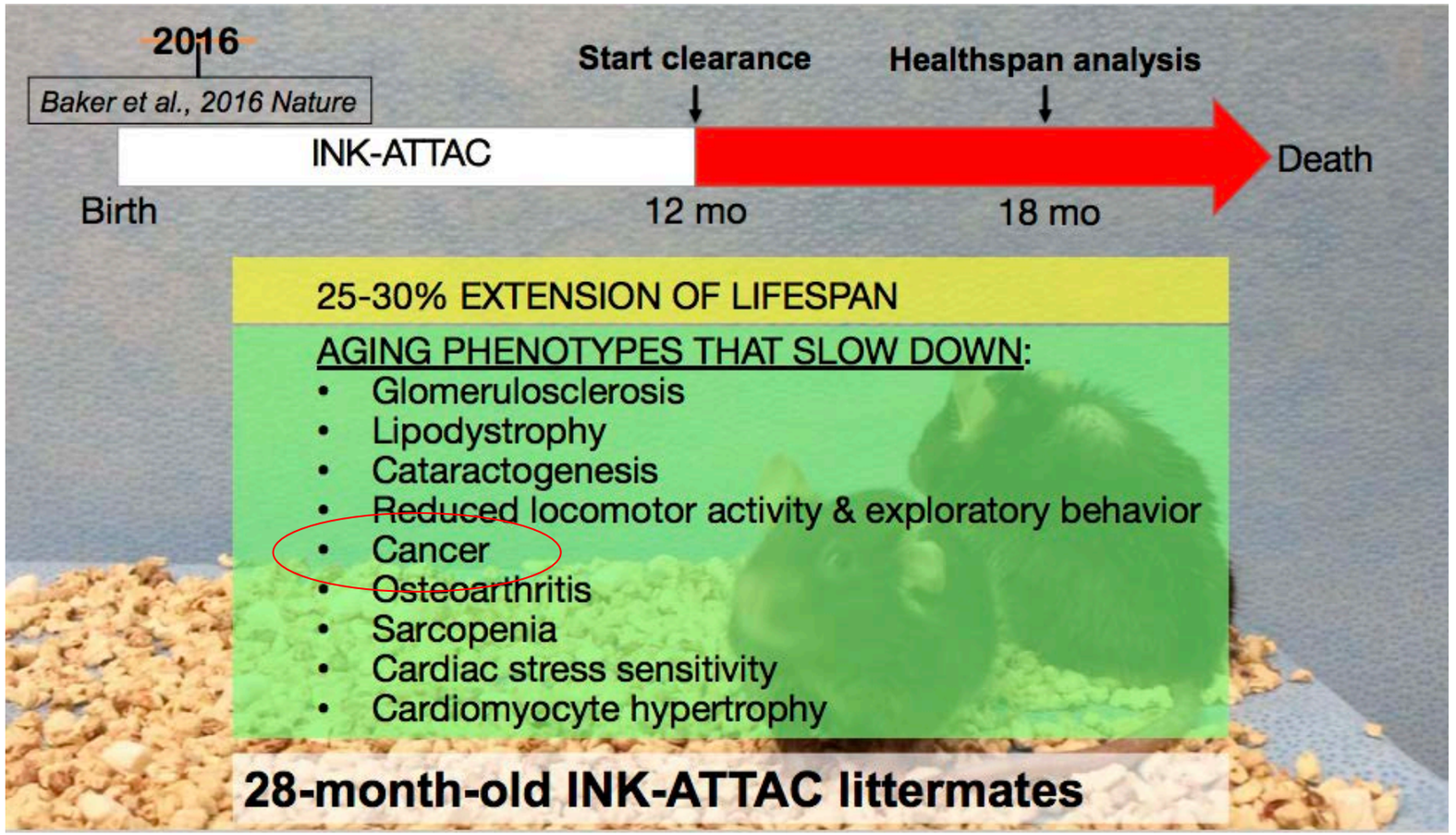
Cellular senescence: functions

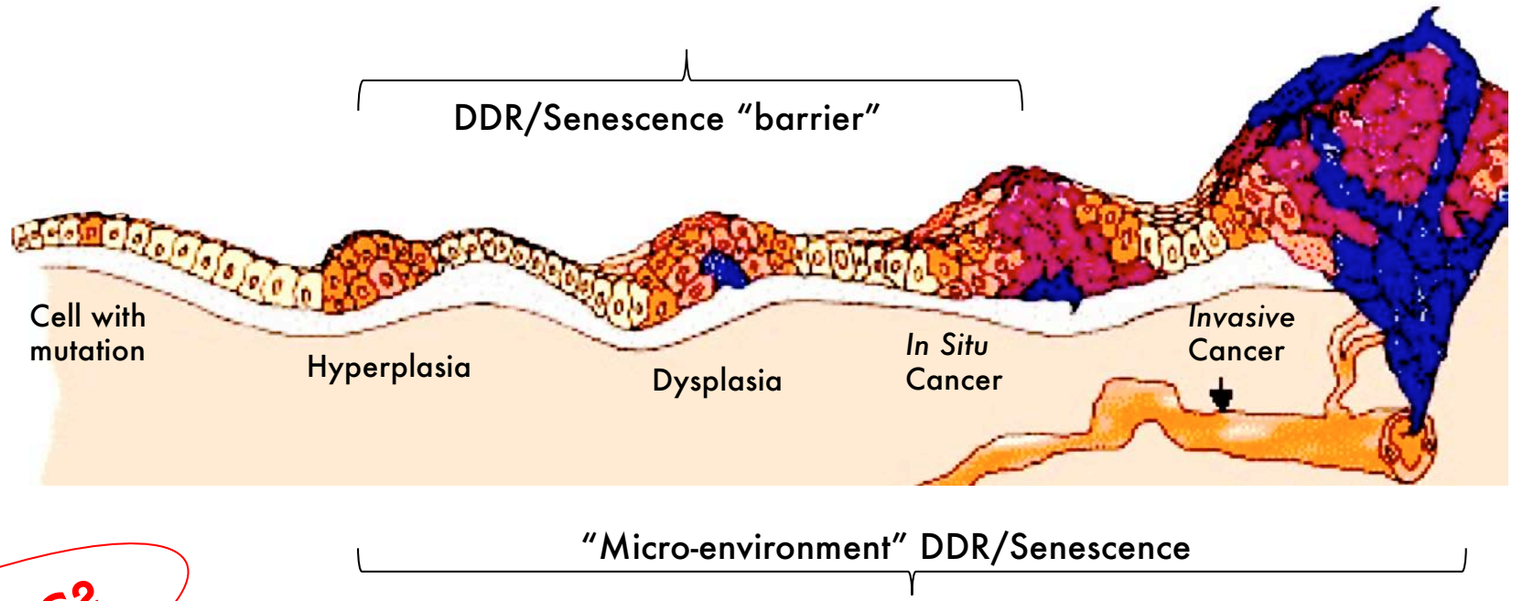
Senescent cells have cell non-autonomous effects on their microenvironment and can promote tissue dysfunction



Baker et al, Nature 2016

Cellular senescence: Functions

Tissue remodeling: Mutations/Oncogene/Cancer-induced senescence



Cell EXTRINSIC?

- SA secretory phenotype/programs (SASP)

- Highly depends on NFKB
- Induction - Genotoxic stresses (DNA DAMAGE SIGNALS)

Multiple mechanisms drive aging

Senescence:

Cell pools exhaustion (**SAPA**)

Extracellular com (**SASP**)

Genome damage (**DNA-SCARS**)

Telomere attrition (**DNA-SCARS**)

Epigenetic alterations (**SAHF**)

Loss of proteostasis (**SAPD**)

Deregulated metabolism (**MiDAS**)

The Hallmarks of aging, Cell

Multiple mechanisms drive aging

Senescent cells cause or contribute to:

Alzheimer's@@ and Parkinson's disease*

*Atherosclerosis***

*Cardiovascular dysfunction**#*

*Cancer metastasis and recurrence****

*Chemotherapy (HAART) cardiotoxicity, blood clots, fatigue****

Cognitive decline/loss of neurogenesis

Diabetes

Myeloid→lymphoid skewing #

*Pulmonary fibrosis#**

Osteoarthritis ##

Osteoporosis ###

Sarcopenia/frailty

Wound healing, tissue regeneration @

*Chinta et al, Cell Reports, 2018; **Childs et al, Science, 2016; **#Baker et al, Nature, 2016; ***Demaria et al, 2017; #Chang et al, Nature Med, 2016; #*Schafer et al, Nature Comm, 2017; ##Jeon et al, Nature Med, 2017; ###Farr et al, Nature Med, 2017; @ Demaria et al, Dev Cell, 2014; @@Bussian et al, Nature, 2018

Shared by Dr. Campisi

REPORT

Senescent intimal foam cells are deleterious at all stages of atherosclerosis

Bennett G. Childs[1], Darren J. Baker[2], Tobias Wijshake[2,3], Cheryl A. Conover[4], Judith Campisi[5,6], Jan M. van Deursen[1,2,*]

+ Author Affiliations

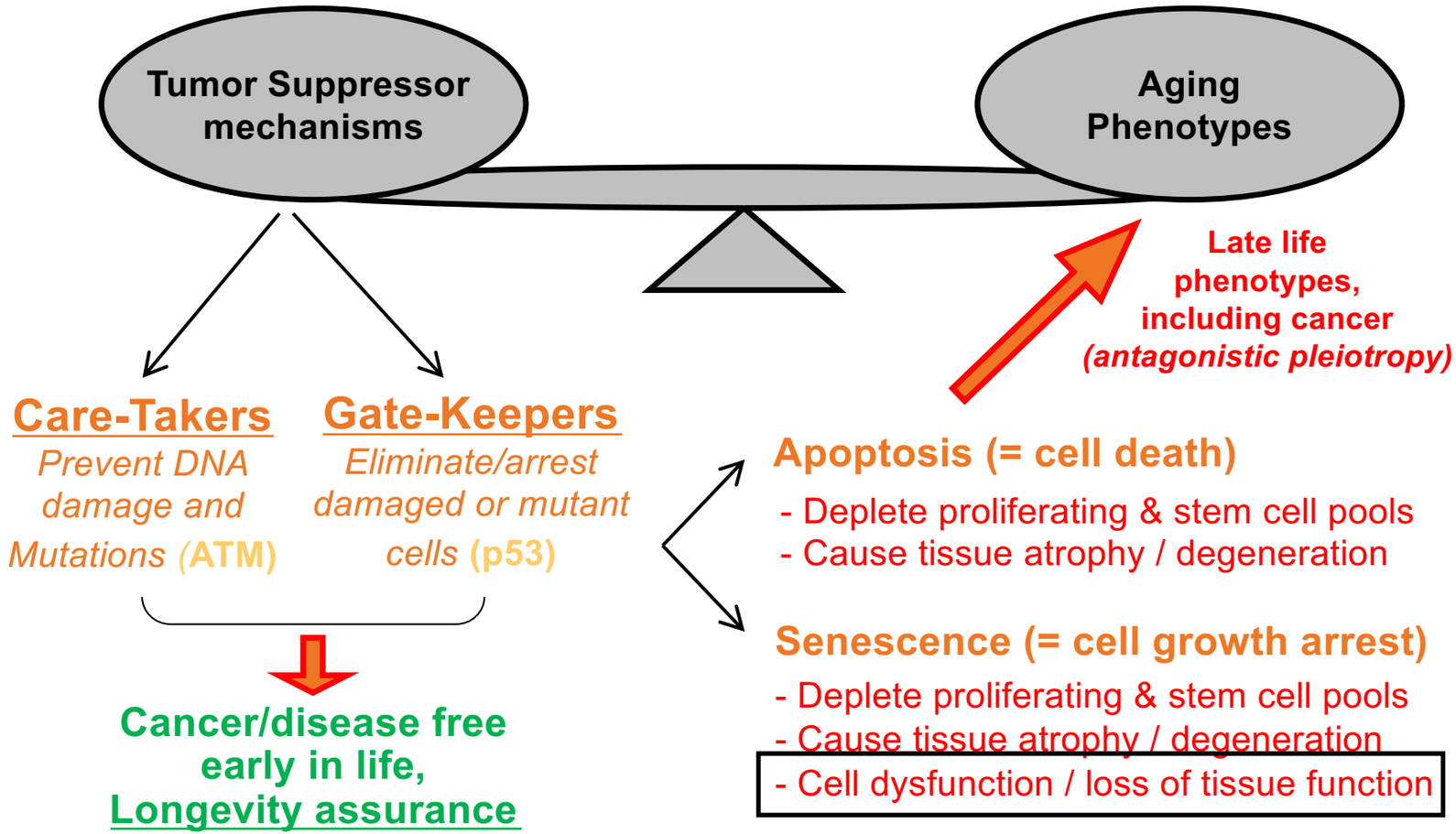
↵* Corresponding author. Email: vandeursen.jan@mayo.edu

Science 28 Oct 2016:
Vol. 354, Issue 6311, pp. 472-477
DOI: 10.1126/science.aaf6659

Instead of eliminating senescent cells,

Why don't we just eliminate senescence?

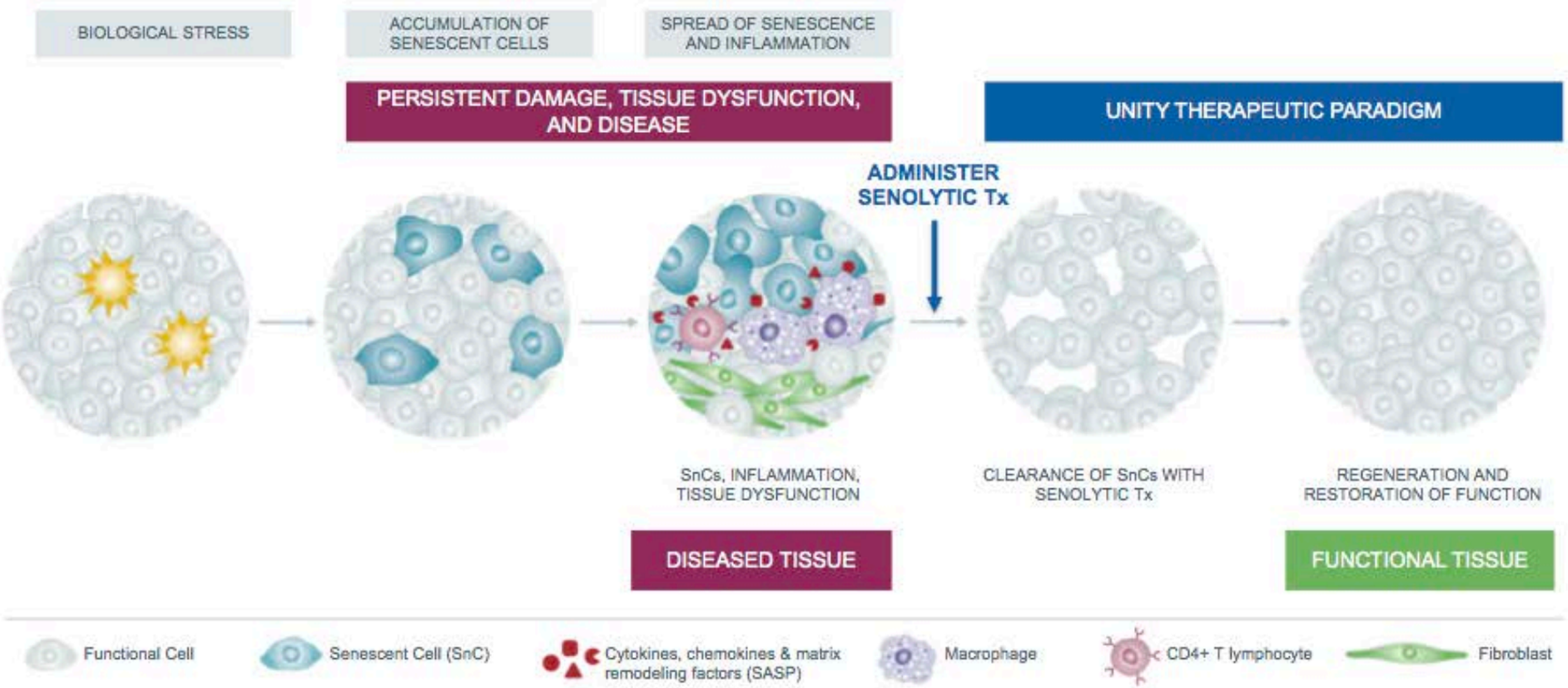
Tumor suppression versus longevity



Targeting senescence to impact aging in humans

Eliminating senescent cells:
An unprecedented opportunity to extend health span
Dr. Campisi:
(not certain about life span)

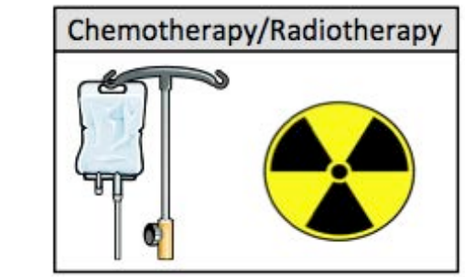
Senolytics: small molecules that can selectively induce programmed cell death (apoptosis) of senescent cells



Adapted From Unity biotech presentation

Therapy-induced cell fate decisions (TICFD)

Cancer cells "UNIVERSAL" Initial treatment responses



Transient Cell cycle arrest

DNA repair/mutations

Cellular Senescence

DDR

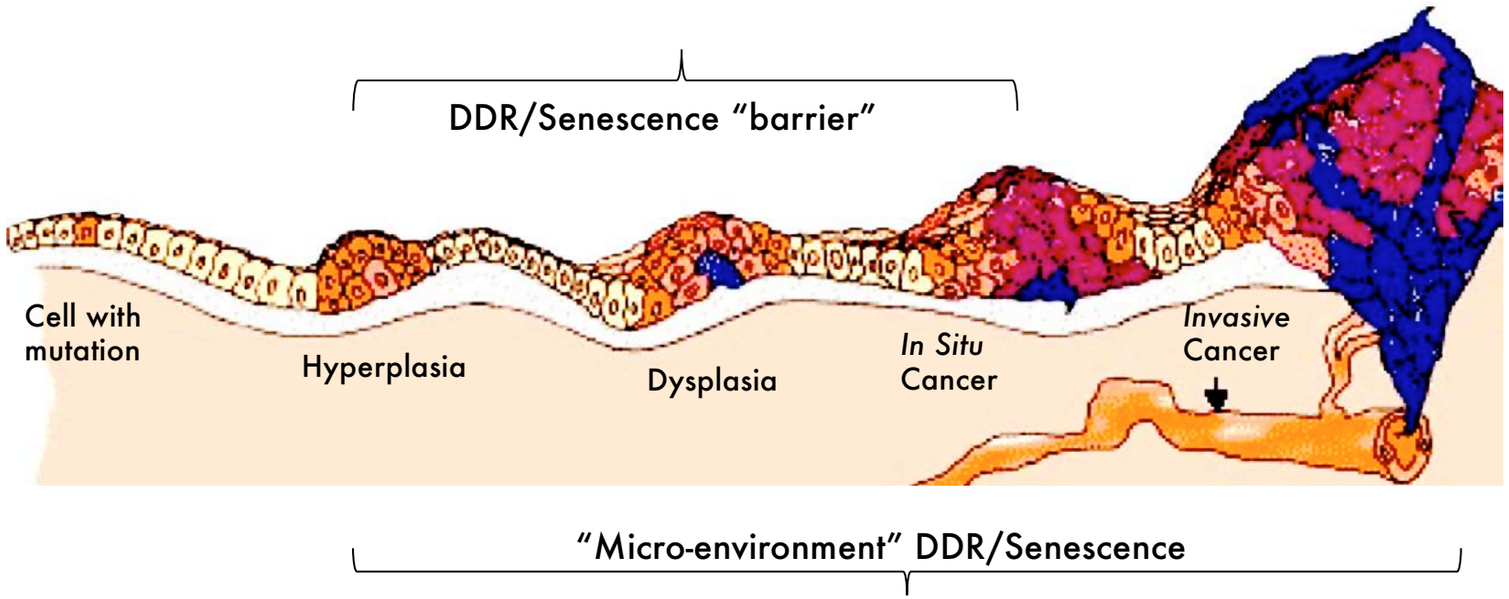
Extracellular signals

Apoptosis
Necroptosis
Mitotic catastrophy

- Does TIS happen during human cancer therapy?

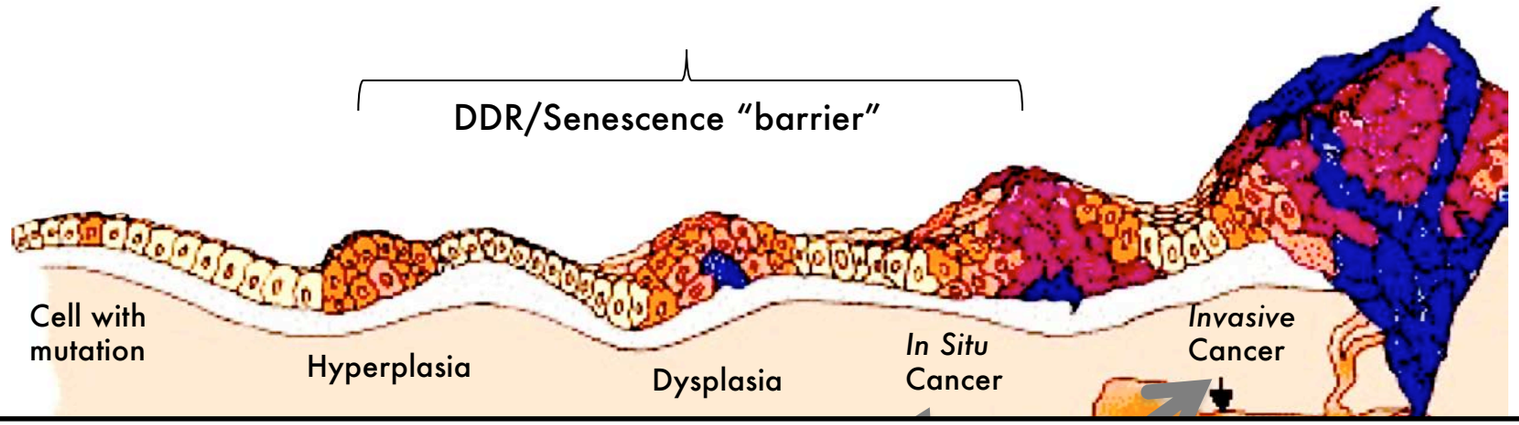
Gonzalez LC et al. Biogerontology 2016

Cellular senescence: Functions



- Can cancer cells still undergo senescence?

Cellular senescence: Functions



[CANCER RESEARCH 59, 3761–3767, August 1, 1999]

A Senescence-like Phenotype Distinguishes Tumor Cells That Undergo Terminal Proliferation Arrest after Exposure to Anticancer Agents[1]

Bey-Dih Chang, Eugenia V. Broude, Milos Dokmanovic, Hongming Zhu, Adam Ruth, Yongzhi Xuan, Eugene S. Kandel, Ekkehart Lausch, Konstantin Christov, and Igor B. Roninson[2]

Departments of Molecular Genetics [B-D. C., E. V. B., M. D., H. Z., A. R., Y. X., E. S. K., E. L., I. B. R.] and Surgical Oncology [K. C.], University of Illinois at Chicago, Chicago, Illinois 60607-7170

Cellular senescence: Functions

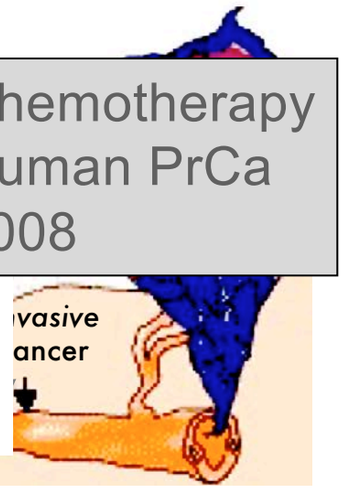
OPEN ACCESS Freely available online PLOS BIOLOGY

Senescence-Associated Secretory Phenotypes Reveal Cell-Nonautonomous Functions of Oncogenic RAS and the p53 Tumor Suppressor

Jean-Philippe Coppé[1], Christopher K. Patil[1☯], Francis Rodier[1,2☯], Yu Sun[3], Denise P. Muñoz[1,2], Joshua Goldstein[1¤], Peter S. Nelson[3], Pierre-Yves Desprez[1,4], Judith Campisi[1,2*]

1 Life Sciences Division, Lawrence Berkeley National Laboratory, Berkeley, California, United States of America, **2** Buck Institute for Age Research, Novato, California, United States of America, **3** Division of Human Biology, Fred Hutchinson Cancer Research Center, Seattle, Washington, United States of America, **4** California Pacific Medical Center Research Institute, San Francisco, California, United States of America

Chemotherapy
Human PrCa
2008



[CANCER RESEARCH 59, 3761–3767, August 1, 1999]

A Senescence-like Phenotype Distinguishes Tumor Cells That Undergo Terminal Proliferation Arrest after Exposure to Anticancer Agents[1]

Bey-Dih Chang, Eugenia V. Broude, Milos Dokmanovic, Hongming Zhu, Adam Ruth, Yongzhi Xuan, Eugene S. Kandel, Ekkehart Lausch, Konstantin Christov, and Igor B. Roninson[2]

Departments of Molecular Genetics [B-D. C., E. V. B., M. D., H. Z., A. R., Y. X., E. S. K., E. L., I. B. R.] and Surgical Oncology [K. C.], University of Illinois at Chicago, Chicago, Illinois 60607-7170

Cellular senescence: Functions

OPEN ACCESS Freely available online PLOS BIOLOGY

CANCER DISCOVERY

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Research Briefs

Cellular Senescence Promotes Adverse Effects of Chemotherapy and Cancer Relapse

Marco Demaria, Monique N. O'Leary, Jianhui Chang, Lijian Shao, Su Liu, Fatouma Alimirah, Kristin Koenig, Catherine Le, Natalia Mitin, Allison M. Deal, Shani Alston, Emmeline C. Academia, Sumner Kilmarx, Alexis Valdovinos, Boshi Wang, Alain de Bruin, Brian K. Kennedy, Simon Melov, Daohong Zhou, Norman E. Sharpless, Hyman Muss, and Judith Campisi

DOI: 10.1158/2159-8290.CD-16-0241 Published 15 December 2016

[CA

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Bey-Dih Chang, Eugenia V. Broude, Milos Dokmanovic, Hongming Zhu, Adam Ruth, Yongzhi Xuan, Eugene S. Kandel, Ekkehart Lausch, Konstantin Christov, and Igor B. Roninson[2]

Departments of Molecular Genetics [B-D. C., E. V. B., M. D., H. Z., A. R., Y. X., E. S. K., E. L., I. B. R.] and Surgical Oncology [K. C.], University of Illinois at Chicago, Chicago, Illinois 60607-7170

What if cancer survivors were suffering ‘accelerated aging’?

Late mortality and chronic health conditions in long-term survivors of early-adolescent and young adult cancers: a retrospective cohort analysis from the Childhood Cancer Survivor Study

Eugene Suh, MD • Kayla L Stratton, MS • Prof Wendy M Leisenring, ScD • Prof Paul C Nathan, MD • Prof Jennifer S Ford, PhD • Prof David R Freyer, DO • et al. Show all authors

THE LANCET Oncology

SPECIAL ARTICLE

Chronic Health Conditions in Adult Survivors of Childhood Cancer

Kevin C. Oeffinger, M.D., Ann C. Mertens, Ph.D., Charles A. Sklar, M.D., Toana Kawashima, M.S., Melissa M. Hudson, M.D., Anna T. Meadows, M.D., Debra L. Friedman, M.D., Neyssa Marina, M.D., Wendy Hobbie, C.P.N.P., Nina S. Kadan-Lottick, M.D., Cindy L. Schwartz, M.D., Wendy Leisenring, Sc.D., et al., for the Childhood Cancer Survivor Study*

Article Figures/Media

38 References 2066 Citing Articles Letters

The NEW ENGLAND JOURNAL of MEDICINE

October 12, 2006
N Engl J Med 2006; 355:1572-1582
DOI: 10.1056/NEJMsa060185

JOURNAL OF CLINICAL ONCOLOGY

Chronic Disease in the Childhood Cancer Survivor Study Cohort: A Review of Published Findings

Medical Assessment of Adverse Health Outcomes in Long-term Survivors of Childhood Cancer

JAMA. 2007;297(24):2705-2715.

CRCHUM

What if cancer survivors were suffering 'accelerated aging'?

Why and how???

Senescence and cancer survivorship

Marcoux *et al. Radiation Oncology* 2013, **8**:252

Expression of the senescence marker $p16^{INK4a}$ in skin biopsies of acute lymphoblastic leukemia survivors: a pilot study

petale

CHU Sainte-Justine
Le centre hospitalier universitaire mère-enfant

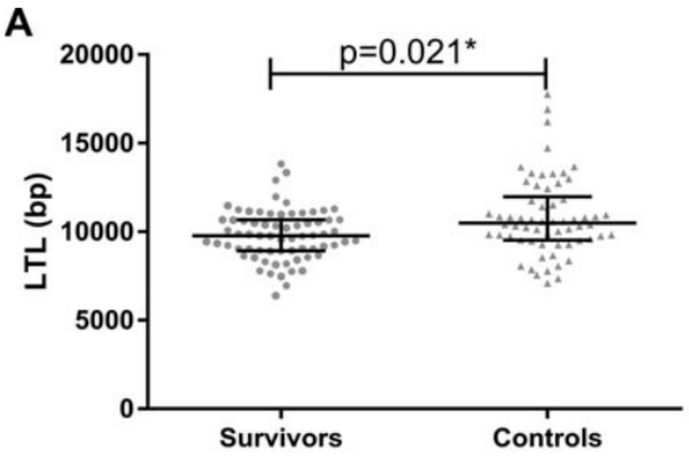
Clinical Trial > Pediatr Blood Cancer. 2017 Jun;64(6). doi: 10.1002/pbc.26361. Epub 2016 Dec 4.

The PETALE study: Late adverse effects and biomarkers in childhood acute lymphoblastic leukemia survivors

CRCHUM

Young Adult Survivors of Childhood Acute Lymphoblastic Leukemia Show Evidence of Chronic Inflammation and Cellular Aging

Hany Ariffin MD, PhD[1]; Mohamad Shafiq Azanan BS [1]; Sayyidatul Syahirah Abd Ghafar MStat[1]; Lixian Oh BS[1]; Kee Hie Lau BS[1]; Tharshanadhevasheri Thirunavakarasu MS[1]; Atiqah Sedan BS[1]; Kamariah Ibrahim PhD[1]; Adelyne Chan MS[1]; Tong Foh Chin BS[1]; Fong Fong Liew, PhD[1]; Shareni Jeyamogan MS[1]; Erda Syerena Rosli, MS[1]; Rashidah Baharudin MS[1]; Tsiao Yi Yap, MD[1]; Roderick Skinner, MD, PhD[2]; Su Han Lum, MD[1]; and Pierre Hainaut PhD[3]



Leukocytes telomere length

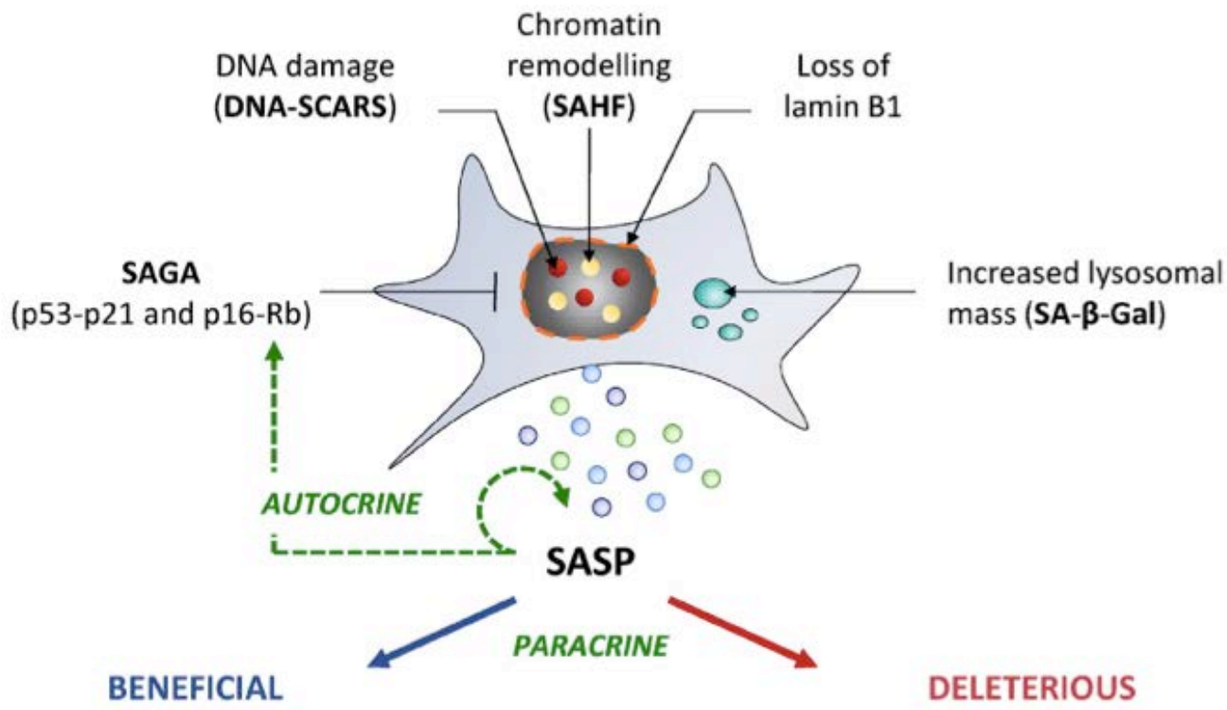
Senescence and cancer survivorship

Tests
Labs
Exome-seq.
↓
TREC and SASP?

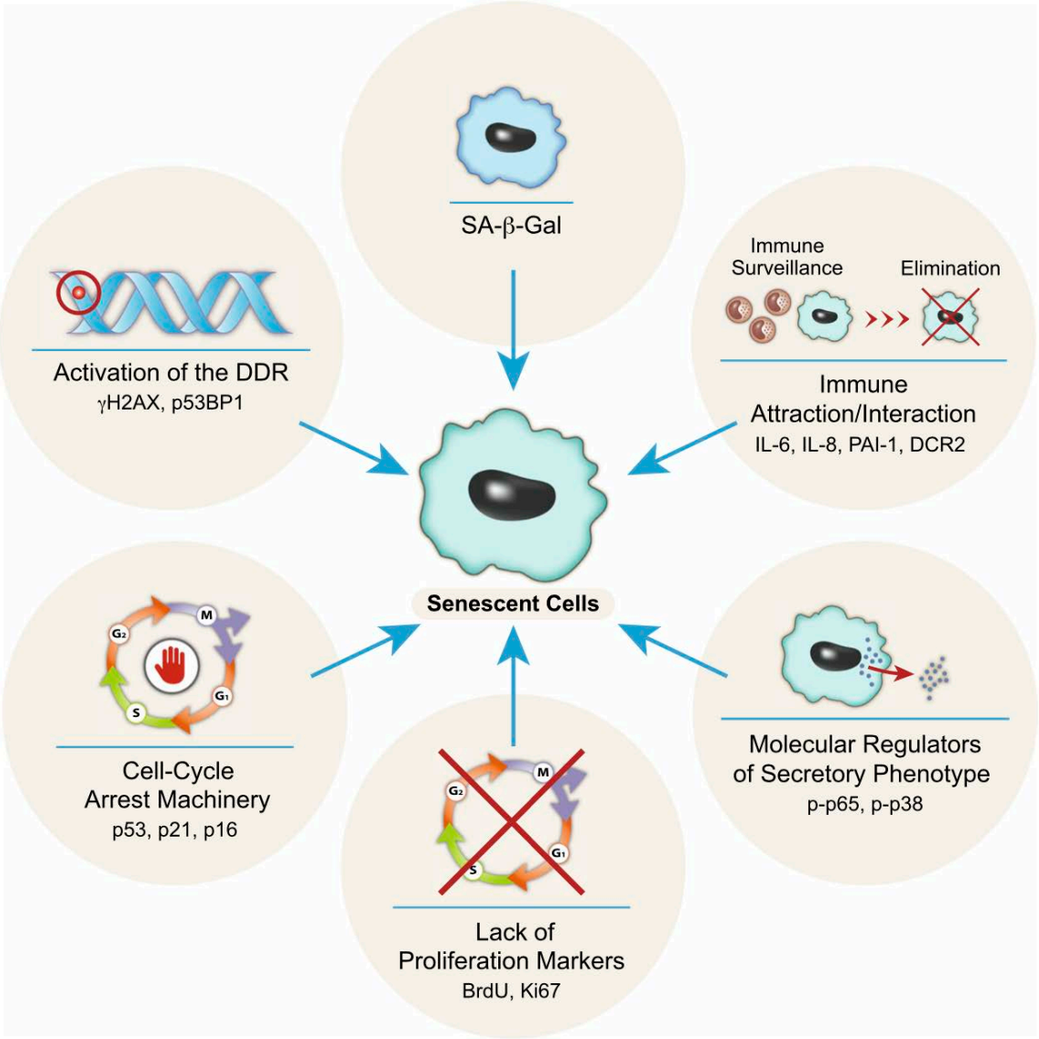
TABLE 1 Participants' sociodemographic characteristics

DFCI protocol	87-01	91-01	95-01	2000-01	2005-01	Combined
Participants, n (%)[a]	24 (9.8)	47 (19.1)	73 (29.7)	76 (30.9)	26 (10.6)	246 (100)
Gender						
Female, n (%)	14 (58.3)	22 (46.8)	33 (45.2)	42 (55.3)	13 (50.0)	124 (50.4)
Male, n (%)	10 (41.7)	25 (53.2)	40 (54.8)	34 (44.7)	13 (50.0)	122 (49.6)
Ethnicity						
European, n (%)	23 (95.8)	46 (97.9)	68 (93.2)	72 (94.7)	26 (100)	235 (95.5)
Other, n (%)	1 (4.2)	1 (2.1)	5 (6.8)	4 (5.3)	0 (0)	11 (4.5)
Highest education level achieved[b]						
High school not completed, n (%)	5 (20.8)	6 (12.8)	22 (30.1)	51 (67.1)	14 (53.8)	98 (39.8)
High school, n (%)	6 (25.0)	17 (36.2)	30 (41.1)	11 (14.5)	6 (23.1)	70 (28.5)
College, n (%)	9 (37.5)	16 (34.0)	14 (19.2)	7 (9.2)	5 (19.2)	51 (20.7)
University, n (%)	4 (16.7)	8 (17.0)	7 (9.6)	7 (9.2)	1 (3.8)	27 (11.0)
Average age at diagnosis (SD of distribution)	5.9 (4.6)	5.5 (4.7)	5.6 (4.4)	5.7 (4.1)	10.3 (4.4)	6.1 (4.6)
Average number of years after diagnosis (SD of distribution)	23.9 (1.6)	21.0 (1.3)	15.9 (2.0)	11.7 (1.8)	7.4 (1.4)	15.5 (5.2)
Average age at Phase I (SD of distribution)	29.7 (4.5)	26.5 (4.5)	21.5 (5.3)	17.5 (4.4)	17.8 (4.1)	21.6 (6.3)

qSA-Bs: QUANTITATIVE CELL SENESCENCE-ASSOCIATED BIOMARKERS



Detecting senescence in tissues



1- Very complicated

2- Often require complex tissue samples preserved using specific protocols

- Prevent access to retrospective biobanks
- What can we measure in simple blood samples?

SASP (proteins)
Cells - Telomere
Cells - RNA

Some solutions?
TREC
VPLEX

Burton et al. Cell. Mol. Life Sci. (2014)

Accelerated immunosenescence in childhood acute lymphoblastic leukemia survivors is associated to metabolic syndrome

Tibila Kientega et Sophie Marcoux, in collaboration with Daniel Sinnett

With exceptional undergrad students:
Jessica Bourbonnais (now PhD) and Jade Montpetit

Immunosenescence and the thymus

Central Immune Senescence, Reversal Potentials

Krisztian Kvell and Judit E. Pongracz
Department of Medical Biotechnology, University of Pecs, Hungary

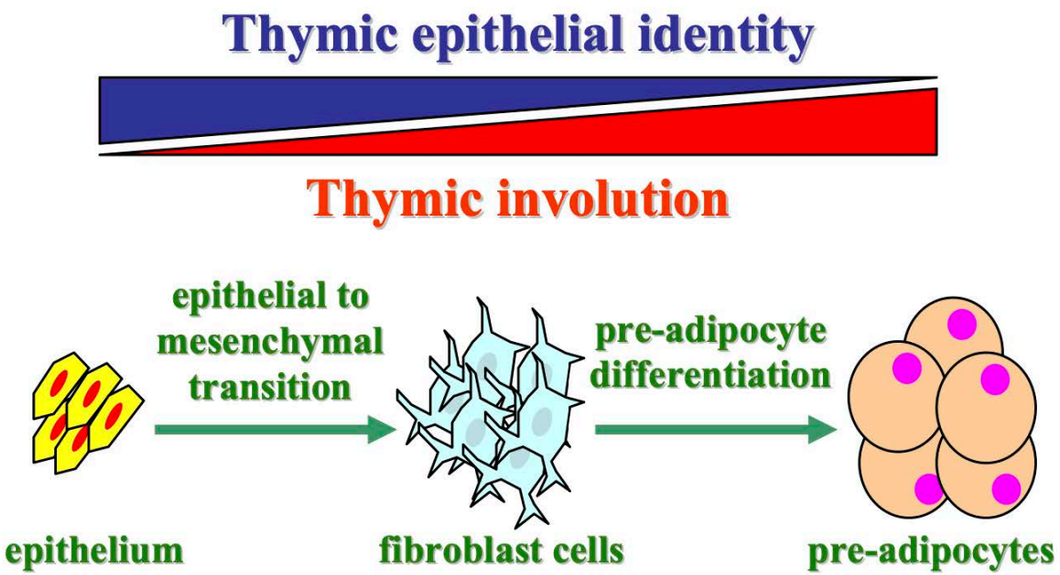


Fig. 1. Model of thymic involution process
Dedifferentiation of thymic epithelial cells triggers EMT (epithelial to mesenchymal transition) first, and then the resulting fibroblast cells undergo the conventional route of differentiation program towards adipocyte-lineage.

ELSEVIER

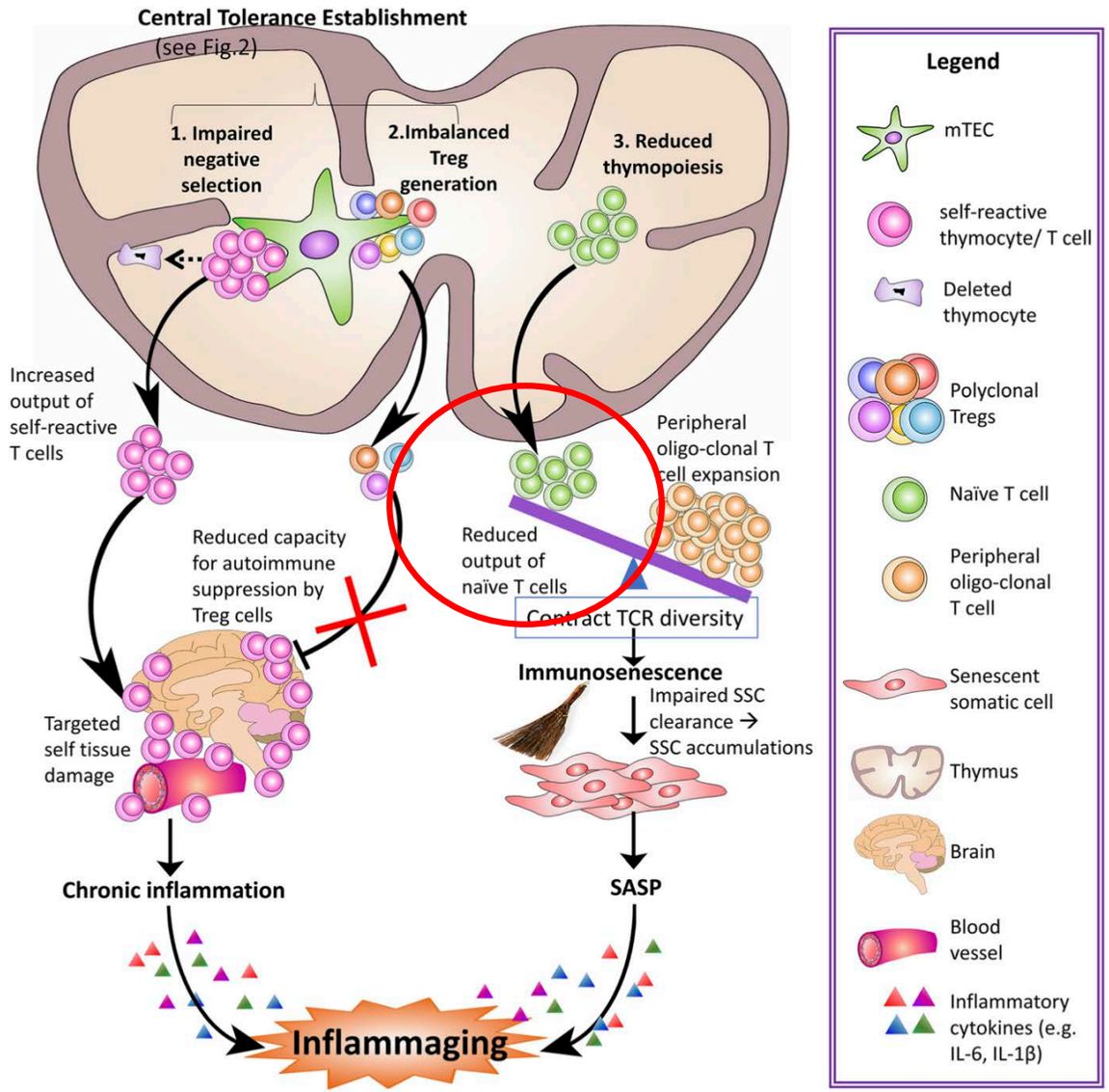
Mechanisms of Ageing and Development
Volume 177, January 2019, Pages 88-90

Short communication

In situ evidence of cellular senescence in Thymic Epithelial Cells (TECs) during human thymic involution

Alexandra Barbouti [a, 1], Konstantinos Evangelou [a, b, 1] ✉, Ioannis S. Pateras [b], Alexandra Papoudou-Bai [c], Amalia Patereli [d], Kalliopi Stefanaki [d], Dimitra Rontogianni [e], Daniel Muñoz-Espín [f], Panagiotis Kanavaros [a], Vassilis G. Gorgoulis [b, g, h] ✉

Immunosenescence and the thymus



REVIEW Open Access

Contributions of Age-Related Thymic Involution to Immunosenescence and Inflammaging

Rachel Thomas[1], Weikan Wang[1] and Dong-Ming Su[2*]

Reduced output of naïve T-Cells reflect:
Thymic senescence, impaired T-cell generation, increased T-cell mediated inflammation, impaired senescence clearance, INFLAMMAGING

Physiologic Thymic Involution Underlies Age-Dependent Accumulation of Senescence-Associated CD4$^+$ T Cells

Kyosuke Sato, Aiko Kato, Miho Sekai, Yoko Hamazaki and Nagahiro Minato

J Immunol 2017; 199:138-148; Prepublished online 24 May 2017;
doi: 10.4049/jimmunol.1602005
http://www.jimmunol.org/content/199/1/138

Immunosenescence and the thymus

bioRxiv
THE PREPRINT SERVER FOR BIOLOGY

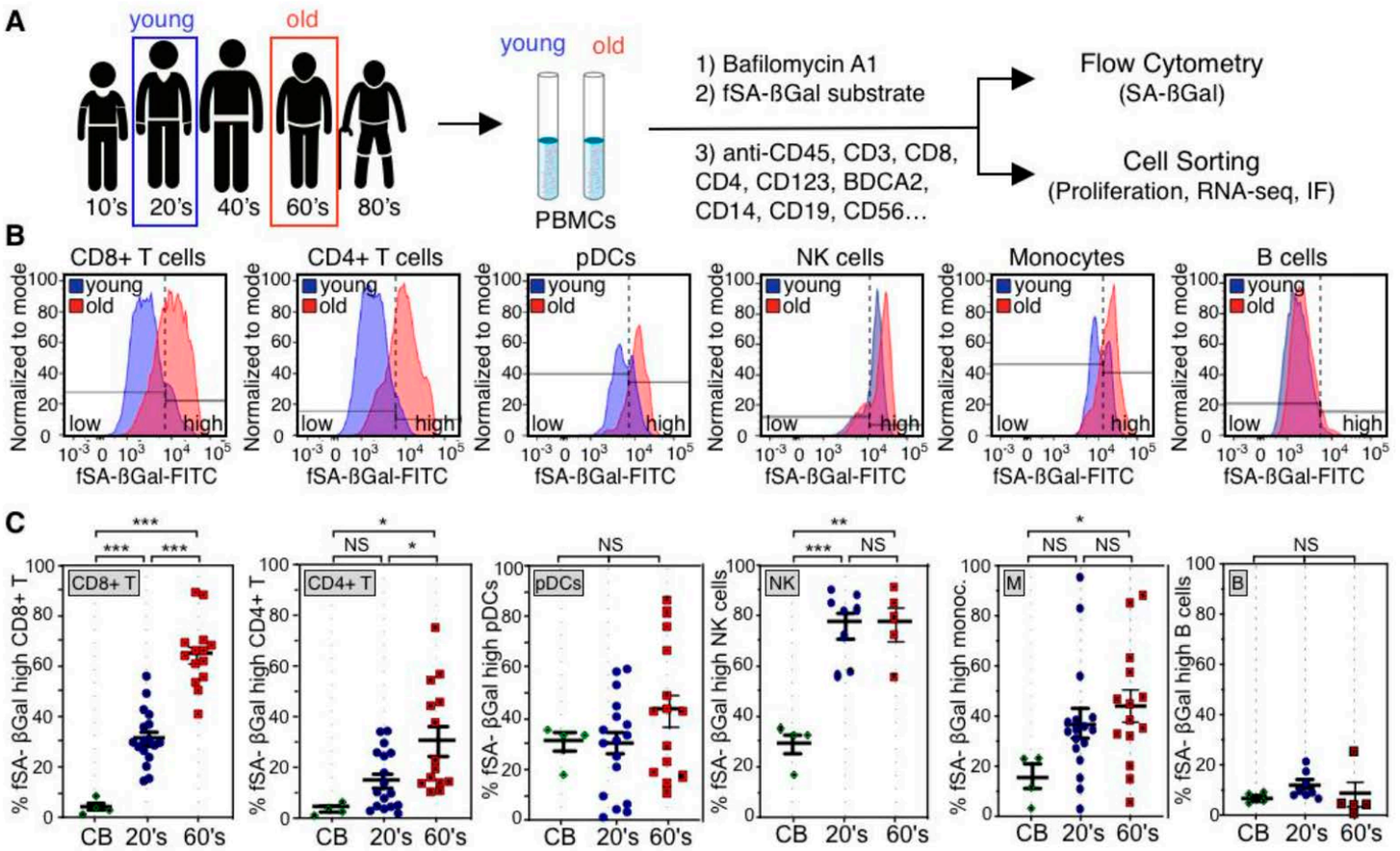
New Results

Comment on this paper

Conclusive Identification of Senescent T Cells Reveals Their Abundance in Aging Humans

Ricardo Iván Martínez-Zamudio, Hannah K. Dewald, Themistoklis Vasilopoulos, Lisa Gittens-Williams, Patricia Fitzgerald-Bocarsly, Utz Herbig

doi: https://doi.org/10.1101/2020.06.17.157826

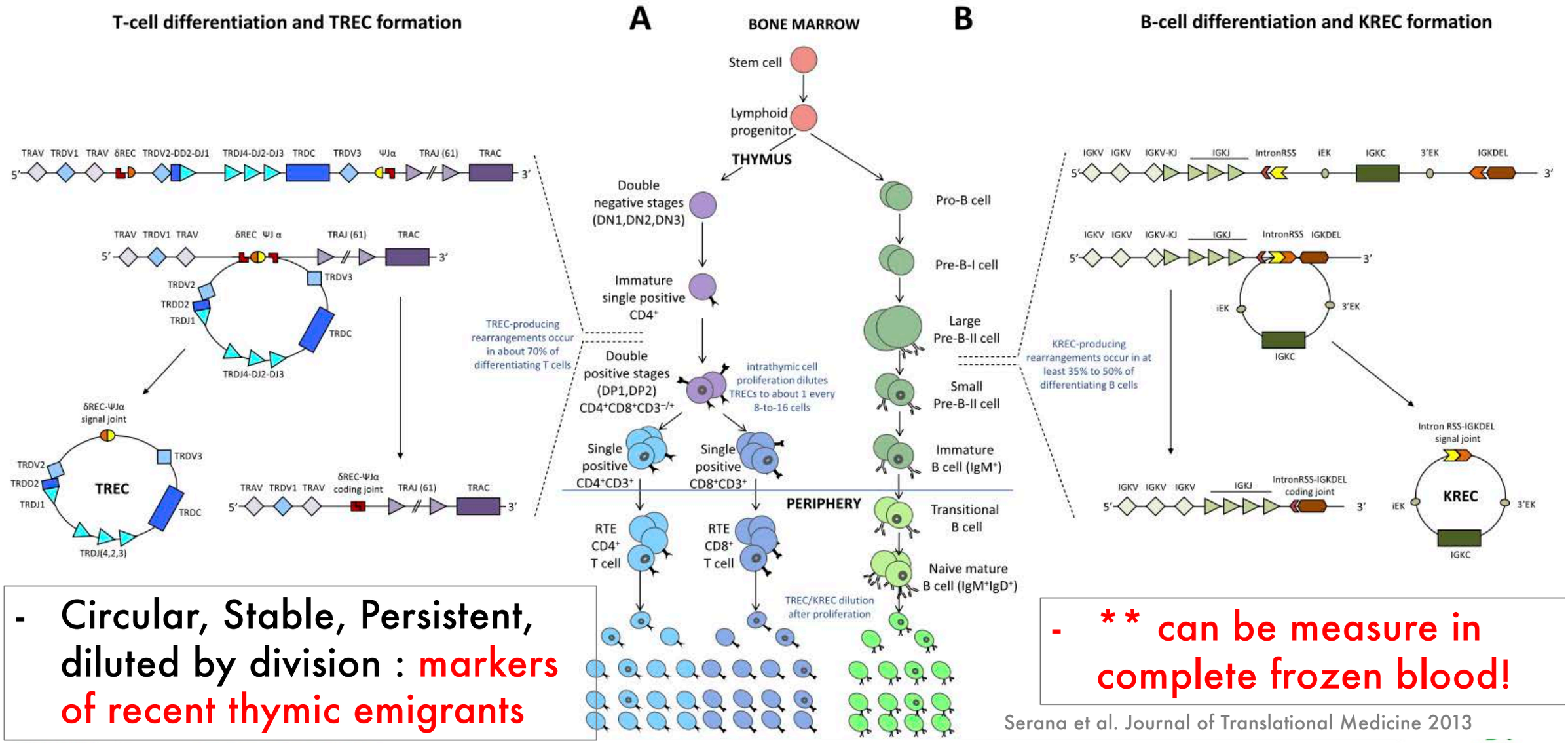


1- Very complicated

2- Often require complex tissue samples preserved using specific protocols

- Prevent access to retrospective biobanks
- What can we measure in simple blood samples?

T-cell receptor excision circles (TRECs) and kappa-deleting recombination excision circles (KRECs)



- Circular, Stable, Persistent, diluted by division : markers of recent thymic emigrants

- ** can be measure in complete frozen blood!

Serana et al. Journal of Translational Medicine 2013

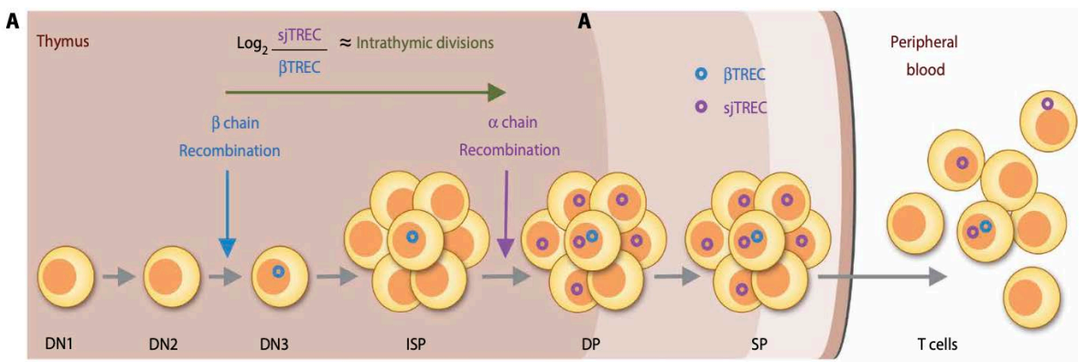
TREC and Immunoage

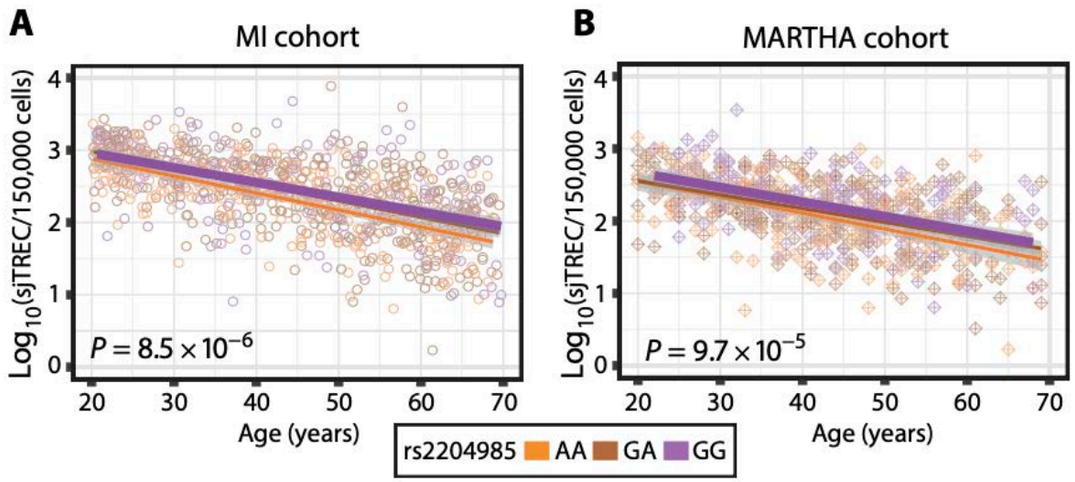
SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

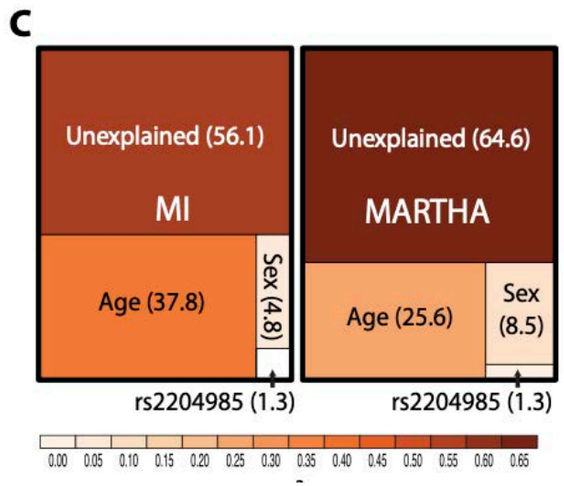
ADAPTIVE IMMUNITY

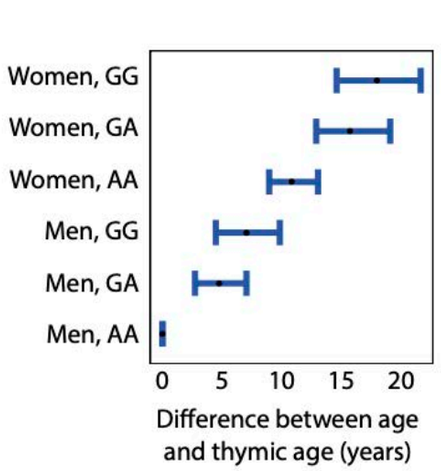
Human thymopoiesis is influenced by a common genetic variant within the *TCRA-TCRD* locus

Emmanuel Clave[1,2]*, Itauá Leston Araujo[1,2]*, Cécile Alanio[3,4,5]*, Etienne Patin[6,7,8]*, Jacob Bergstedt[9]*, Alejandra Urrutia[3,4,5,10], Silvia Lopez-Lastra[5,11], Yan Li[5,11], Bruno Charbit[3], Cameron Ross MacPherson[3], Milena Hasan[3], Breno Luiz Melo-Lima[1,2], Corinne Douay[1,2], Noémie Saut[12,13], Marine Germain[14,15], David-Alexandre Trégouët[14,15], Pierre-Emmanuel Morange[12,13], Magnus Fontes[10,16], Darragh Duffy[3,4,5], James P. Di Santo[5,11], Lluis Quintana-Murci[6,7,8†], Matthew L. Albert[3,4,5,10†‡], Antoine Toubert[1,2,17‡], The Milieu Intérieur Consortium[§]







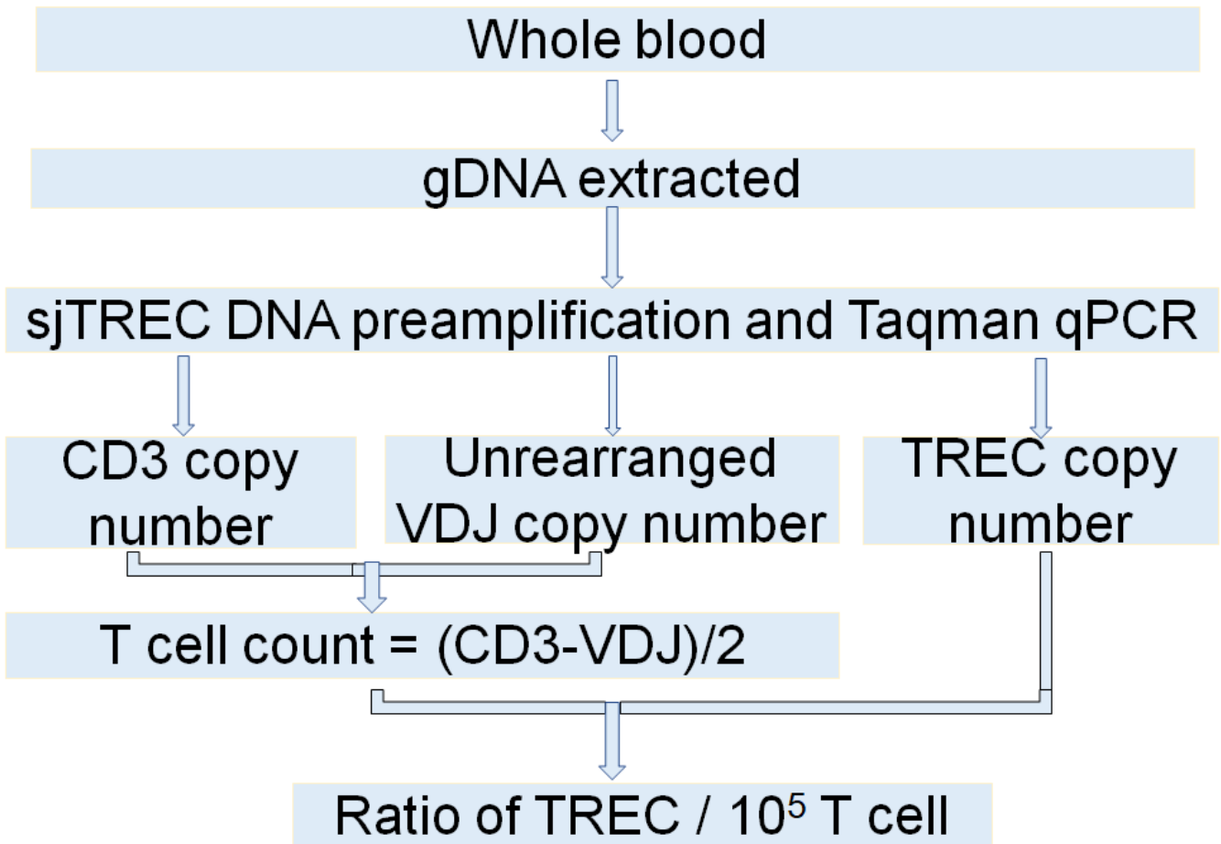


DEFINING A FIRST CANADIAN TREC-IMMUNOAGE CURVE

330,000 Canadians are followed longitudinally

Quantitative TREC measurement

qPCR - TREC-TEST



Or PBMC or gDNA

Going back to the cohort of childhood leukemia survivors (PETALE): are they suffering accelerated aging as hypothesized?

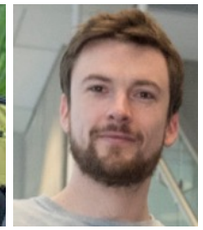
What can we conclude from the PETALE study data?

-↑ ↑ ↑ immunoage gain for **everybody**
-Typical risk factors for survivorship issues?
-Phenotypic correlations: careful with how frailty or 'accelerated aging' is defined!
-Nothing about adults, solid cancers, impact of cancer itself…

nature COMMUNICATIONS

ARTICLE

https://doi.org/10.1038/s41467-019-10460-1 OPEN



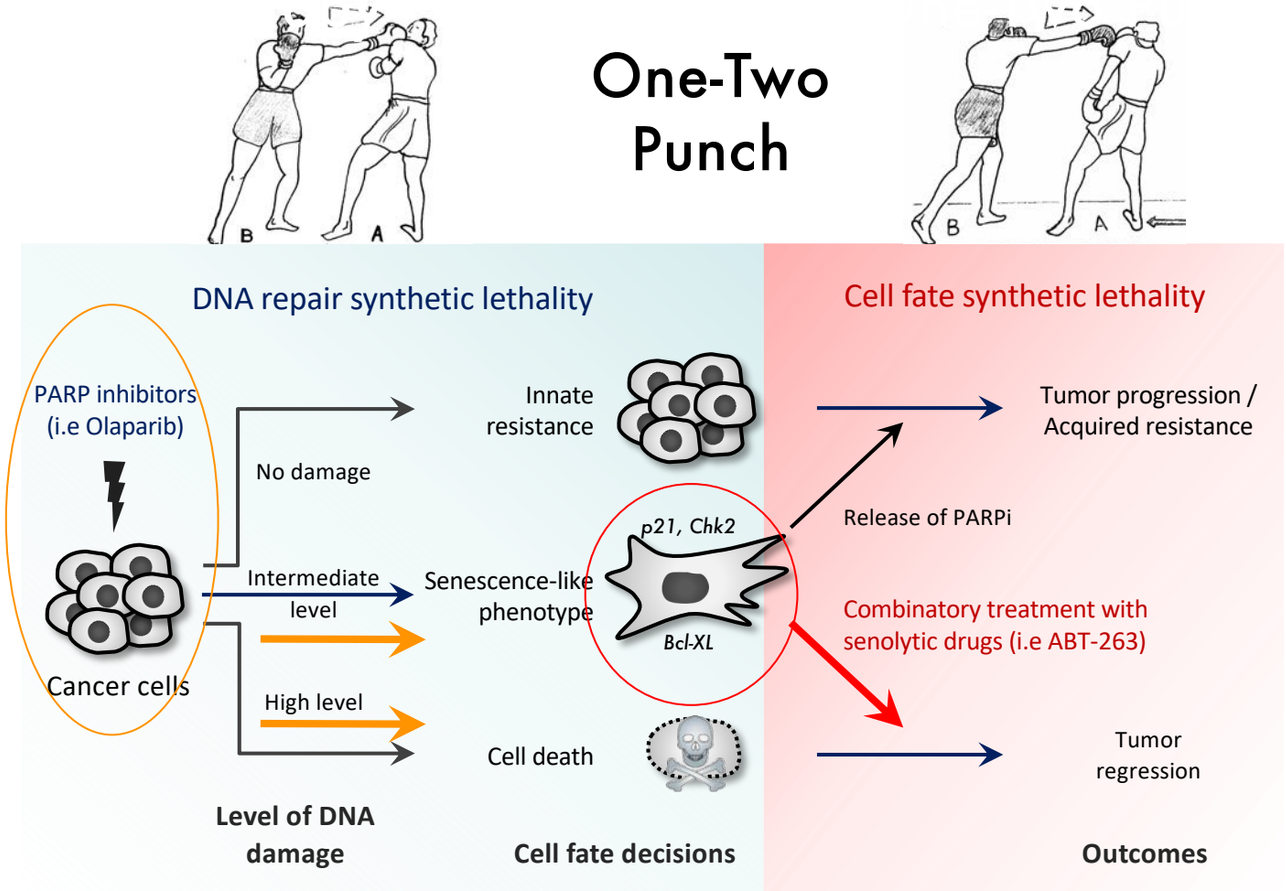
Exploiting interconnected synthetic lethal interactions between PARP inhibition and cancer cell reversible senescence

Hubert Fleury[1,2,6], Nicolas Malaquin[1,2,6], Véronique Tu[1,2], Sophie Gilbert[1,2], Aurélie Martinez[1,2], Marc-Alexandre Olivier[1,2], Alexandre Sauriol[1,2], Laudine Communal[1,2], Kim Leclerc-Desaulniers[1,2], Euridice Carmona[1,2], Diane Provencher[1,2,3], Anne-Marie Mes-Masson[1,2,4] & Francis Rodier[1,2,5]

Multilayered senescence-centric synthetic lethal approaches for cancer therapy

Block checkpoints
Block repair
Increased damage

Reinforce checkpoints



Senolytic
Senomorphic
Immunotherapy

One-two-three-four....

Fleury*, Malaquin* et al. Nat. Com 2019

Therapeutically Targeting Cancer cell TIS: PARPi & BCL2i synergistically eliminate OvCa cells

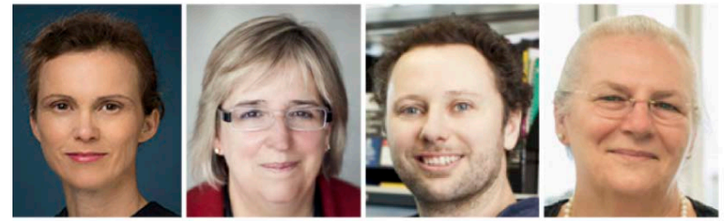
EXACTIS

11-JUL-2019

Exactis Innovation to drive network-based precision oncology research with $1M grant

July 11, 2019

MONTREAL – **Exactis Innovation** (Exactis) is pleased to award $1M CDN to catalyze clinical research on innovative precision oncology therapeutics in Canada. This grant will support a multi-centre clinical trial in the Exactis research network comprising eleven premier cancer care institutions across Canada.



Dr. Helen Mackay | Dr. Diane Provencher | Dr. Francis Rodier | Dr. Anne-Marie Mes-Masson

Study Title

A phase I/II basket trial investigating augmentation of apoptosis in High Grade Serous Epithelial Ovarian Cancer (HGSOC) and Triple Negative Breast Cancer (TNBC) incorporating translational and ex vivo patient derived predictive models

Phase of Study

Phase I/II

CRCHUM

EXACTIS TRIAL

Study Title

A phase I/II basket trial investigating augmentation of apoptosis in High Grade Serous Epithelial Ovarian Cancer (HGSOC) and Triple Negative Breast Cancer (TNBC) incorporating translational and ex vivo patient derived predictive models

Phase of Study

Phase I/II

-measure TREC and other qSA-Bs pre-post OvCa treatment
-Compare to control CARTaGENE data
-Verify the impact of senolytic therapy?

What should we also look at?

Potential major implications…

1) Screening
2) What else could trigger ‘accelerated aging’?

Screening: for cancers and… other diseases?! 2 examples:

Canadian Task Force on Preventive Health Care

Recommendations

- We recommend screening adults aged 60 to 74 for CRC with FOBT (either gFOBT or FIT) every two years OR flexible sigmoidoscopy every 10 years.
  (Strong recommendation; moderate quality evidence)

Fiche de prévention clinique

Adultes

COLLÈGE DES MÉDECINS DU QUÉBEC

Santé et Services sociaux Québec

Dyslipidémie

Pour les patients de 40 à 75 ans et ceux de moins de 40 ans présentant au moins un facteur de risque cardiovasculaire :

- Appliquer les recommandations de l'INESSS (démarche décrite dans le *Guide des bonnes pratiques en prévention clinique*). Ce sont celles que privilégie le directeur national de santé publique. Les recommandations de la Société canadienne de cardiologie sont également acceptables

(INESSS 2017 et Société canadienne de cardiologie 2016)

Could senescence be the mechanism behind ‘accelerated aging’ and chronic diseases in… Chronic stress? Poverty? Pollution?… 2 examples:

Poverty ⟺ **Cancer**

Acknowledgements PETALE cohort

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E. Levy, V. Marcil

Santé osseuse
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Santé neuropsychologique
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Qualité de vie
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Logistique
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Surtout: merci aux participants…

Et tous les membres de chacun de ces labos!

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Guillaume Cardin MSc

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Anne-Marie Mes-Masson (CRCHUM)
Nicolas Chomont (CRCHUM)

CARTaGENE:
Catherine Labbé
Nolwenn Noisel

La Société de recherche sur le cancer
The Cancer Research Society

Fonds de la recherche en santé Québec

CIHR IRSC
Canadian Institutes of Health Research
Instituts de recherche en santé du Canada