Common Fund proposal for a Cellular Senescence Network

The Common Fund

Concept Clearance: New Common Fund Program

TITLE: Cellular Senescence Network

Objective: To identify and functionally characterize the heterogeneity of senescent cells across multiple tissues in human health, disease, and lifespan at single cell resolution.

1. Generate a multimodal, multidimensional Atlas of senescent cells in various human tissues.
2. Develop innovative tools and technologies to identify and characterize senescent cells.
3. Aggregate data across the Network into a searchable Atlas of Cellular Senescence, ensure utility of the database (FAIR), and promote collaboration through Network engagement with the research community.

Funds Available $144.25 over 5 years

Program Duration: 5 years (Phase 1)

Council Action: Vote on support of Program

Cellular Senescence Network
A Brief History of Cellular Senescence

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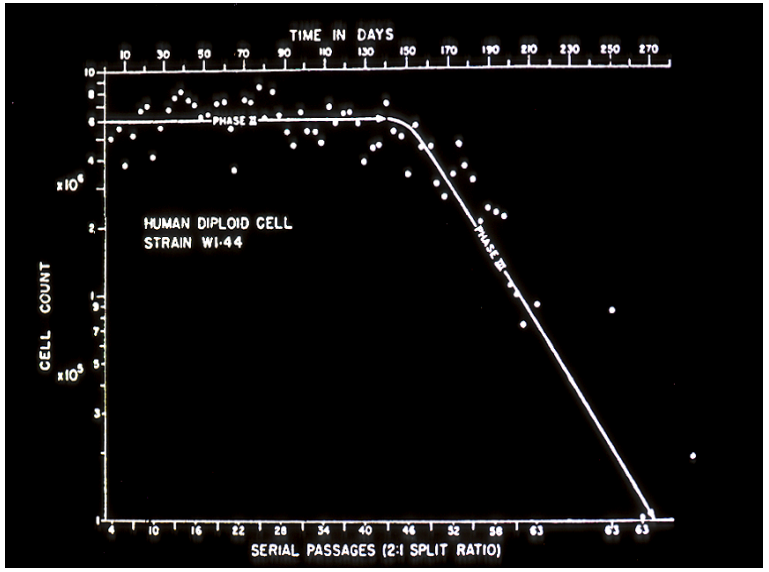
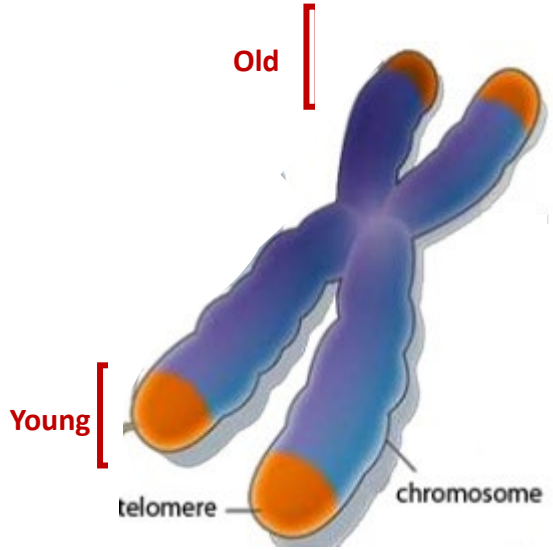
Cellular senescence was first observed in *in vitro* culture and termed replicative senescence

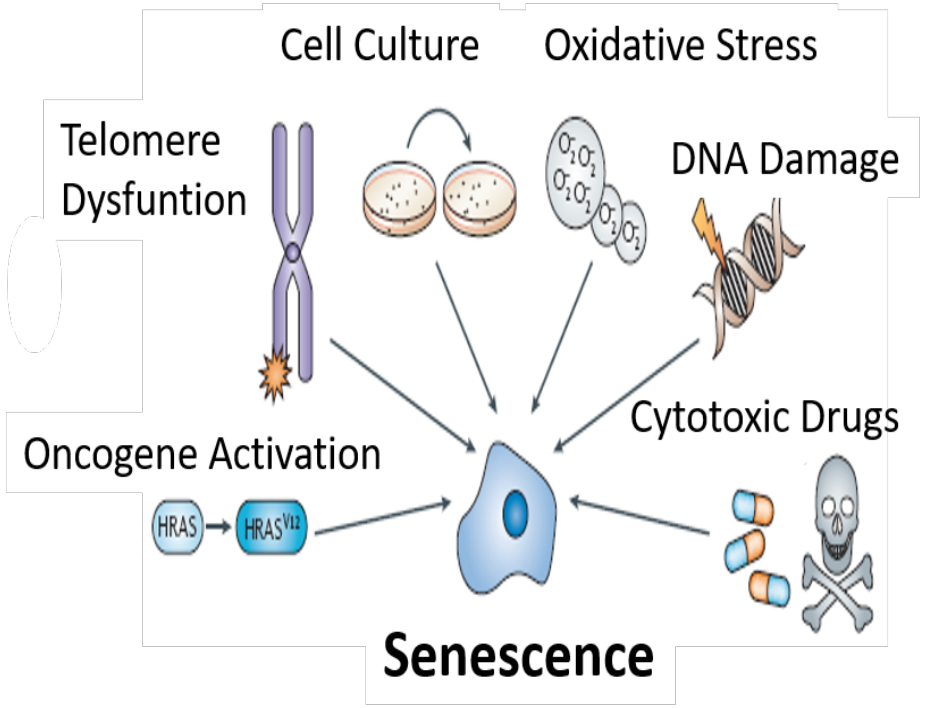


Hayflick & Moorhead
Exp. Cell Res. 25:585 (1961)

Replicative cellular senescence is driven by the shortening of telomeres with every cell division



But there are many different ways to induce the 'same' phenotype



Cellular Senescence Network

Senescent Cells are Involved in Health and Disease

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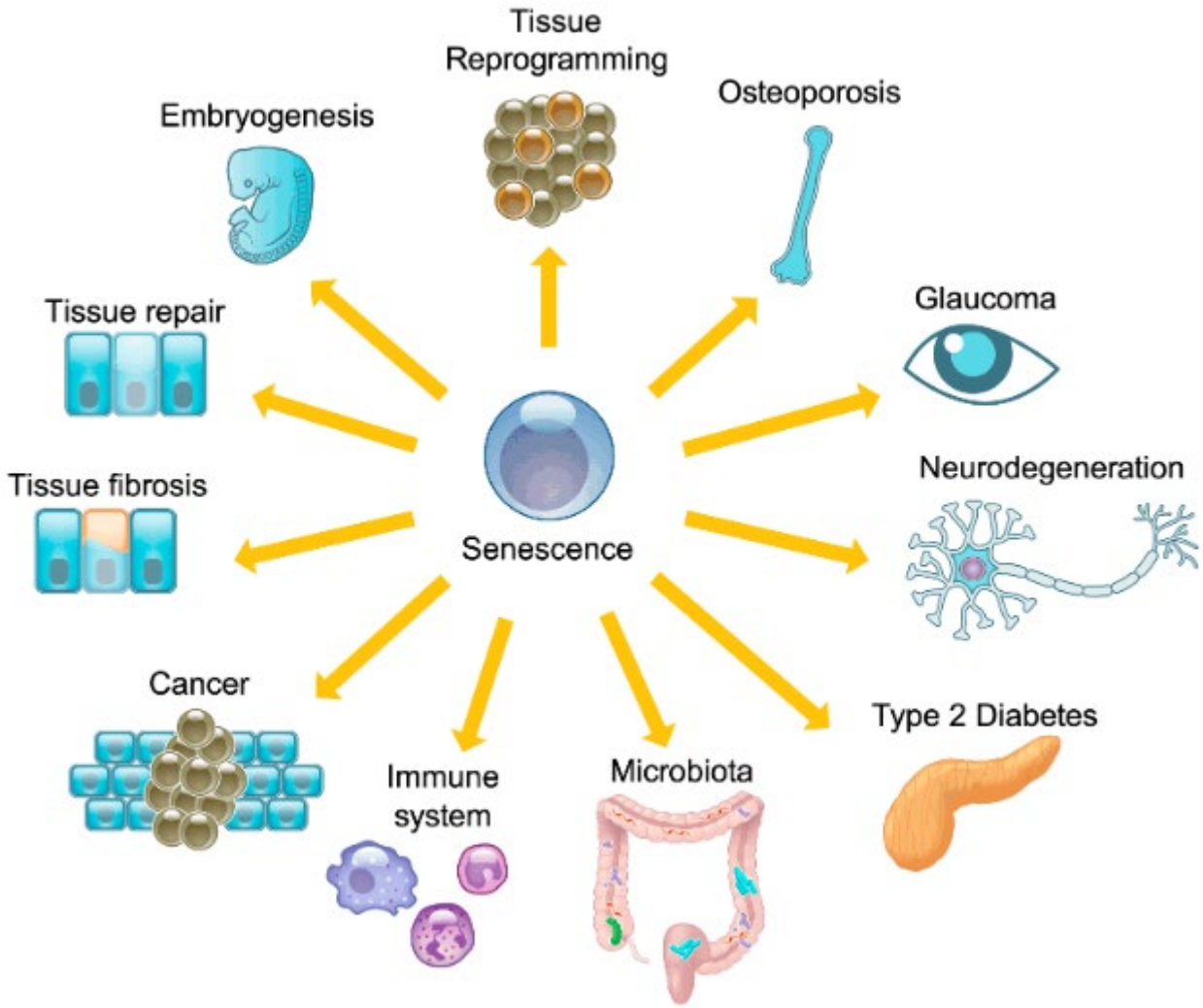

Cellular Senescence Network
Senescent Cells Alter the Microenvironment

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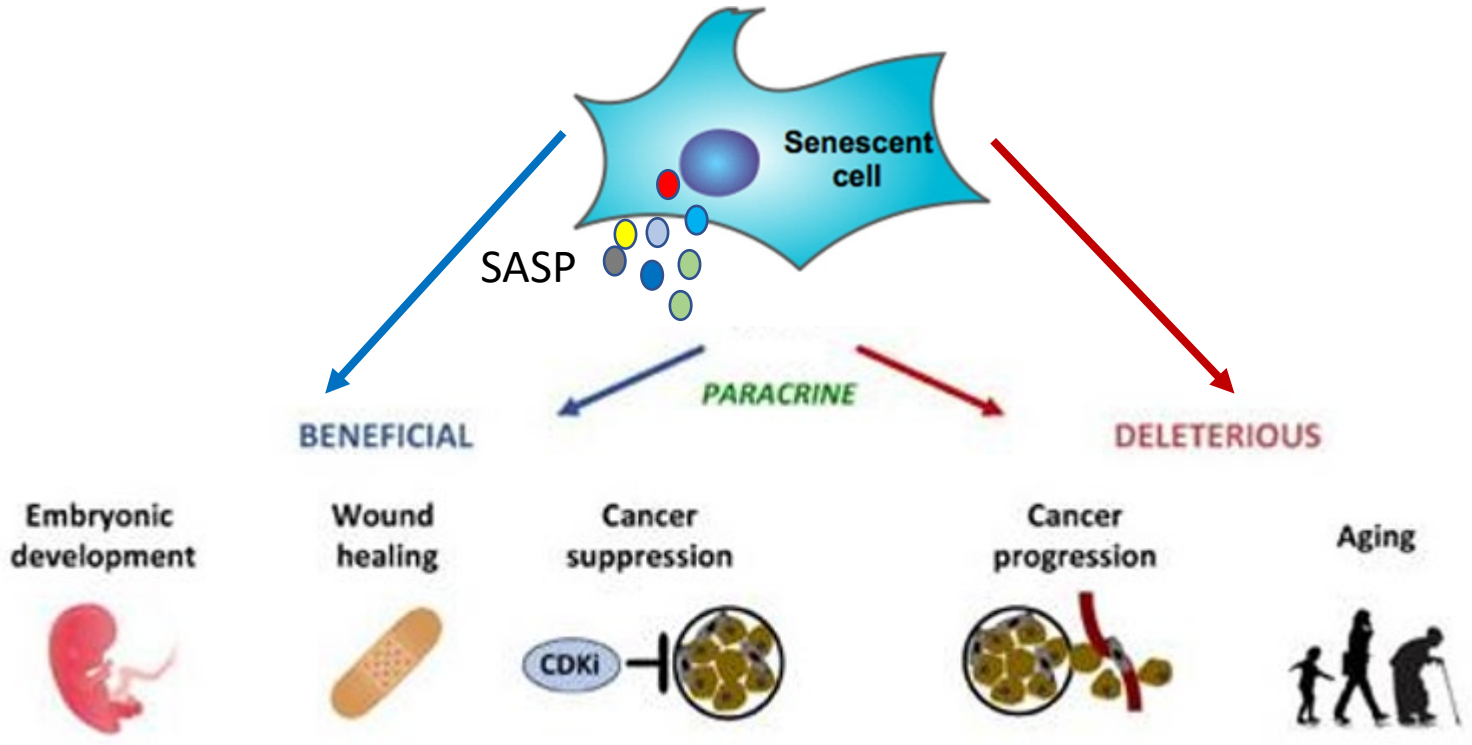
Senescent Cells can affect neighboring cells through multiple mechanisms.



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Senescent Cell Removal Improves Health

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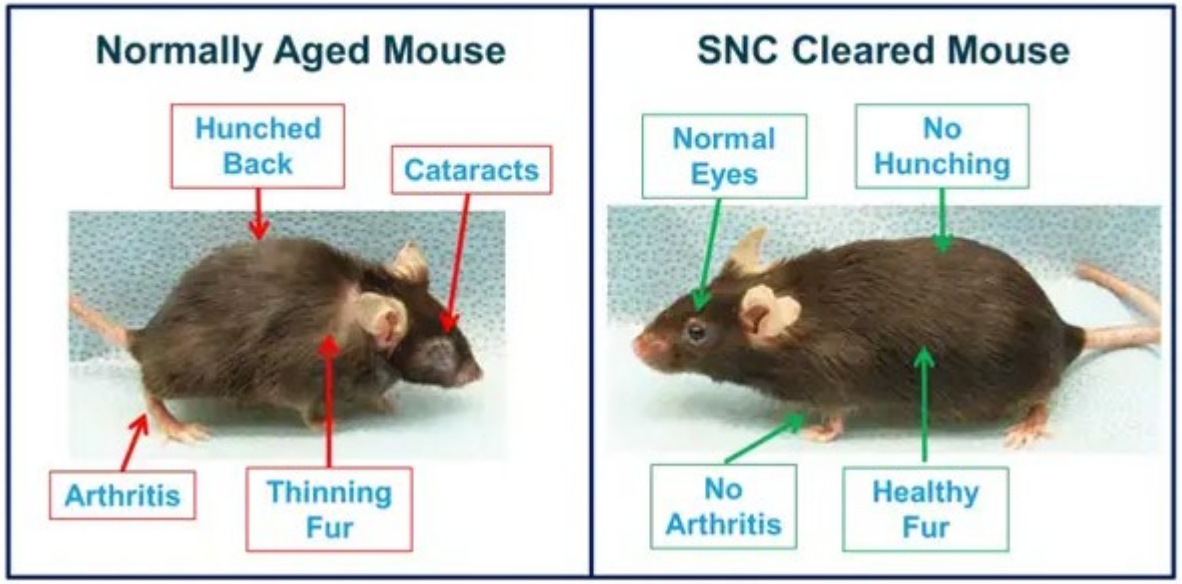
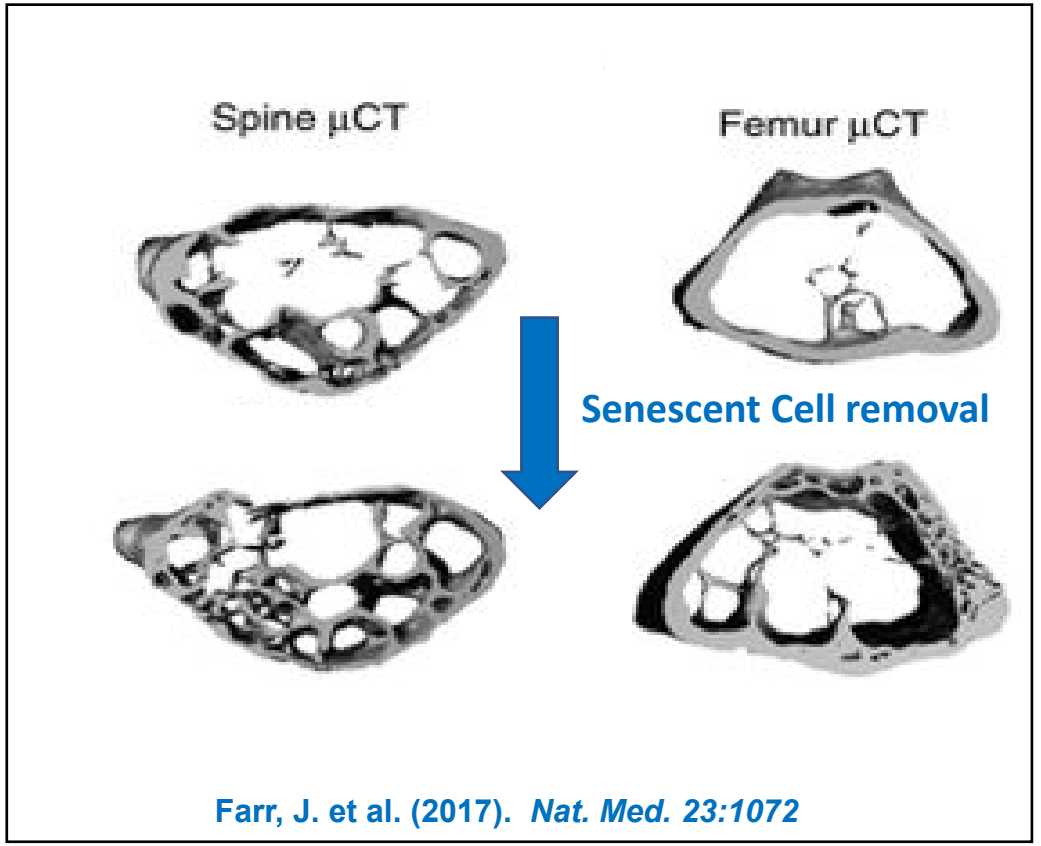
Aged-Matched Litter Mates



Bone Health



Farr, J. et al. (2017). *Nat. Med. 23:1072*

Cellular Senescence Network
Challenges in the field

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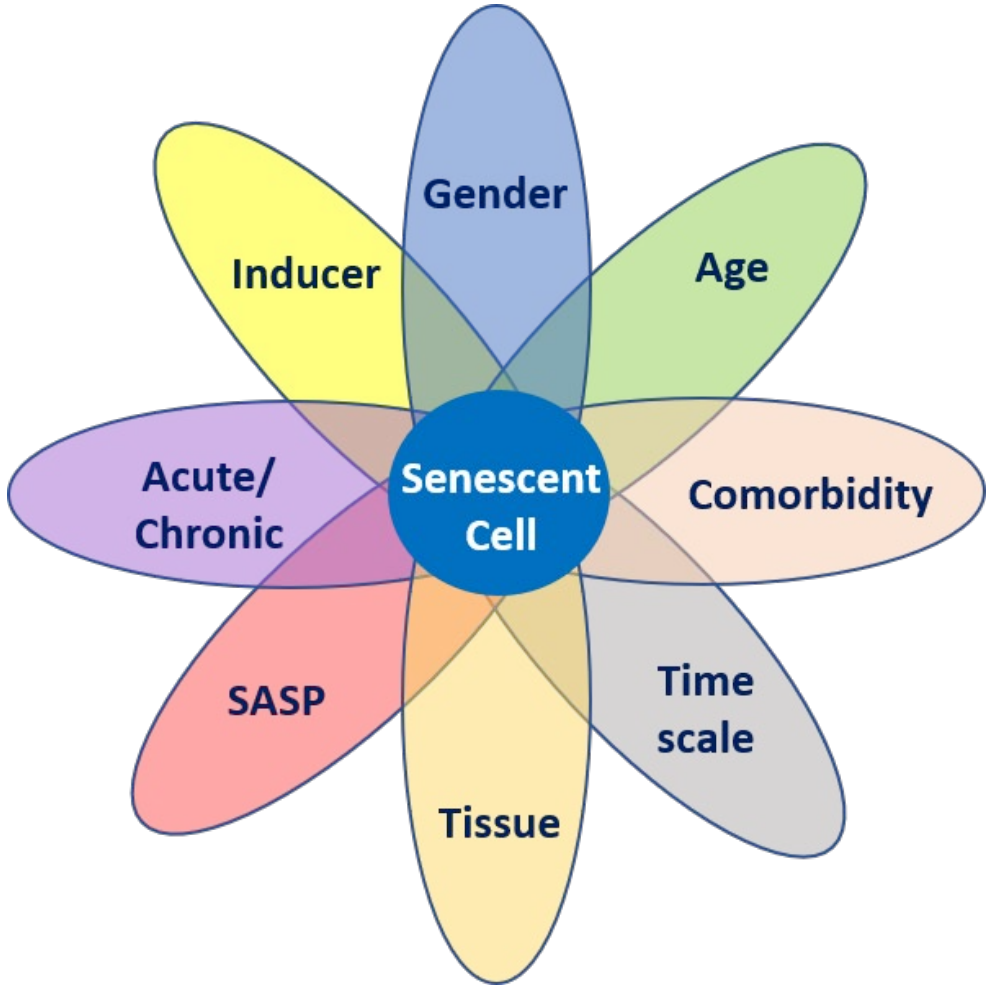
- Cellular Senescence is heterogeneous across cell types, tissues, and timescales
- Inducers of senescence and behaviors of senescent cells can vary dramatically
- Harnessing senescence for human health will require new tools and resources to gain a deeper understanding of senescent cell biology and heterogeneity



Establishing a Cellular Senescence Network will address these challenges

Cellular Senescence Network
Engaging the Scientific Community

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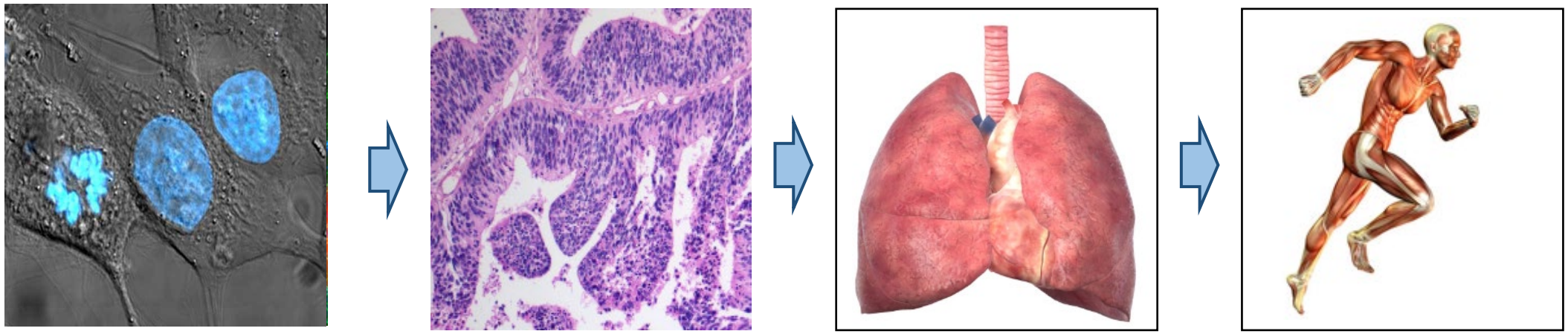
To identify gaps, challenges and potential programmatic scope, input was sought from the scientific community via an RFI (NOT RM 20-014), and three virtual Think Tanks held in April 2020. Five broad areas were identified:

- Create a multimodal, multi-dimensional **Atlas** of Senescent Cells to identify heterogeneity and states of senescent cells.
- Determine a set of "gold standard" **biomarkers** to characterize senescent cells *in vivo.*
- Establish experimental and computational/AI **predictive models** to analyze, benchmark, and determine the causal effects of different perturbations.
- Develop **imaging** and **visualization** tools to track and trace senescence—both at cellular and whole-body levels.
- Deploy tools, technologies and senolytics to **perturb**, demonstrate and validate senescence *in vivo.*

Cellular Senescence Network
Program Overview – An atlas of Cellular Senescence

NIH The Common Fund

A 4D Multi-modal Atlas will describe the distribution and functional attributes of senescent cells across a variety of tissues at single cell resolution and longitudinal timescales.



- **A searchable database that captures multi-omic, molecular signatures of senescent cells.**
- **Capture spatial relationships of senescent cells with other microenvironmental cell types and features.**
- **A taxonomy to classify cellular senescence.**

Cellular Senescence Network
A Transformative, Catalytic Proposal for Improving Health

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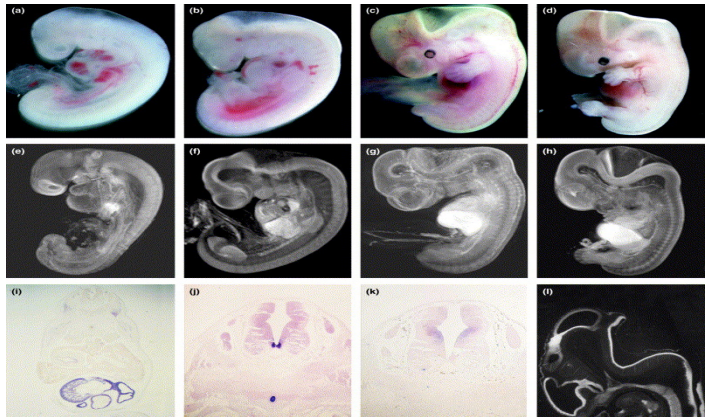
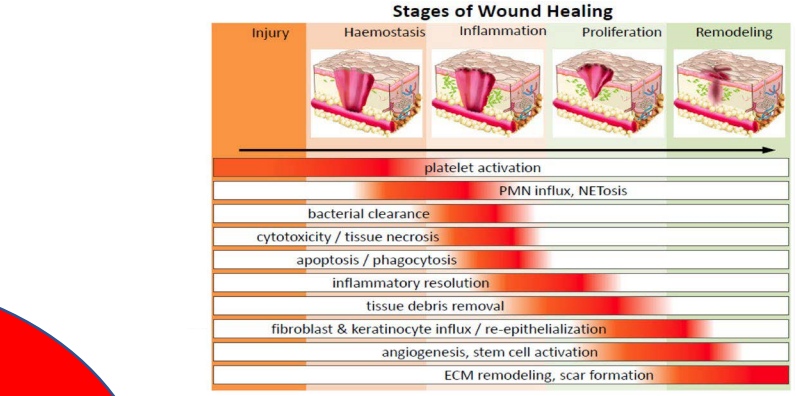


Development

CELL SENESCENCE ATLAS



Wound Healing

Multiple Chronic Diseases

Aging

Cellular Senescence Network
A Cross-cutting Proposal

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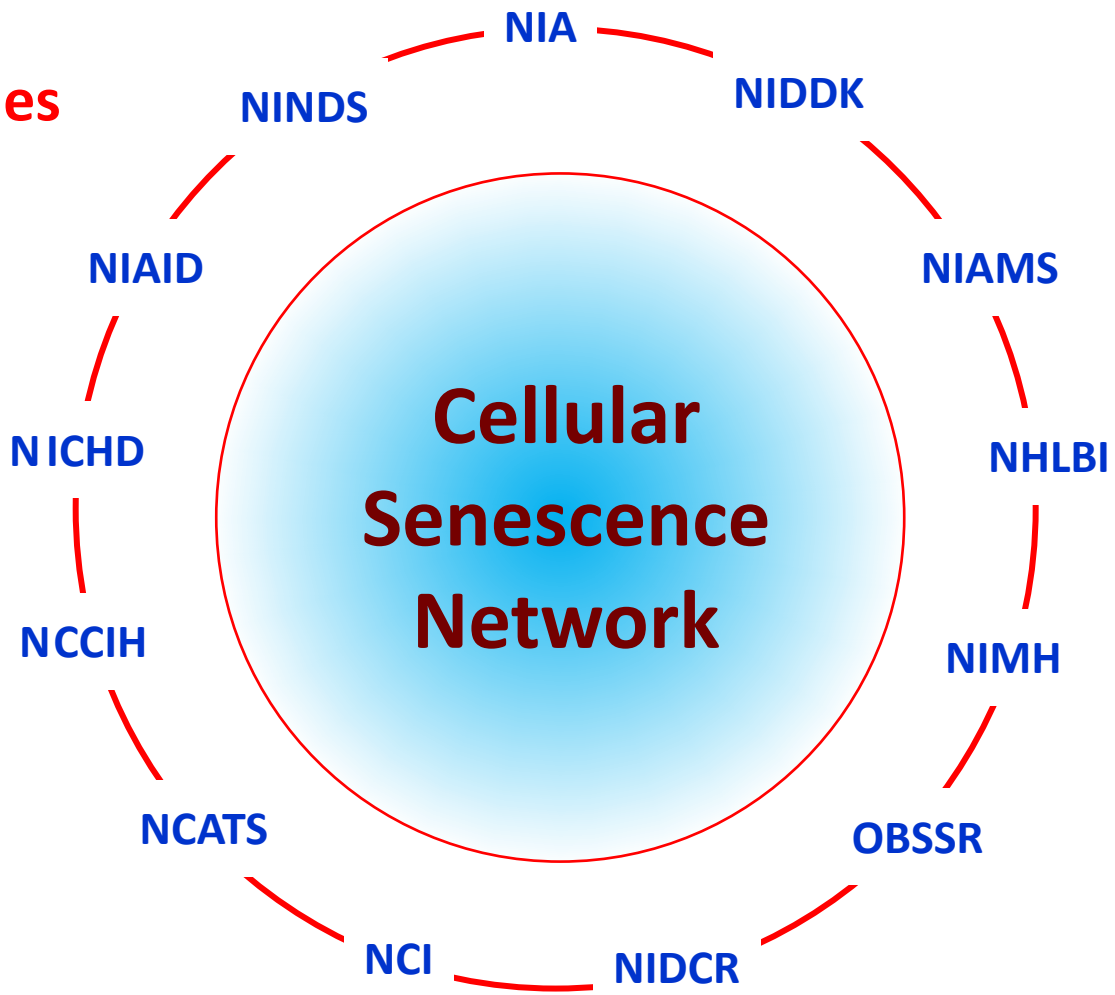

Health Disparities

Wound Healing

Environment

Immunity

Development

Gender

Chronic Diseases

Accelerated Aging

Cellular Senescence Network
Proposed Initiatives

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Initiative 1: Tissue Mapping Centers

- Each Center will have an administrative core and three research units: a Biospecimen Collection Unit, a Data Analysis and Computational Modeling Unit, and a Molecular, Cellular and Tissue Analysis Unit.

Initiative 2: Technology Development Projects

- Develop single cell technology to capture senescent cells--due to their large size and relative rarity; technologies to label and visualize senescent cells for fate mapping/lineage tracing and response to perturbations in vivo ; and immunotherapy approaches to eliminate senescent cells.
- Two RFA calls in Years 1 and 2 of the project

Initiative 3: Consortium Organization and Data Coordination Center

- Will serve as an organizational hub for the consortium
- Will leverage existing standards and analysis pipelines of a suitable single cell atlas data platform to ensure interoperability and sustainability

Cellular Senescence Network
Program Structure

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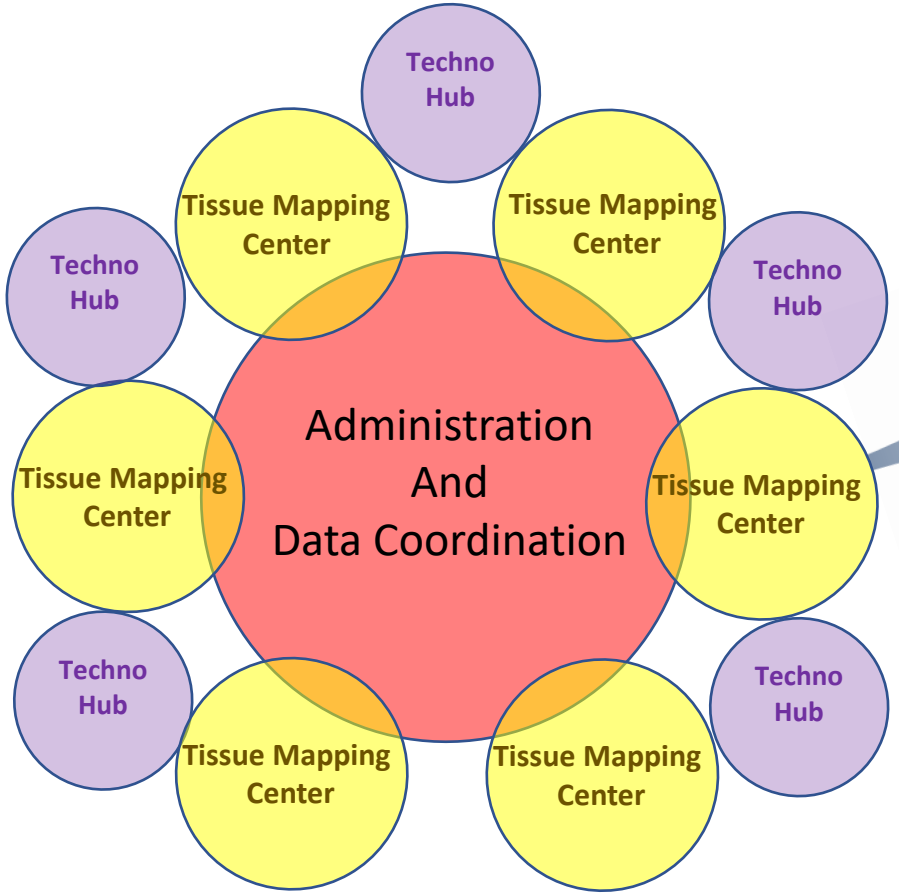
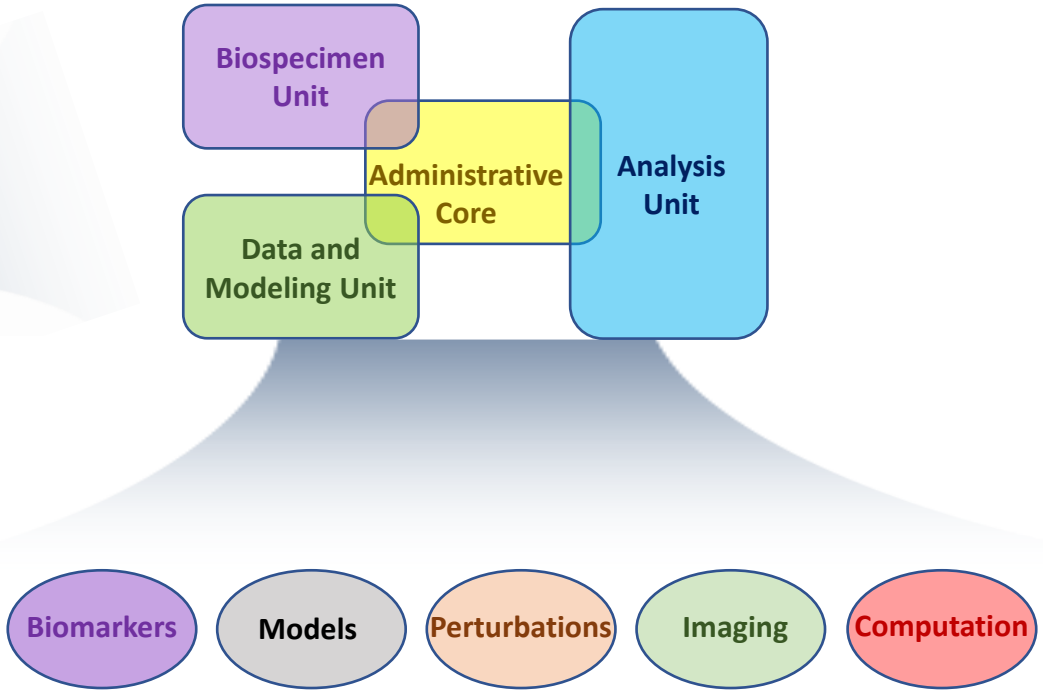


TISSUE MAPPING CENTER COMPONENTS



Cellular Senescence Network
Requested Budget for Phase 1

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Cellular Senescence Network (CSN)	Lead IC	FY22	FY23	FY24	FY25	FY26	Total
Initiative 1: Tissue Mapping Centers (6 Centers)	TBD	18	18	18	18	18	90
Initiative 2: Technology Development Projects (5-10 Projects)	TBD	3.75	7.5	8.75	10	5	35
Initiative 3: Administrative and Data Coordination Center	TBD	3.5	3.5	3.5	3.5	3.5	17.5
RMS: NIH staff salary, travel and organized workshops		0.35	0.35	0.35	0.35	0.35	1.75
TOTAL		25.6	29.35	30.6	31.85	26.85	144.25

Figures are in Million $

Cellular Senescence Network
Phase I Program Deliverables

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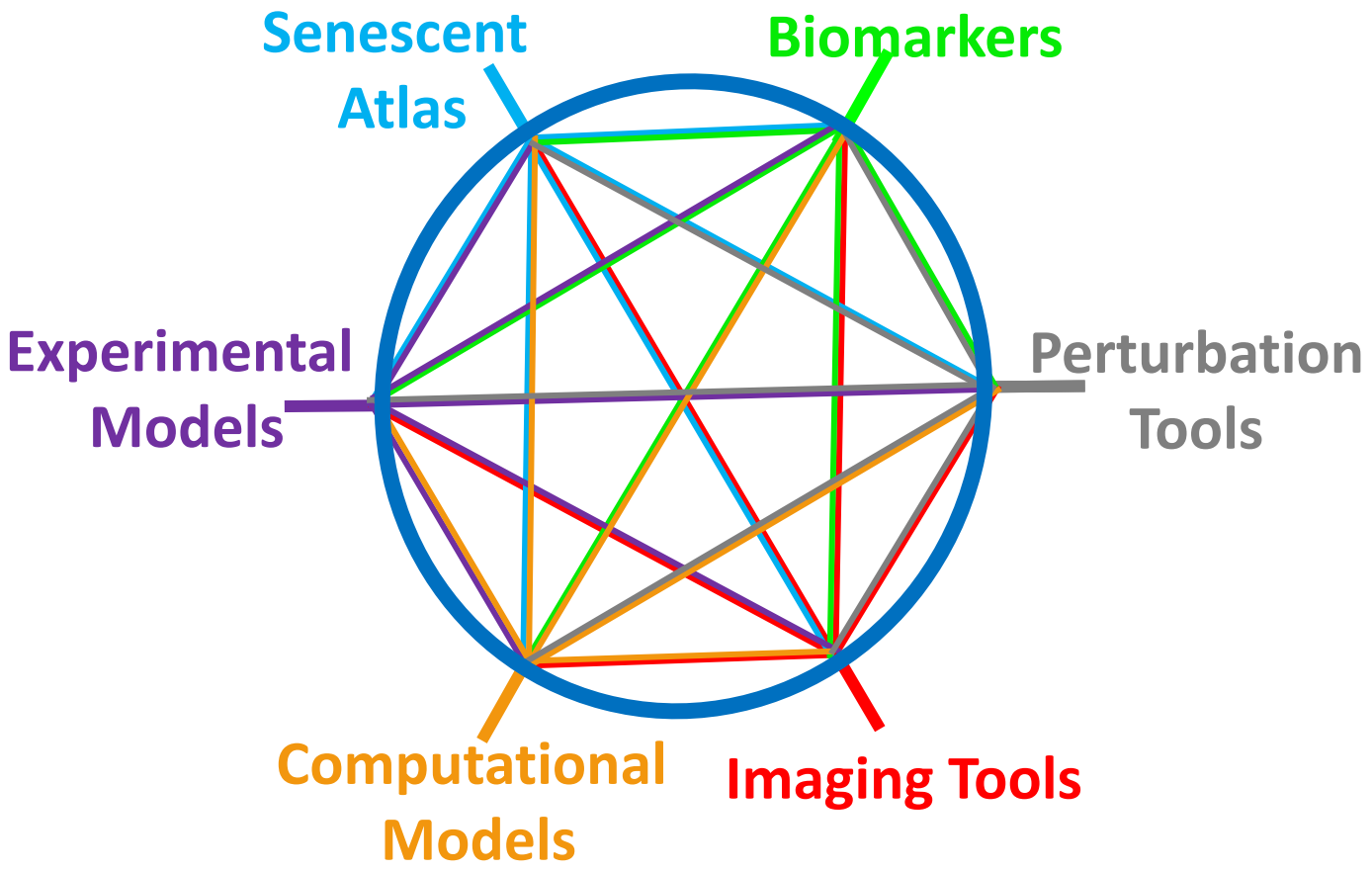

Depending on the assessment of successes, persistent roadblocks and emerging opportunities, a second stage of the program is anticipated to support studies to validate the significance of senescence in appropriate physiological systems.

Cellular Senescence Network
The NIH Working Group

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Inception: Nov 2019 Leadership Forum (Carter, Gibbons, Koroshetz, Sharpless, Hodes)

Input: RFI RM 20-014 plus three Think Tanks in April 2020 (43 total participants)

Co-Chairs:
Richard Hodes (NIA)
Ned Sharpless (NCI)
Dinah Singer (NCI)

Coordinators:
Felipe Sierra (NIA)
Kevin Howcroft (NCI)

Common Fund Program Leader:
Ananda Roy (OSC/OD)

Working Group Members:

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Andrew Bremer (NICHD)
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Janet Cyr (NIDCD)
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Zhigang (Peter) Gao (NIAAA)
Paige Green (NCI)
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Chyren Hunter (ORWH)
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Roger Little (NIDA)
Linnia Mayeenuddin (NCI)
Dan Miller (NINDS)
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Laura Rowland (NIMH)
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