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Unlocking Female Reproductive Longevity :The Role of Cellular Senescence in Ovarian Aging

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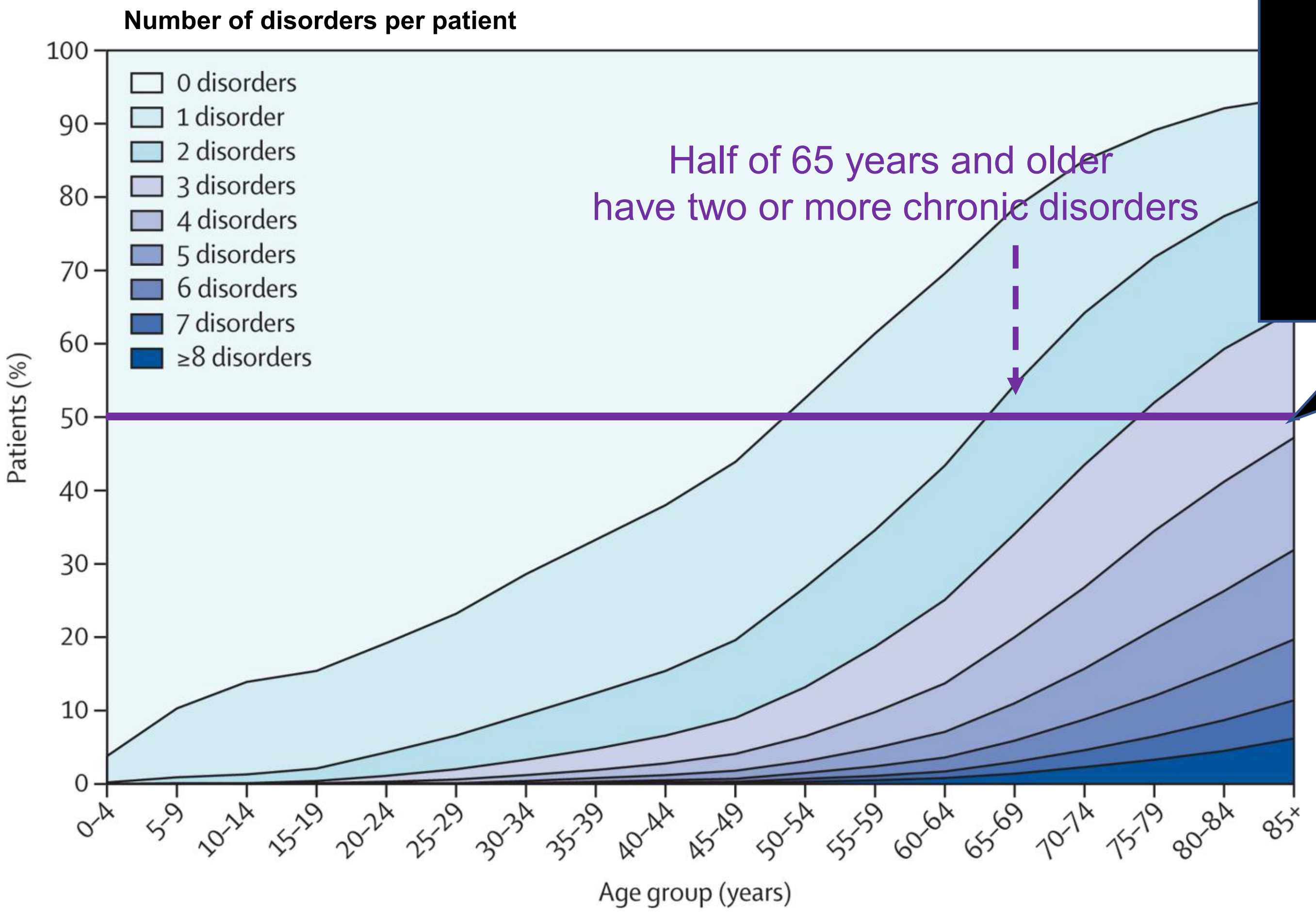
Aging as a root cause of age-related chronic diseases



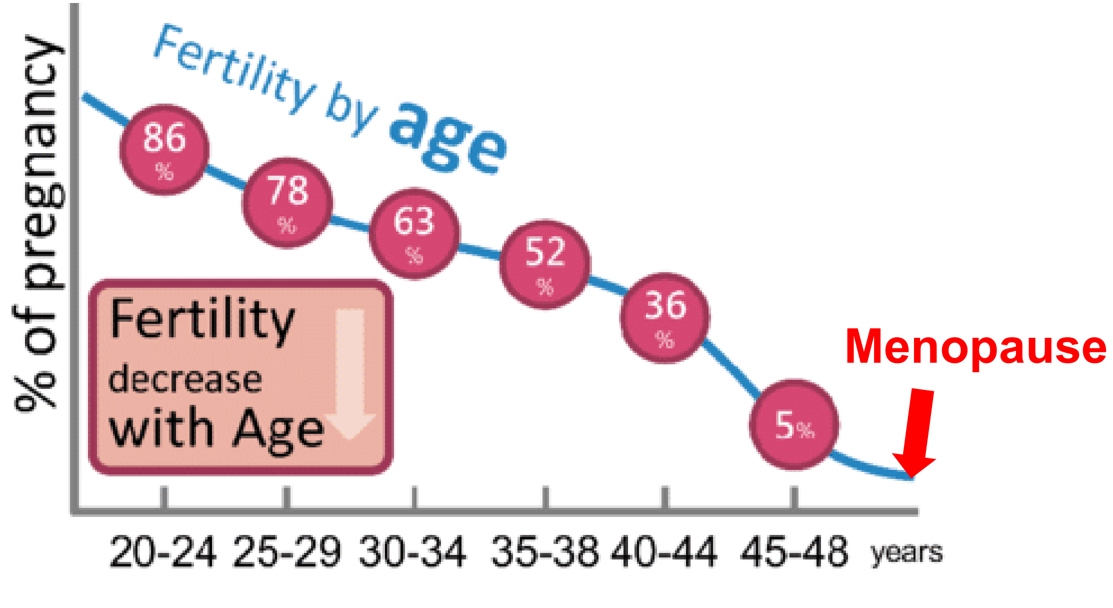
Targeting aging biology may delay or prevent multiple age-related diseases — including reproductive aging— rather than treating each one individually

Aging is the primary risk factor for multimorbidity and chronic diseases

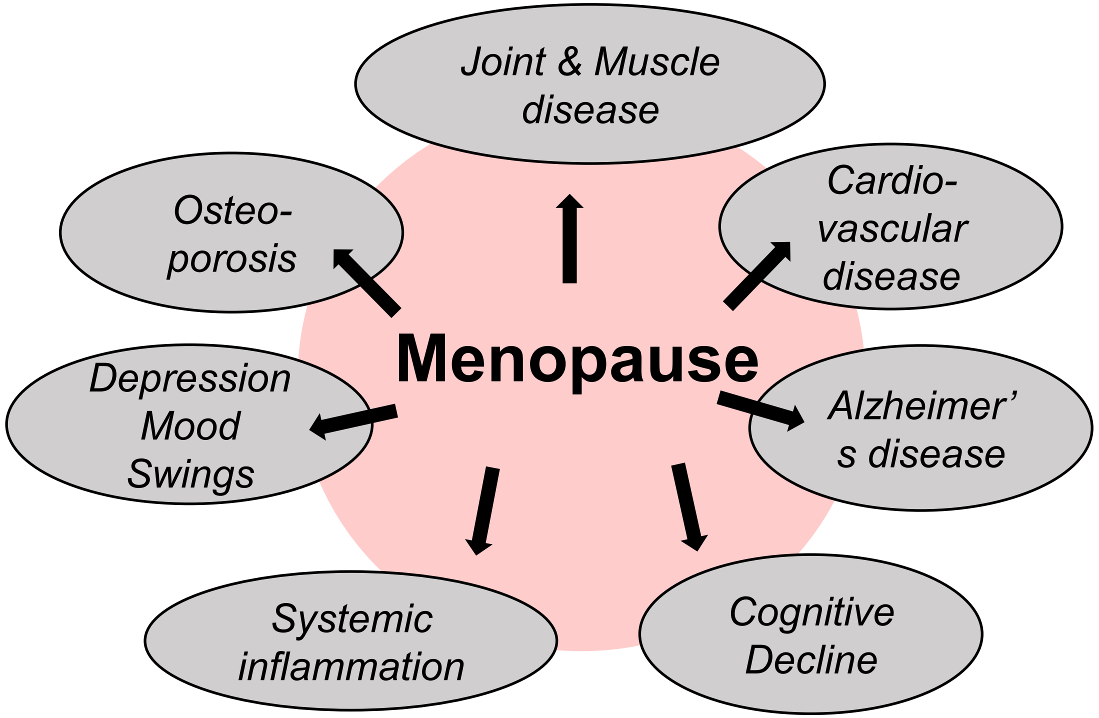
Barbett et al., Lancet, 2012

Why ovarian aging matters?

Ovary is the first organ to undergo functional decline



Menopause marks a systemic shift, increasing risks for various chronic conditions

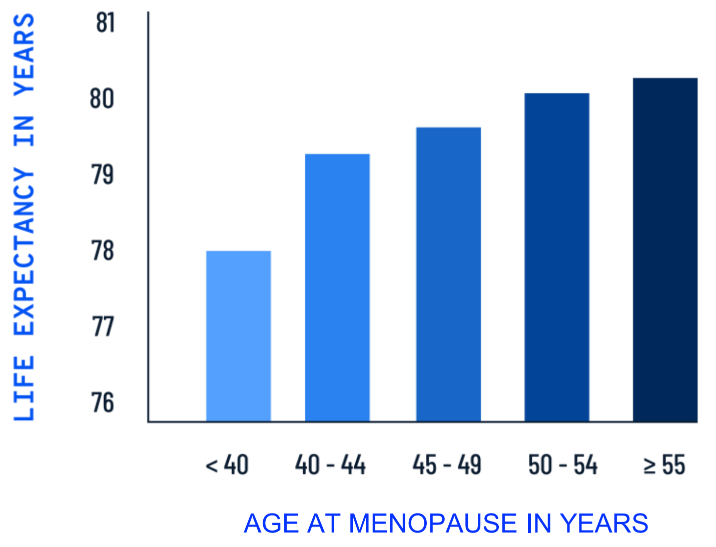


Menopause, the endpoint of ovarian aging, marks the onset of accelerated biological aging and chronic disease risk

Li et al., Aging Dis, 2021; Levine et al., PNAS, 2016

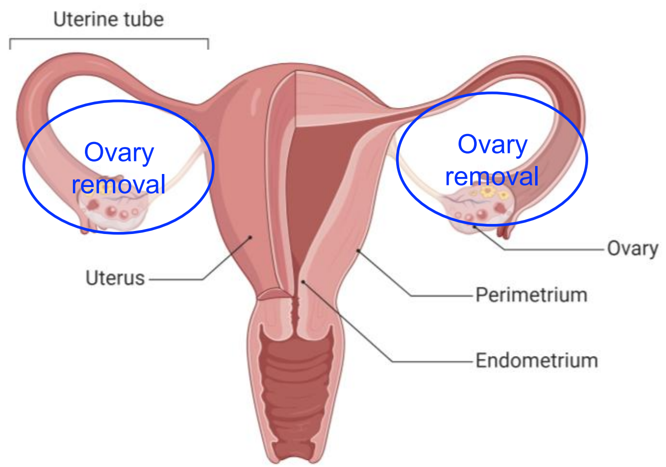
Ovarian function influences systemic aging in women

Women with later age of menopause live longer

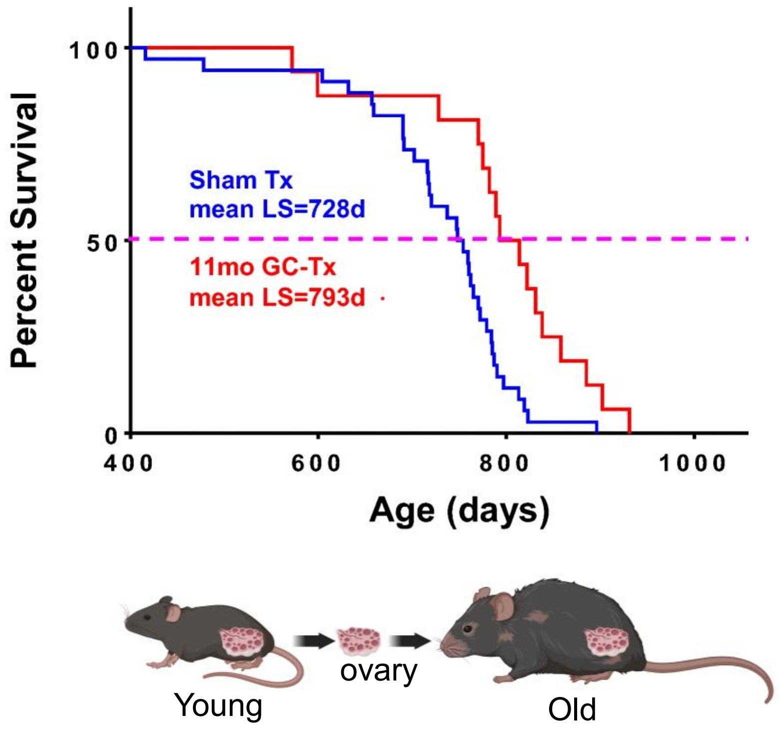


Negative impacts of oophorectomy in women

Multimorbidity ⬆
All-cause mortality ⬆



Transplanting young ovaries extends lifespan in aged mice

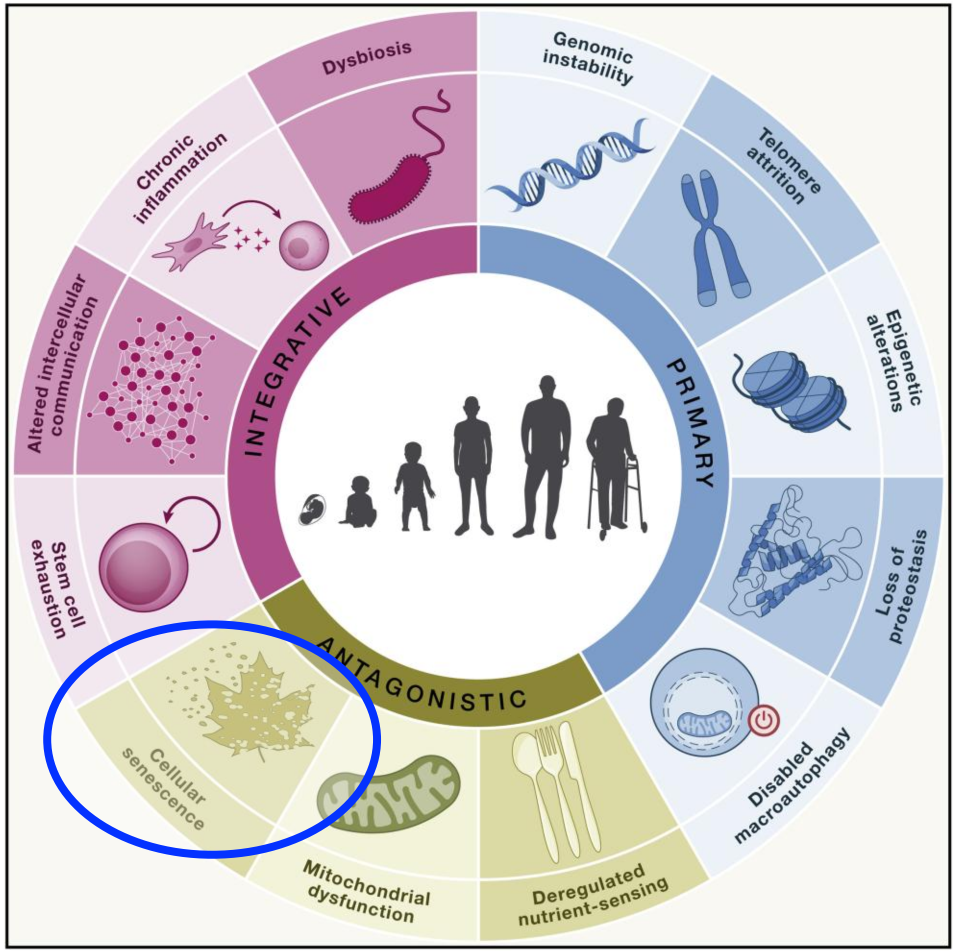


Preserving ovarian function may delay systemic aging and promote overall healthspan

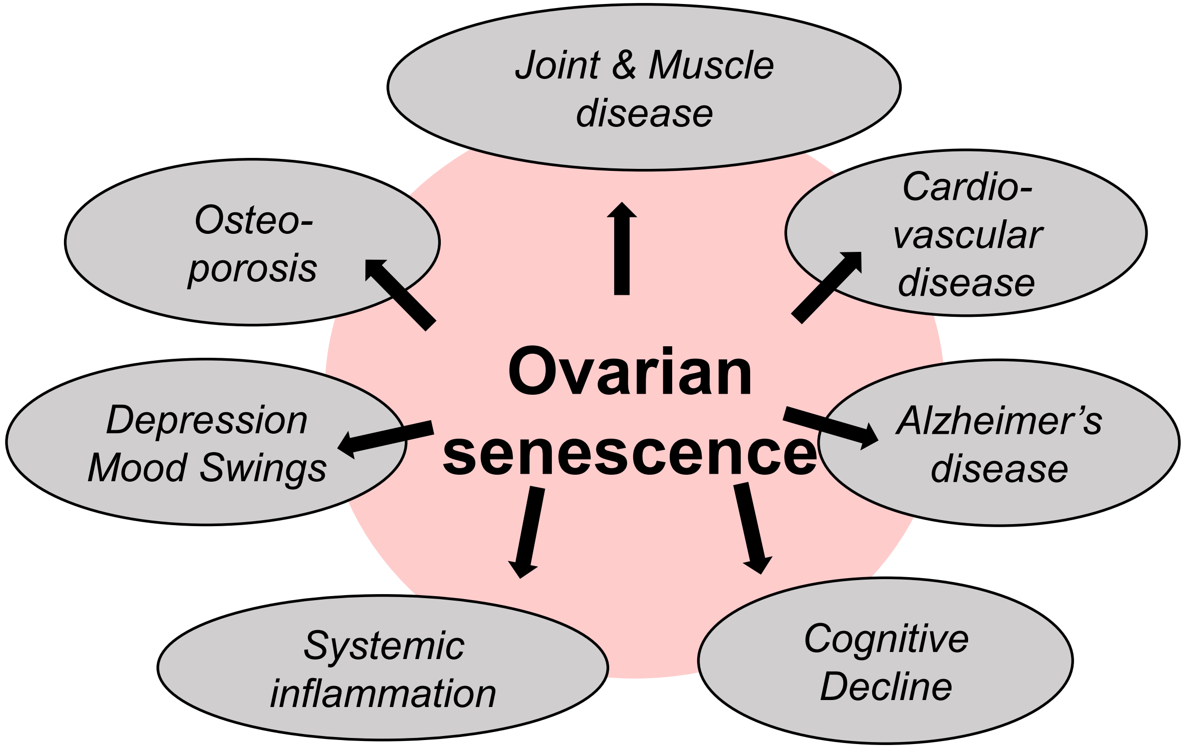
Ossewaarde et al., Epidemiology, 2005; Wilson et al., American Journal of Obsterics and Gynecology, 2019; Habermehl et al., Geroscience, 2019

Cellular senescence :
One of the biological processes behind ovarian aging

13 hallmarks of aging (+ECM discruption)



Potential links between ovarian senescence and systemic outcomes



Could senescent cells in the ovary be accelerating both reproductive decline and systemic aging in women?

What is cellular senescence?

Aging doesn't just happen at the tissue or organ level. It starts with changes inside individual cells

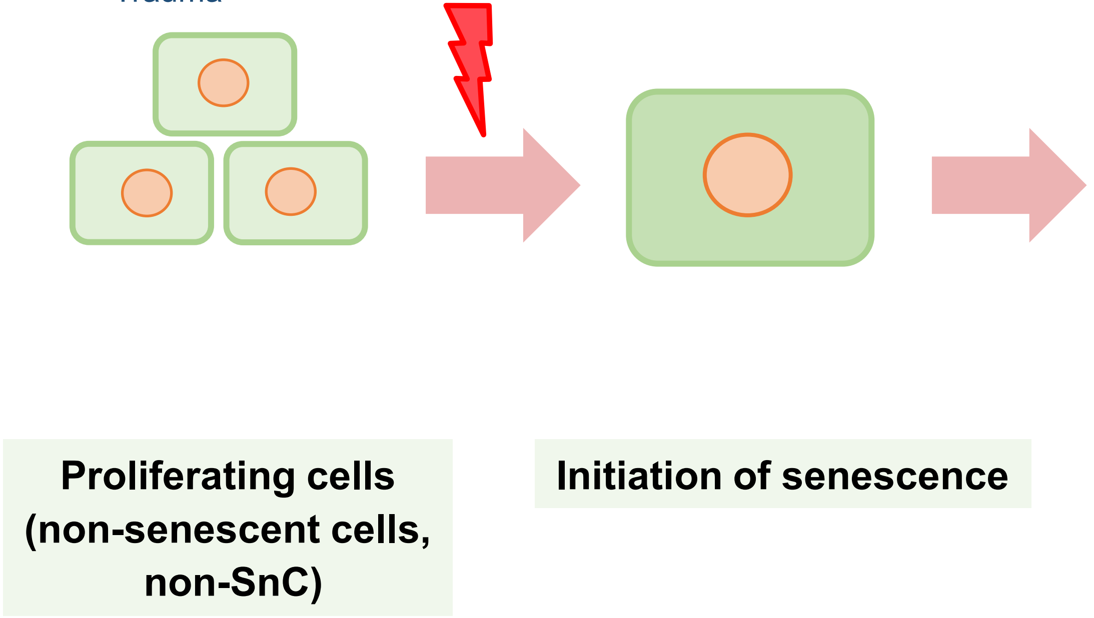
Senescent-initiating factors

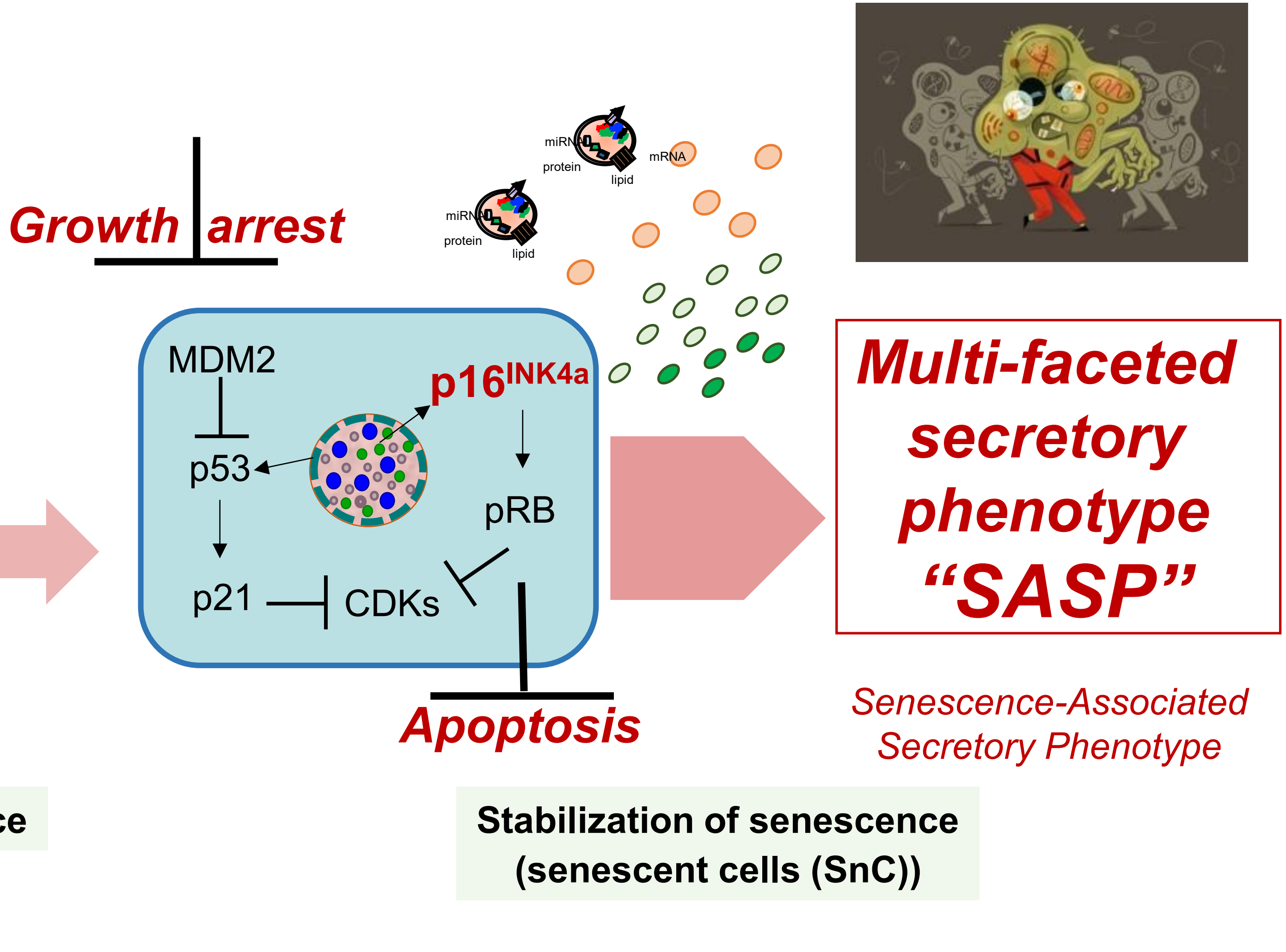
Telomere shortening

DNA damage

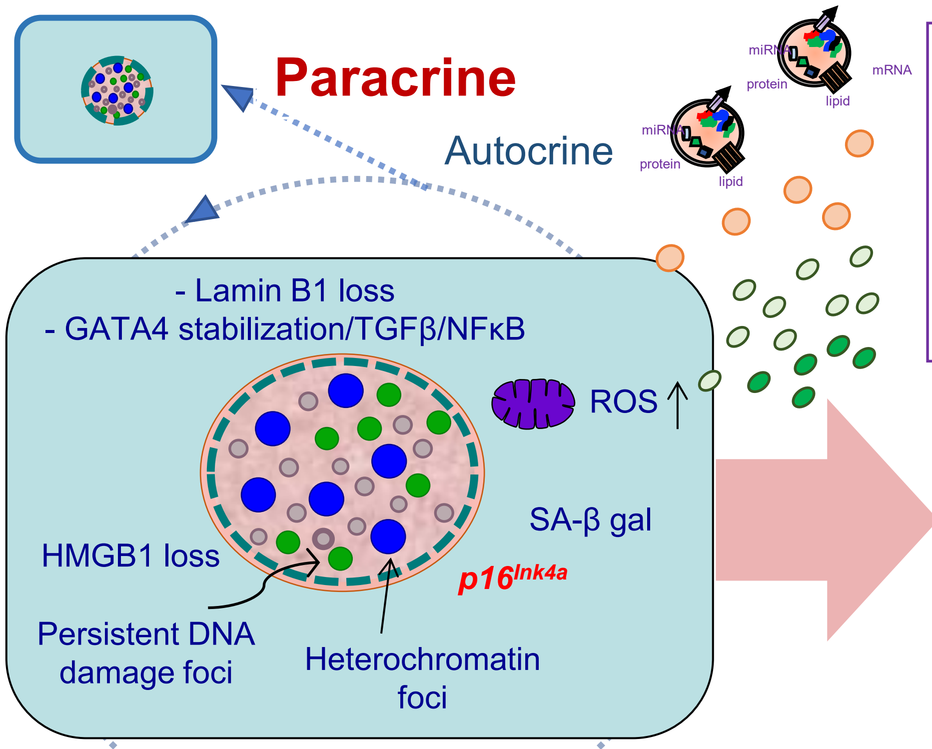
Stress-induced or pre-mature senescence
- Metabolic imbalances (high glucose, AGEs)
- Oncogenic mutations
- (epi)genomic damage

Tissue Injury
- Trauma





How senescent cells drive aging and diseases?



ps… These features are not specific to all SnCs!
Not all SnCs express these markers

Accumulation of SnC

Pro-inflammatory *(cytokines, chemokines, growth factors, proteases)*

DAMP *(HMGB1 loss/secretion, cf-mt-DNA)*

Extracellular Vesicles (MVs & exosomes)

Bioactive lipids, miRNAs, microsomes etc

Inflammation + (Inflamm-aging)

Spread of SnC and "sterile" Inflammation

Perturbed signaling

Destroy tissues
(ECM disruption)

Disrupt normal cell functions

Prevent stem cell functions

Our question: Ovarian to Systemic aging in women

Diseased tissues

SASP factors drive a chronic inflammatory environment that contributes to aging-related pathologies

When and where do senescent cells occur?

- **With increasing age**

Human, non-human primates, rodents, etc

- **At sites of age-related pathology**
  - Neurodegenerative diseases (Senescent neurons & glial cells)
  - Eye degenerative diseases (Senescent RPE, lens, retinal cells)
  - Pulmonary fibrosis (Senescent pulmonary cells)
  - Cardiac fibrosis (Senescent cardiomyocytes)
  - Cancer metastasis and recurrence (Senescent cancer cells)
  - Degenerative disc diseases (Senescent NP/AF cells)
  - Liver fibrosis (Senescent liver cells)
  - Kidney fibrosis (Senescent kidney cells)
  - Ovarian diseases/Infertility (Senescent granulosa cells)
  - Diabetes (Senescent β-cells)
  - Osteoporosis (Senescent osteoblasts and osteocytes)
  - Osteoarthritis (Senescent chondrocytes)
  - Sarcopenia/frailty (Senescent satellite cells and fibro-adipogenic progenitors)

Embryogenesis, timely parturition, wound healing
placental development during pregnancy ← **NOT ALL BAD!**

SnCs accumulate in many organs like ovaries where they may impact fertility and drive reproductive aging

Senotherapies: from joints to ovaries

- Senolytics = a new class of drugs that 'selectively' kill senescent cells
- Senomorphics = drugs that 'selectively' suppress certain SASP modules

- Osteoarthritis

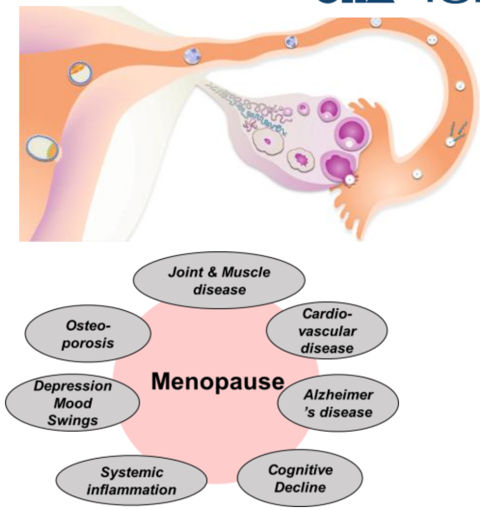
Clinical trial phase 2b (NCT0412994);

Patents 10,130,628; 9,993,472; 9,855,266; 9,849,128

Jeon et al., Nat Med, 2017; Jeon et al., JCI, 2018; Jeon et al., JCI insight, 2019; Faust et al., JCI; Gil et al., Aging, 2022; Chin et al., Aging cell, 2023

- Muscle injury / Sarcopenia

Jeon et al., Nat Met, 2022; Kim and Gil et al., Journal of Cachexia, Sarcopenia and Muscle, 2025

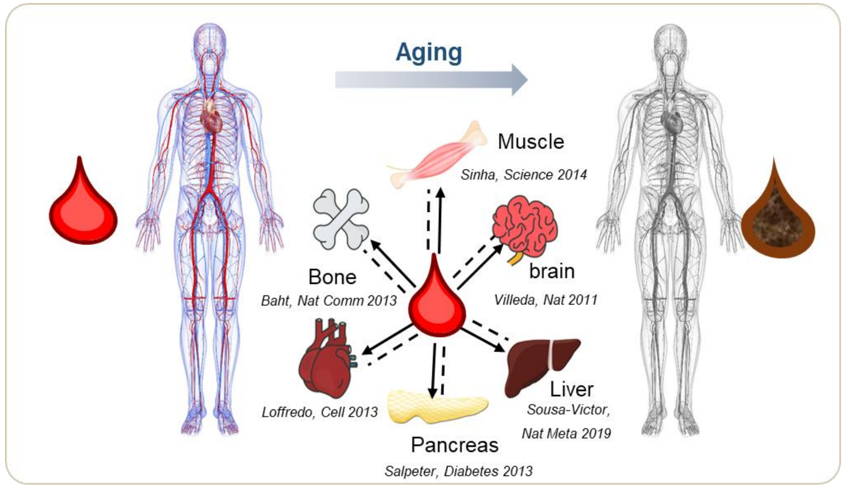


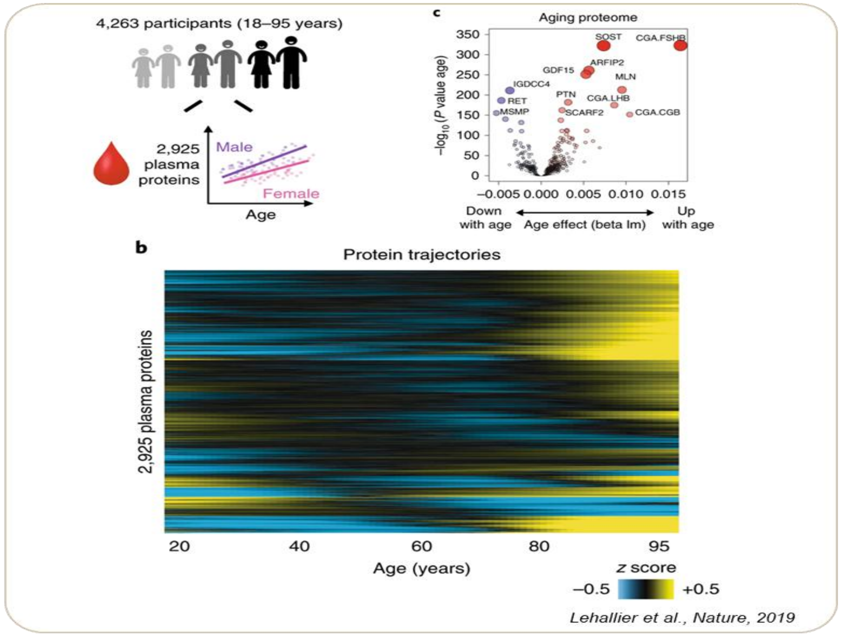
- Ovarian Aging

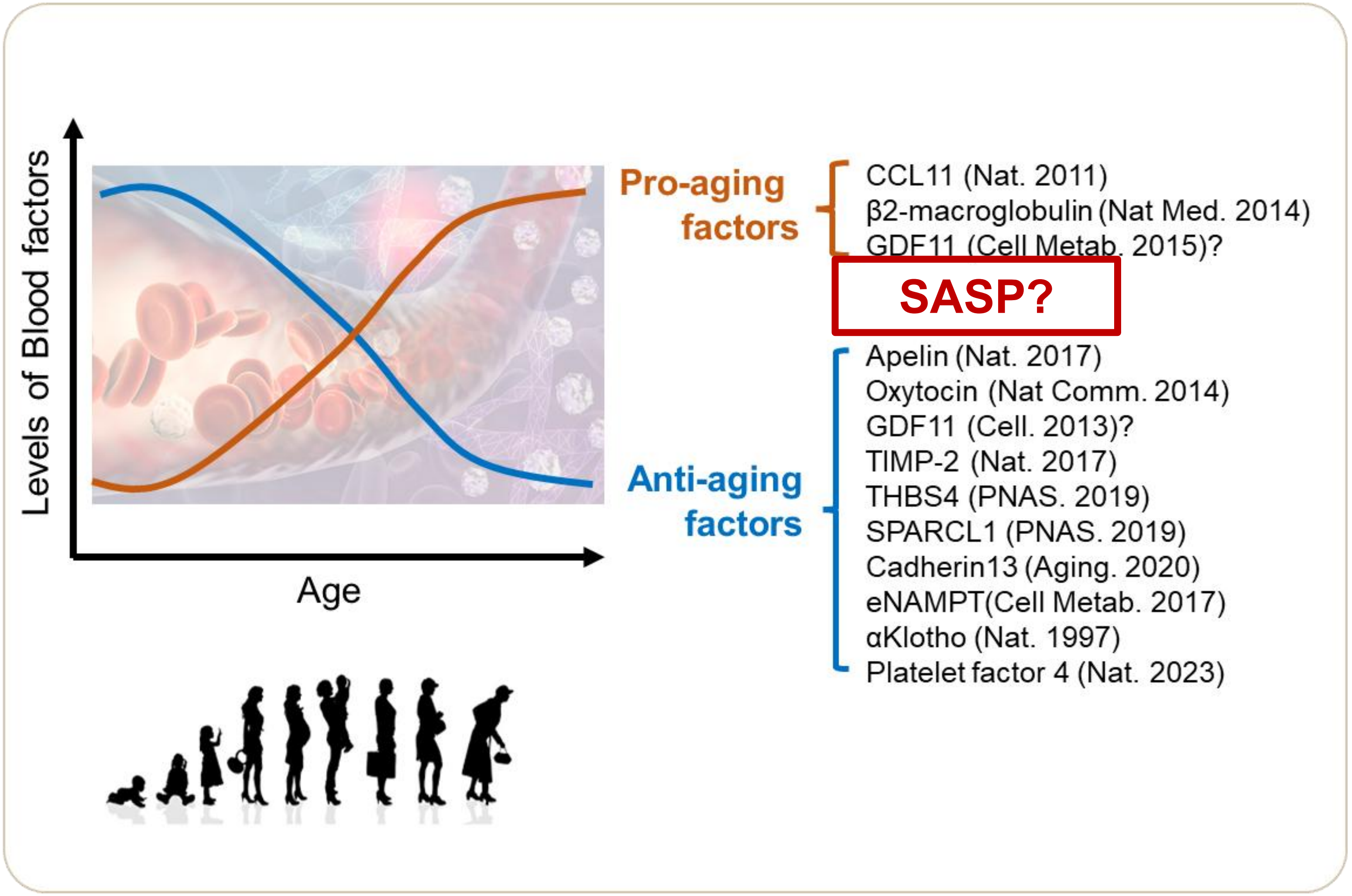
Shin et al., Rejuvenative Research, 2022; Shin et al., Menopause, 2023; Gwak et al., Envir Res, 2024

Could targeting senescent cells help preserve ovarian function and improve women's health overall?

Blood-borne factors reflect biological aging







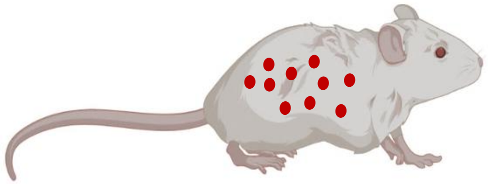
Circulating factors like SASPs link local senescence to systemic aging

Systemic circulation of SASPs may link aging and rejuvenation

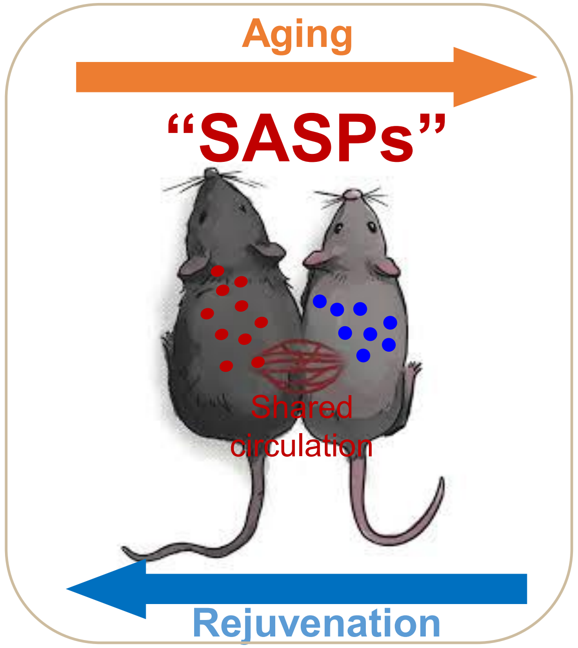
“Heterochronic Parabiosis”

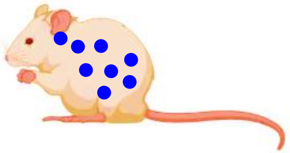
- **Pro-aging factors**

- Scare in young animals
- Increase with age
- **Reduce tissue homeostasis** in young animals



18-mon-old mouse
(≈ 65-yr-old human)



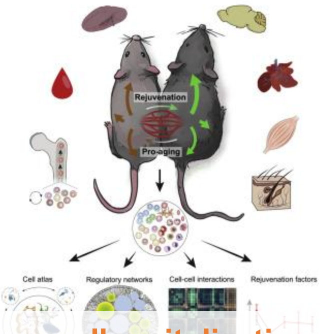


3-mon-old mouse
(≈ 20-yr-old human)

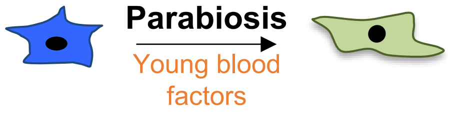
- **Anti-aging factors**

- Abundant in young animals
- Decline with age
- **Rejuvenate tissues** (heart, brain, muscle, liver, bone, pancreas, kidney, liver, aorta, intervertebral disc) when supplied to old animal

Stem cell revitalization and systemic rejuvenation



Stem cell revitalization and systemic rejuvenation



Adult stem cell rejuvenation

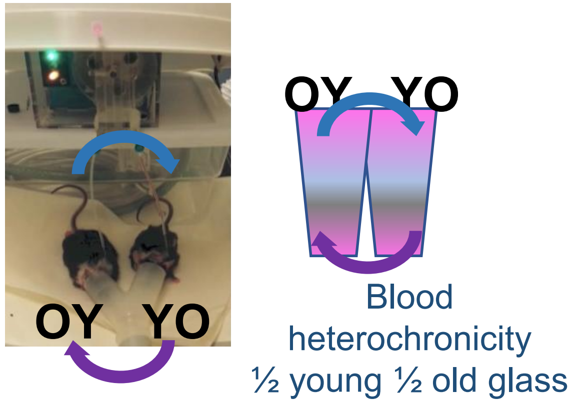
Ma et al., Cell Stem Cell, 2022

Muscle (Conboy, Nat 2005; Sinha, Science 2014)
Brain (Villeda, Nat 2011, 2014; Yousef 2019; Kim, IJMS 2020),
Liver (Conboy, Nat 2005; Sousa-Victor, Nat Meta 2019)
Pancreas (Salpeter, Diabetes 2013)
Heart (Loffredo. Cell 2013)
Bone (Baht, Nat Comm 2013; Yi, Swiss Med Wkly 2018; Li Metabolites 2020)

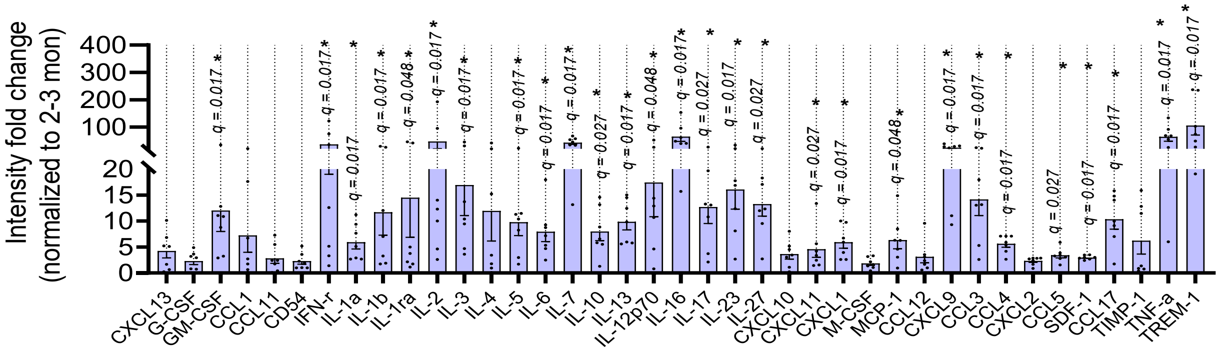
So what if SASPs are causing aging in distant organs, maybe they’re playing a role in reproductive decline?

Do circulating SASPs spread aging?

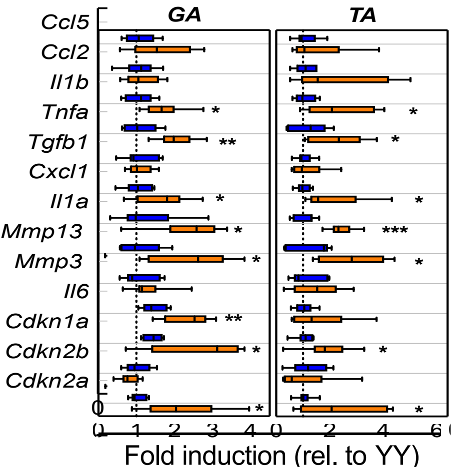
Heterochronic apheresis

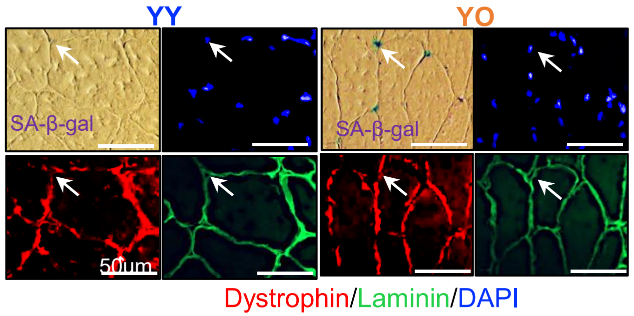


Circulating SASP factors in the old blood



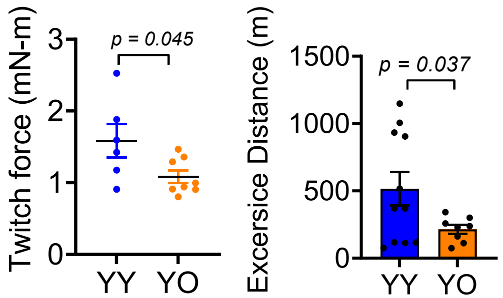
Induced senescence in young skeletal muscle



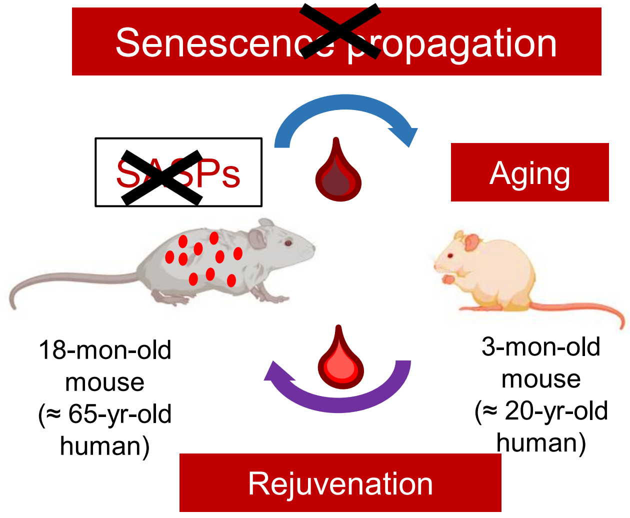


* SA-β-gal+ satellite cells that were located between the laminin+ basal lamina and dystrophin-outlined sub-sarcolemma

Functional tests



Our in vivo model



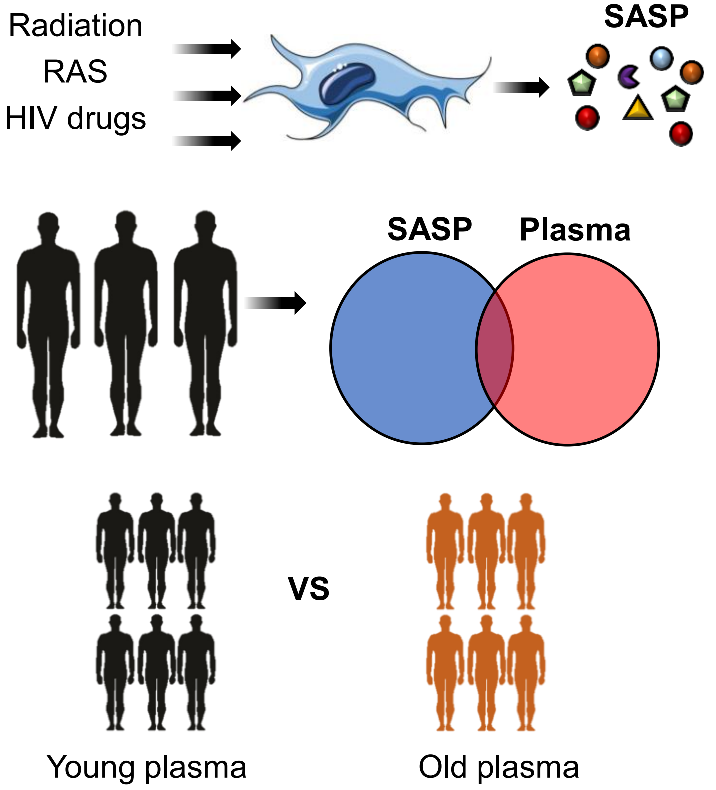
Jeon et al., Nature Metabolism, 2022

Circulating SASPs may not just be aging biomarkers they also could be causative mediators of systemic aging

Core SASPs overlap with plasma aging markers in human cohorts

SASPs are in aged human blood

Biomarker discovery pipeline -> Proteome

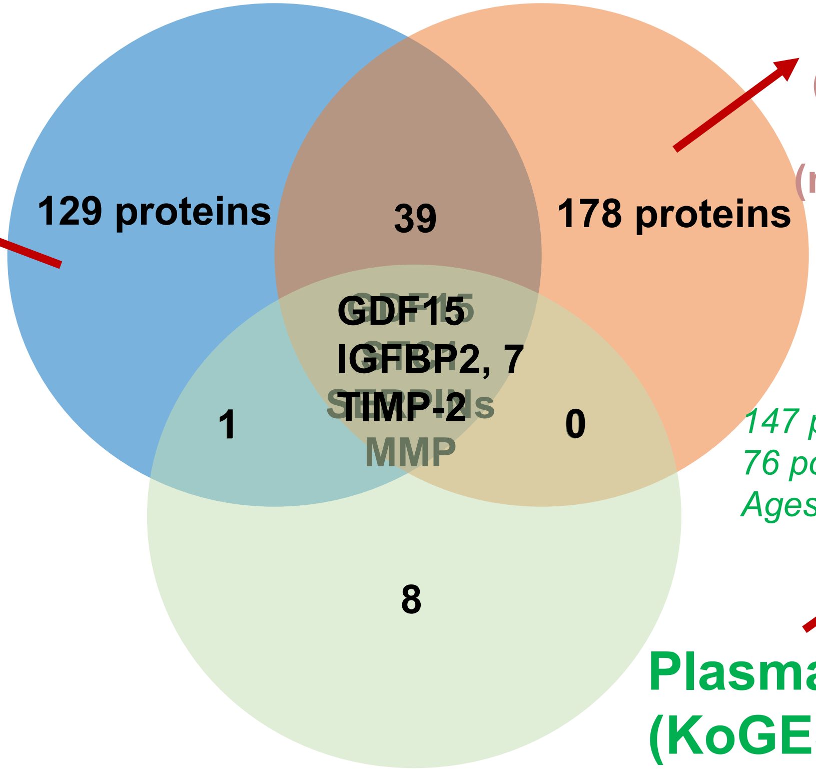


SASP Atlas

http://www.saspatlas.com

Core SASPs

Plasma Aging Biomarkers
(NIA healthy aging cohort)
InCHIANTI cohort
(n=240) Ages 22 to 93 years



147 premenopausal +
76 postmenopausal women (n=223)
Ages 40 to 82 years

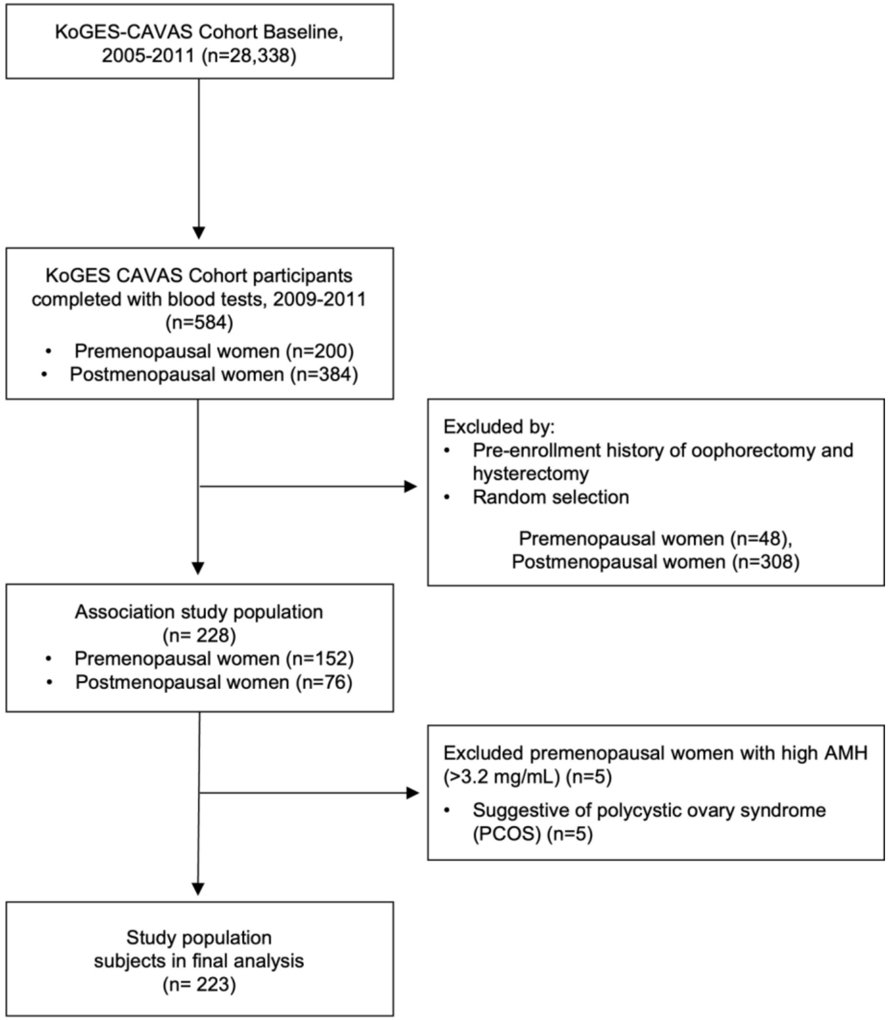
Plasma Aging Biomarkers (KoGES-CAVAS)

Do circulating SASPs reflect systemic signals of ovarian aging, particularly in postmenopausal women?

Basisty et al., PLOS Biology, 2020; Tanaka et al., Aging cells, 2018

SASP and ovarian aging in a prospective population-based cohort study

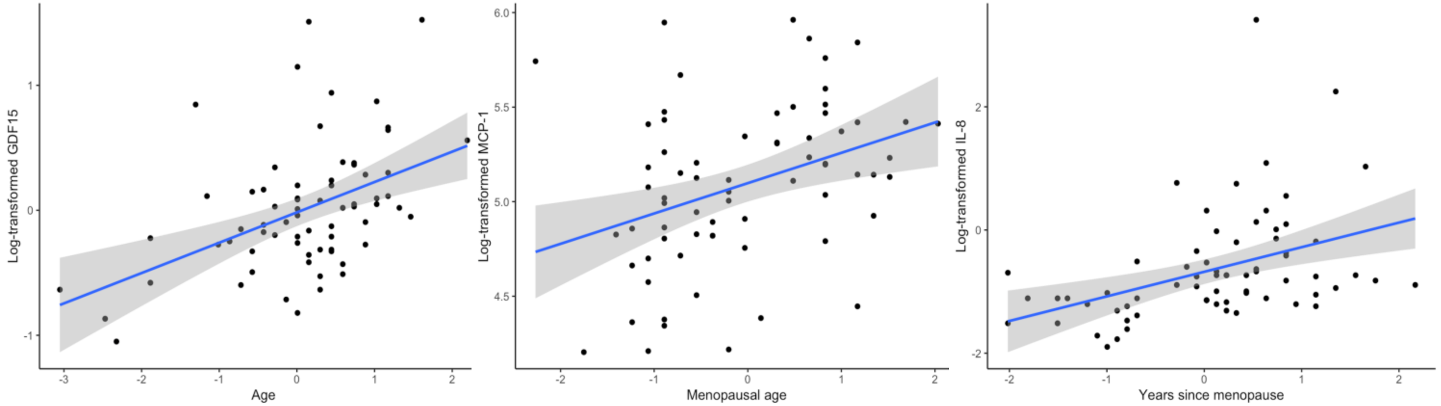
- **Study participants**
  - 147 pre- (46.4 ± 3.9 y) and 76 (67.0 ± 6.9 y) post-menopausal women in the Korean Genome and Epidemiology Study Cardiovascular Disease Association Study (KoGES-CAVAS), a population-based prospective cohort study conducted by Korea NIH
- **Measured markers**
  - 32 SASP proteins overlapped with aging-related markers and AMH in human plasma
- **Outcomes**
  - **Chronological age**
  - **Biological age:** menopausal state (menopausal age and years since menopause) and AMH level (mean 0.5 ± 0.7ng/ml)
- **Statistical methods**
  - Multivariate analysis adjusted for age and BMI



Shin et al., Menopause, 2023

Plasma SASPs reflects menopausal and chronological ages

- Investigated circulating 32 SASP proteins in 76 post-menopausal women (avg 67 ± 6.6 y; range 46–82 y) from KoGES-CAVAS study
- Identified GDF-15, IGFBP-2, and TNFα as correlates of chronological age
- IL-8 and MCP-1 were associated with menopausal age and years since menopause
- *A combination of 13 SASPs proteins are selected to be associated with chronological, menopausal age and years since menopause* using multi-proteins model



Variables	Chronological age		Menopausal age	Years since menopause
	Adjusted for menopausal age	Adjusted for years since menopause		
GDF15	0.400	0.141	-	-
IFN-γ	-	-	-0.019	-
IGFBP-2	0.213	0.053	-	-
IGFBP-7	0.284	-	-	-
IL-1β	-	-0.250	-0.218	0.155
IL-15	-	-	-0.025	0.004
IL-17A	0.153	0.040	-	-
IL-8	0.020	-	-0.132	0.090
MCP-1	-	0.225	0.495	-0.336
TIMP-2	-	-0.120	-0.349	0.169
TNF-α	0.113	-	-0.120	0.046
VEGF-A	-	-0.021	-0.045	0.023
IP-10	0.006	0.104	0.048	-

SASPs can act as systemic indicators of ovarian aging, reflecting senescence burden that evolves with ovarian aging

Shin et al., Rejuvenative Research, 2022

Association of SASP proteins with menopausal status

SASP	Coefficient (SE)	*p*-value	Adjusted *p*-value[a]
Eotaxin	0.457 (0.126)	<0.001	0.001
GDF15	−0.643 (0.266)	0.017	0.030
IFN-γ	0.544 (0.165)	0.001	0.003
IGFBP-2	6.838 (0.181)	<0.001	<0.001
IGFBP-4	7.038 (0.145)	<0.001	<0.001
IGFBP-5	7.057 (0.238)	<0.001	<0.001
IGFBP-7	6.940 (0.068)	<0.001	<0.001
IL-1α	−1.047 (0.392)	0.009	0.017
IL-2	-0.414(0.145)	0.004	0.009
IL-6	−0.757 (0.282)	0.008	0.016
IL-7	−0.567 (0.139)	<0.001	<0.001
IL-8	−0.597 (0.219)	0.007	0.015
IL-10	−0.354 (0.154)	0.022	0.036
MCP-1	0.821 (0.153)	<0.001	<0.001
MIP1α	−0.628 (0.208)	0.003	0.008
TIMP-1	0.378 (0.105)	<0.001	<0.001
TIMP-2	0.249 (0.078)	0.001	0.003

* Pearson correlation coefficient (SE) was calculated by linear association using generalized linear regression model. Adjusted p-value for the false discovery rate derived with the Benjamini–Hochberg method.

** Blue boxes indicate SASPs that are positively associated with chronological age

17 SASP proteins associated with menopausal status after age and BMI adjustment in middle-aged/older women

Shin et al., Menopause, 2023

Association of SASP proteins with AMH level

SASP	Coefficient (SE)	*p*-value	Adjusted *p*-value[a]
IL-6	0.186 (0.082)	0.026	0.560
IFN-γ	0.075 (0.036)	0.040	0.560
VEGF-A	0.112 (0.077)	0.147	0.714
IGFBP-7	−0.015 (0.011)	0.176	0.714
GDF15	−0.093 (0.075)	0.212	0.714
TIMP-2	0.112(0.077)	0.255	0.714

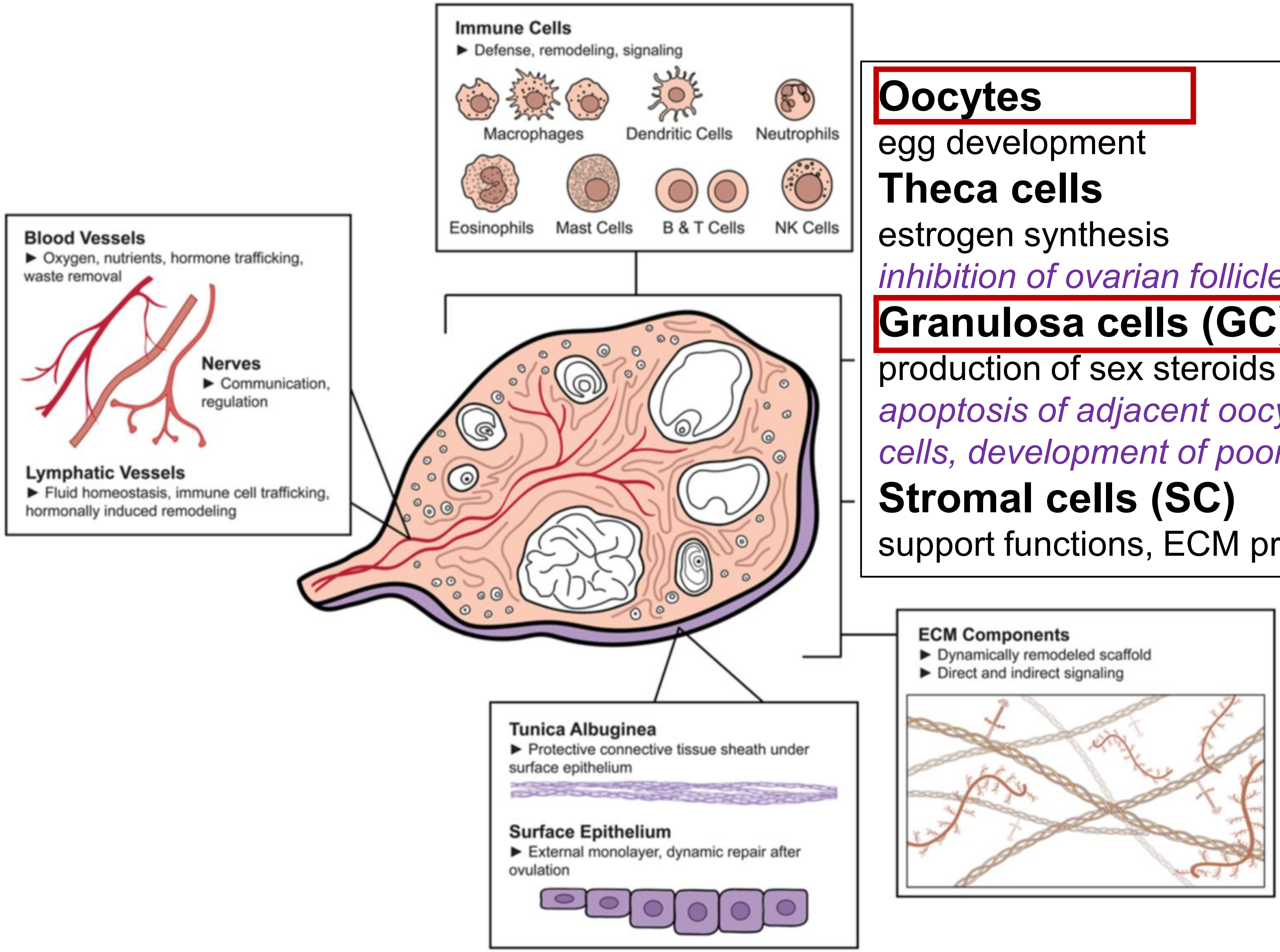
*Pearson correlation coefficient values (standard error) were calculated by linear association using generalized linear regression (GLM) model. Adjusted p-value for the false discovery rate derived with the Benjamini–Hochberg method.
** Blue boxes indicate SASPs that are positively associated with chronological age

- *No significant associations between SASP levels and AMH in premenopausal middle-aged/older women*
- Subgroup analysis (<45 y) showed lack of association: lack of younger participants ?

Plasma SASPs reflect menopausal status but may not be reliable biomarkers of ovarian reserve in midlife women

Shin et al., Menopause, 2023

Complex biology of human ovarian aging and senescence



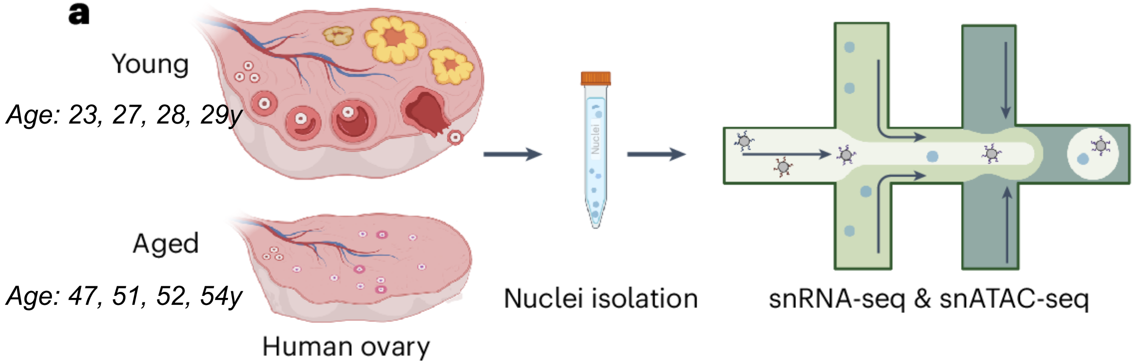
Oocytes
egg development
Theca cells
estrogen synthesis
inhibition of ovarian follicle's ability to mature? etc
Granulosa cells (GC)
production of sex steroids and growth factors
apoptosis of adjacent oocyte by transferring ceramide from cumulus cells, development of poor embryos etc
Stromal cells (SC)
support functions, ECM production

Ovary is composed of various cell types, each potentially contributing differently to cellular senescence and aging

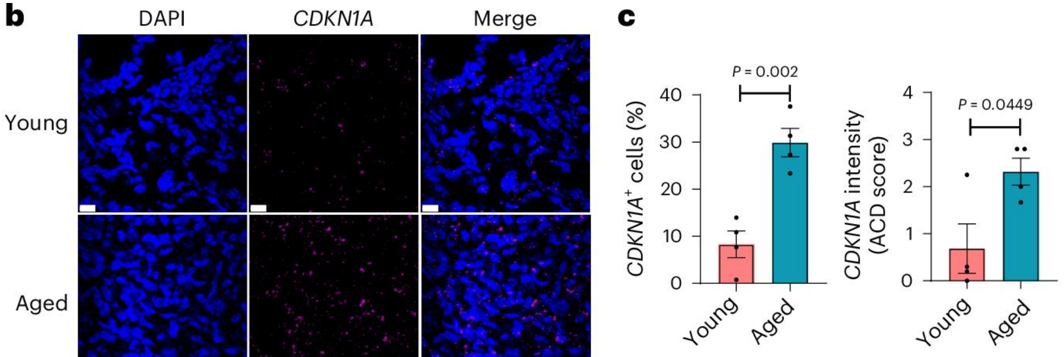
Kinnear et al., Reproduction, 2020; Secomandi et al., Human Reproductive Update, 2022

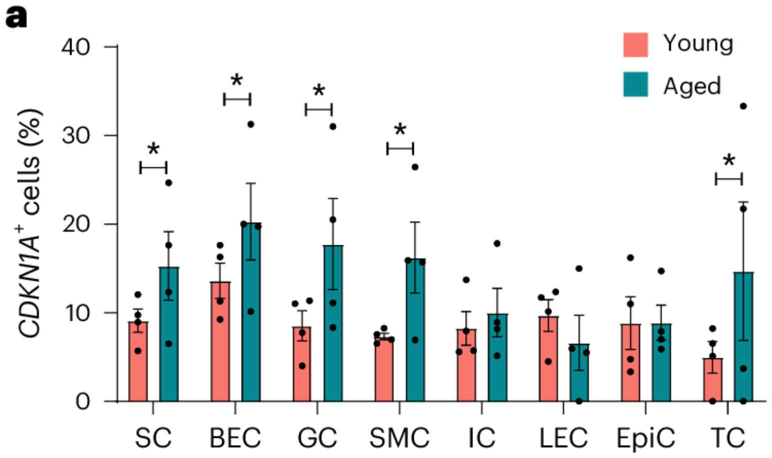
Which cells become senescence in human aged ovary?

Increased proportion of senescent cells (p21+ cells) in the aged ovary

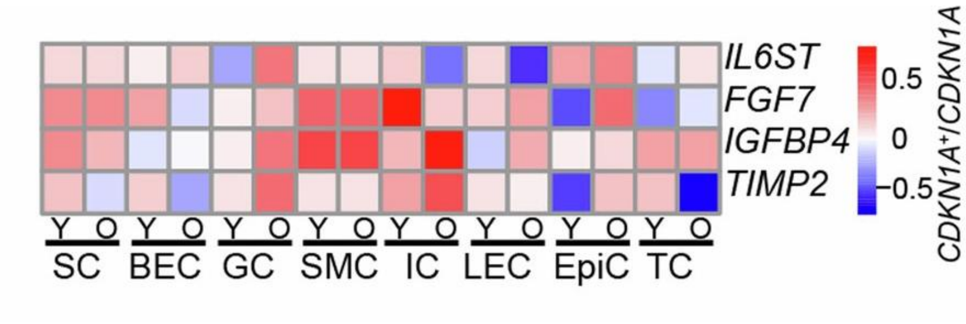


(Aging from late 20s to early 50s)





SASP secretome



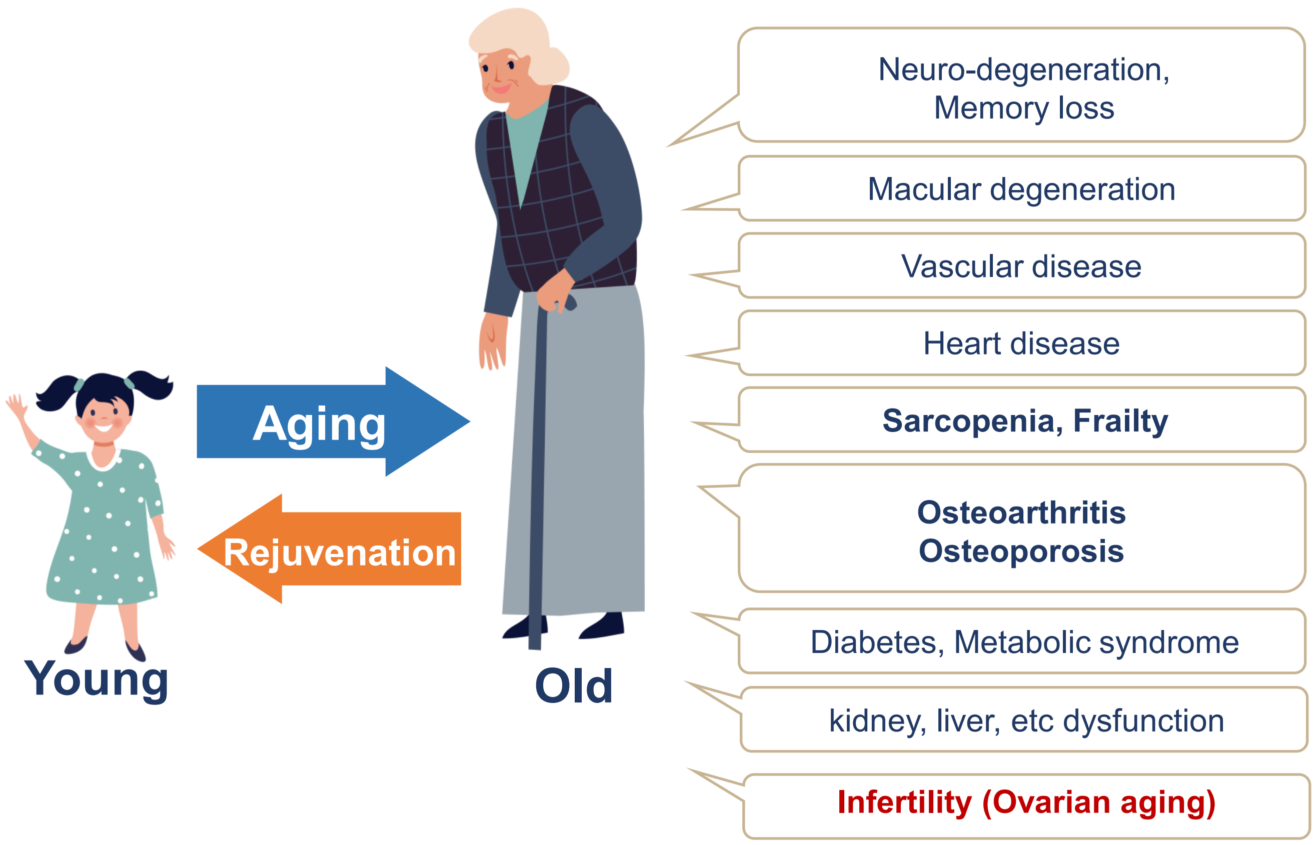
SASPs in blood can serve as systemic indicators of ovarian aging, providing biomarkers for ovarian decline?

Jin et al., Nature aging, 2024

Aging can be modified by anti-aging interventions

Rejuvenation —not just slowing aging but actually reversing it — is feasible at least in mice!

- Epigenetic reprogramming of aged cells
- Metabolic interventions (dietary restriction, exercise, etc.)
- **Elimination of harmful senescent cells**
  : Senotherapeutics (senolytics & senomorphics)
- **Utilization of factors within bloodstream**
  : Young blood plasma treatment



Targeting SASPs rejuvenate ovaries and delay aging in women

Senotherapy shows variable efficacy in delaying ovarian aging in mice

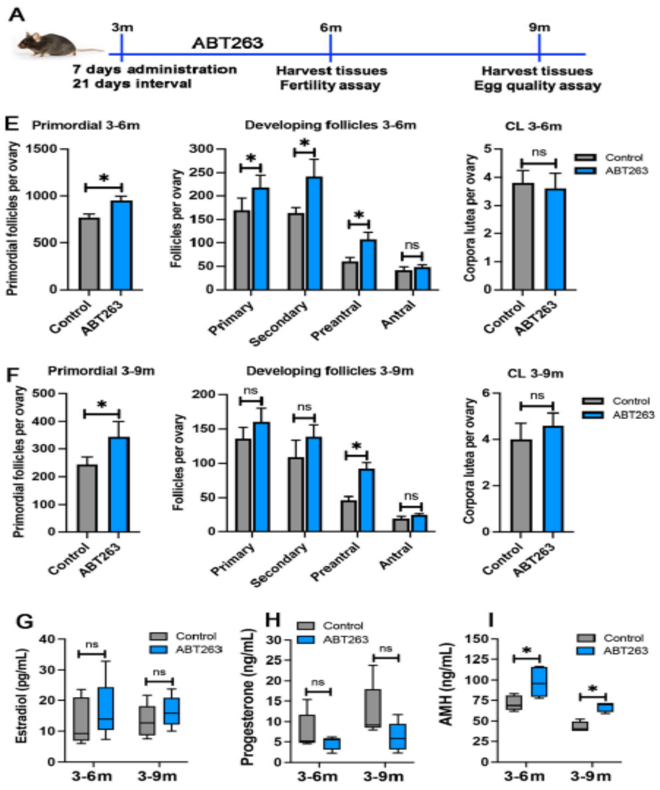
scientific reports

Check for updates

OPEN

Primary oocytes with cellular senescence features are involved in ovarian aging in mice

Hao Yan[1,6,7], Edgar Andres Diaz Miranda[2,7], Shiying Jin[2], Faith Wilson[2,3], Kang An[2], Brooke Godbee[2,4], Xiaobin Zheng[5], Astrid Roshealy Brau-Rodríguez[2] & Lei Lei[2,3]✉



GeroScience (2024) 46:3445–3455
https://doi.org/10.1007/s11357-024-01089-0

ORIGINAL ARTICLE

Check for updates

Senolytic treatment fails to improve ovarian reserve or fertility in female mice

Driele N. Garcia · Jessica D. Hense · Bianka M. Zanini · Jose V. V. Isola · Juliane B. Prosczek · Sarah Ashiqueali · Thais L. Oliveira · Jeffrey B. Mason · Ines C. Schadock · Carlos C. Barros · Michael B. Stout · Michal M. Masternak · Augusto Schneider

Fig. 1 Follicular count per section of six-month-old females in the control or treated (D + Q) groups. **a** Primordial, **b** transition, **c** primary, **d** secondary, **e** tertiary, and **f** total follicles. *P* values < 0.05 were considered statistically different

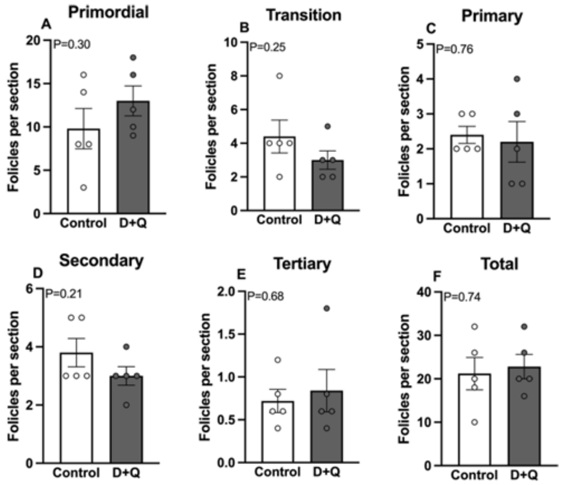
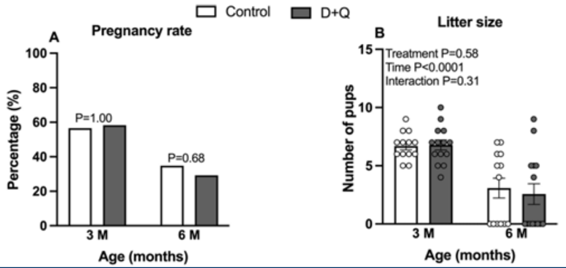


Fig. 2 Pregnancy rate and litter size of 6-month-old females in the control or treated (D + Q) groups. Mice were mated for seven days with control 3-month-old male mice. *P* values < 0.05 were considered statistically different



Better understanding of ovarian senescence is needed for clinical translation

Clinical trial of Rapamycin for delaying ovarian aging in human

A randomized, double-blind, placebo-controlled pilot study
Population: Premenopausal women (age 35-45y)
Primary Endpoint: Ovarian function and aging biomarkers (e.g., AMH levels, follicle count)

ClinicalTrials.gov

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Active, not recruiting

Effect of Rapamycin in Ovarian Aging (Rapamycin)

ClinicalTrials.gov ID NCT05836025

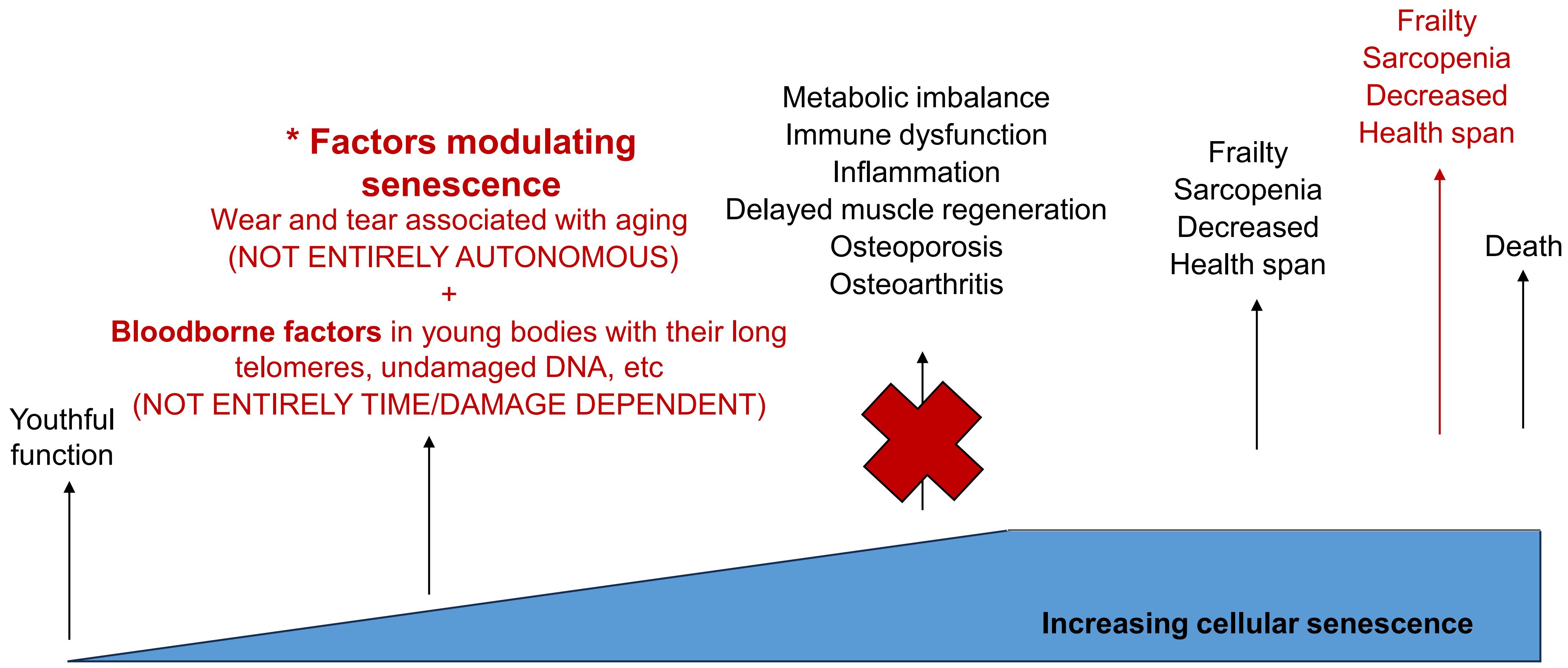
Sponsor Columbia University

Information provided by Samuel Zev Williams, Columbia University (Responsible Party)

Last Update Posted 2025-01-06

In the future, senolytics or anti-SASP strategies might be another tool to preserve ovarian health

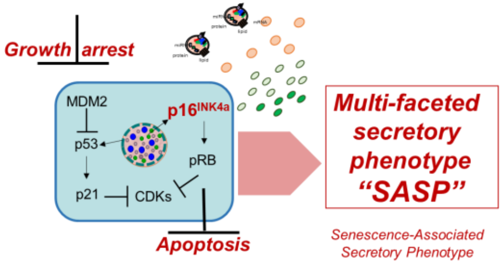
Key Takeaway: Targeting senescence to treat and prevent age-related diseases



Bloodborne factors and senescence are modifiable drivers of aging

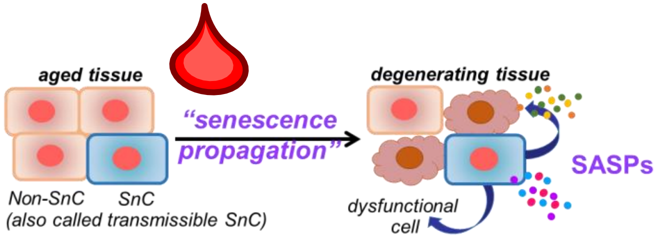
Our lab focus: developing senotherapies for age-related disease

Cellular senescence are key factors in impairing regeneration in response to injury and aging



Map senescence in musculoskeletal diseases and others & Discover associated biomarkers
(scRNA-seq, spatial transcriptomics, proteomics)

Senescent cells trigger secondary aging in neighboring cells, drive systemic aging, and alter tissue microenvironment



Define senescence's impact on young cells and tissue function
(2D, 3D bioprinted and microfluidics based aged tissue model, in vivo, patients)

Develop senotherapies to create a pro-regenerative environment and treat age-related diseases

Develop rejuvenation intervention to target senescent cells (e.g., senolytics)

Senescence is a treatable hallmark, and our lab develops targeted therapies to reverse aging-related degeneration

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MRC Center for Myokine Convergence Research

NRF 한국연구재단

포스코청암재단 POSCO TJ Park Foundation

KOREA UNIVERSITY 1905

Thank you for your attention!

Baseline characteristics of participants

	Premenopausal women (n=147)		Postmenopausal women (n=76)		
Variables	Mean ± SD [a]	Median (IQR) [b]	Mean ± SD	Median (IQR)	P
Age (years)	46.4 ± 3.9	46 (43–50)	66.9 ± 6.9	68 (63.5–71)	<0.001
BMI (kg/m^2)	23.9 ± 3.2	23.7 (21.7–25.7)	23.5 ±3.0	23.3 (21.1–25.3)	0.536
AMH (ng/mL)	0.5 ± 0.7	0.2 (0.1–0.7)	-	-	-

All of ± data indicates mean ± standard deviation of the mean. Median (interquartile range) of the level of SASP in study population. P-values were analyzed by a two-tailed unpaired t-test or the Mann–Whitney U test was used to compare means or medians, respectively, of the SASP according to menopausal status

* Year since menopause: This variable is often used as an indicator of cumulative biological aging or hormonal deprivation over time

Shin et al., Menopause, 2023