Cellular Senescence Network (SenNet) Continuing Program

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Council of Councils
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National Institutes of Health
Office of Strategic Coordination–The Common Fund

OSC (Common Fund) – Cellular Senescence Network (SenNet) Continuing Program

Concept Clearance: Continuing/Stage 2 Common Fund Program

TITLE: Cellular Senescence Network (SenNet) Continuing Program

Objectives: Understand the biological relevance of senescence heterogeneity; Validate diverse senescence signatures in human biospecimens; and Inform senotherapeutic strategies for human health

Initiative 1: Define dynamic, organ-specific senotypes and advance pre-clinical model systems to test and validate senotherapeutic strategies

Initiative 2: Develop technologies, computational tools and multi-scale model systems to identify, characterize and predict the outcomes of modulating levels of senescent cells *in vivo*

Initiative 3: Generate and curate searchable Senescence Atlases of healthy and diseased tissues and organize the consortium and outreach efforts

Funds Available and Anticipated Number of Awards: $30M per year for ~17 meritorious awards (contingent upon funding availability)

Program Duration: 5 years

Council Action: Vote for approval of the concept for Cellular Senescence Network (SenNet) Program

NIH SenNet Management Team

Co-Chairs

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Program Coordinators

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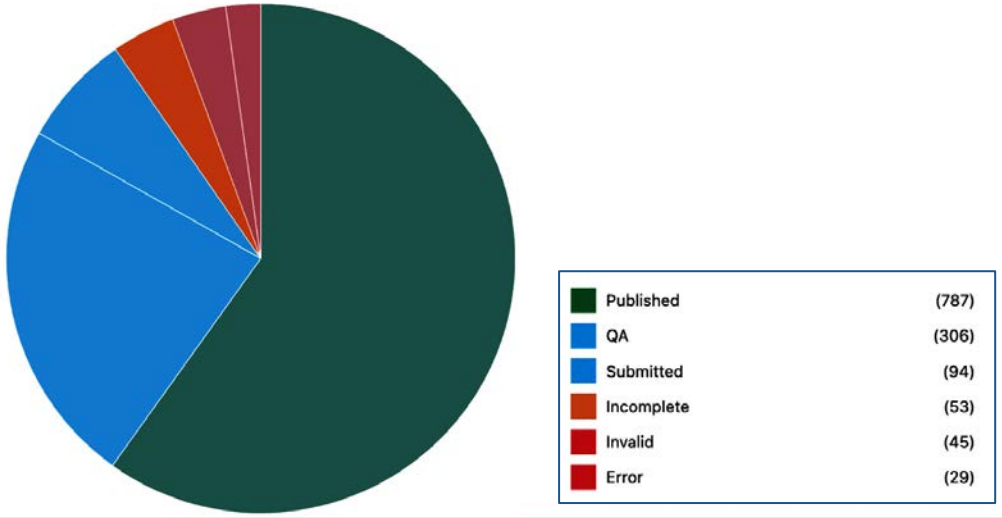
* Project Scientists

Background on Cellular Senescence

- **Durable cell-cycle arrest state with a pro-inflammatory, senescence-associated secretory phenotype (SASP)**
- **Senescent cells have varied biological roles in normal and disease states, including tumor suppression, embryonic development, tissue repair, and wound healing**
- **Accumulation of senescent cells contributes to the pathology of age-associated conditions, while elimination of senescent cells is associated with improved healthspan and lifespan in rodent models**
- **Senescent cells are rare, highly heterogeneous and the mechanisms responsible for senescence *in vivo* are not well understood**
- **NIH Common Fund launched the *Cellular Senescence Network (SenNet)* program to characterize cellular senescence in healthy aging**

Impact of SenNet Stage 1-Data

- **Over 1300 datasets generated across organs**
- **>780 datasets published**
- **153 protocols published**

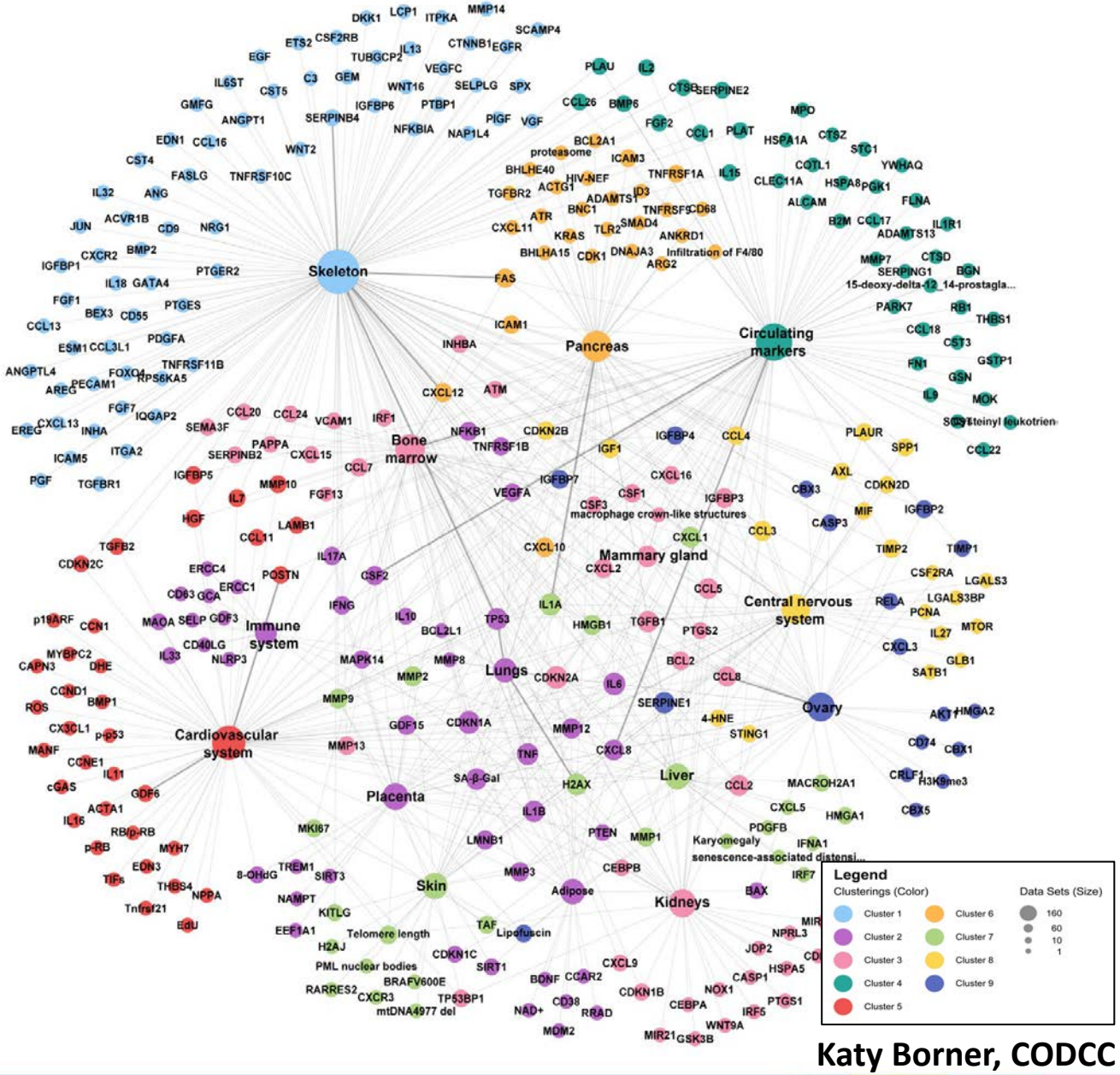


	10x Multiome	ATACseq	CosMx	GeoMx (NGS)	Histology	LC-MS	PhenoCycler	RNAseq	RNAseq (with probes)	Visium (no probes)	Visium (with probes)	Xenium	Grand Total
Adipose Tissue								**27**		**4**	**9**		**40**
Human										4	9		13
Mouse								27					27
Bone Marrow								**7**					**7**
Human								7					7
Brain		**1**	**3**	**1**				**17**		**122**			**144**
Human										122			122
Mouse		1	3	1				17					22
Heart					**82**			**48**					**130**
Human					82			48					130
Heart					**20**								**20**
Human					20								20
Large Intestine	**4**									**4**			**8**
Human	4									4			8
Liver	**20**			**47**				**26**			**21**		**114**
Human	20			47				2			21		90
Mouse								24					24
Lung	**8**				**95**	**128**	**6**	**128**	**11**	**12**			**388**
Human	8				95	128	6	120	11	12			380
Mouse								8					8
Lymph Node							**17**						**17**
Human							17						17
Muscle								**71**					**71**
Mouse								71					71
Other								**4**					**4**
Mouse								4					4
Ovary						**22**		**26**					**48**
Human						22		26					48
Pancreas					**180**			**12**	**30**		**40**	**32**	**294**
Human					180			12	30		40	32	294
Skin						**29**							**29**
Mouse						29							29
Grand Total	**32**	**1**	**3**	**48**	**377**	**179**	**23**	**366**	**41**	**142**	**70**	**32**	**1314**

Impact of SenNet Stage 1-Senescence Biomarkers Visualized

Organ and Biomarker Bi-modal Network

- Represents the connections between 15 human organ tissues and 327 biomarkers identified by SenNet.
- Extensive heterogeneity-few biomarkers are associated with more than 10 organs
- Senotype: A conceptual framework to define heterogeneous senescent cells that are biological context- and environmental factor-dependent



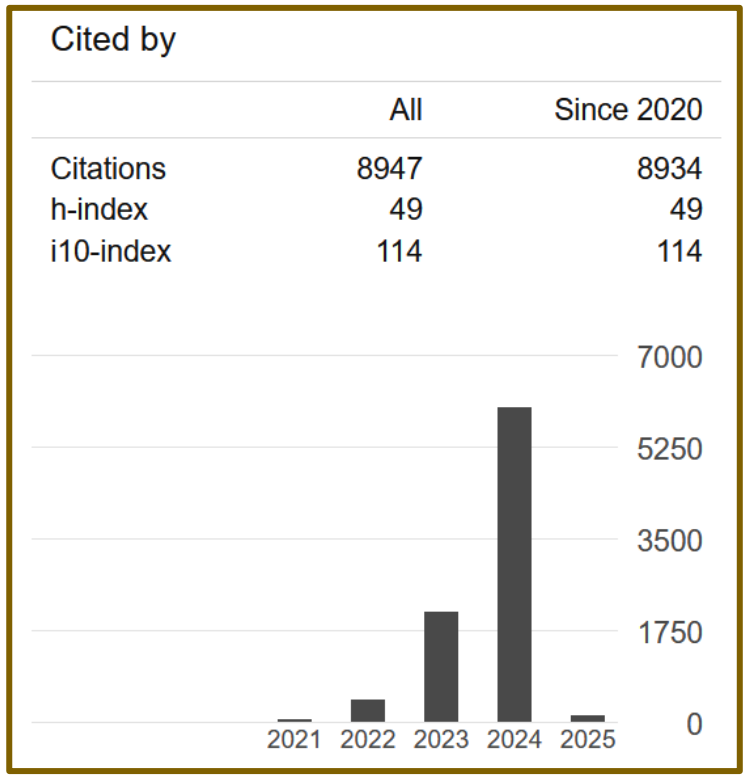
Katy Borner, CODCC

Impact of SenNet Stage 1-Development of Novel Tools and Technologies to Facilitate Senescence Characterization

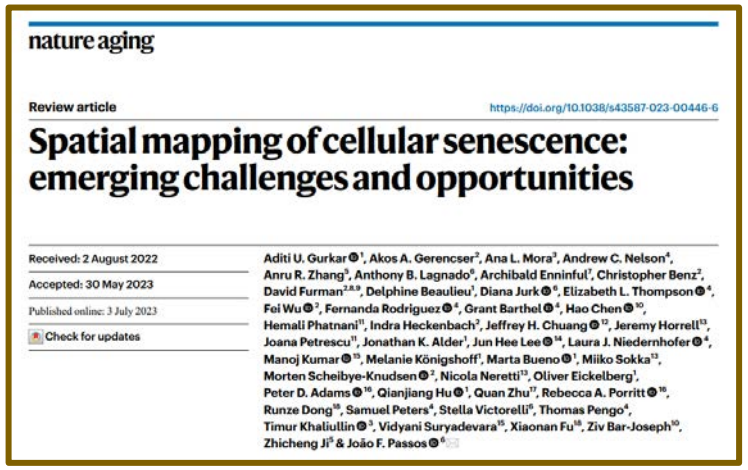
- **^{18}F-PyGal radiotracer:** *in vivo* β-Gal detection with PET/MRI imaging (Stanford)
- **Pixel-Seq:** Integrated single-cell spatial transcriptomic and proteomic assay for mapping senescent cells (UWA) *Cell*. 2022
- **Seq-scope:** High resolution spatial transcriptomics for detecting rare cells (UMI)
- **SenoQuant:** A fast and precise analytical tool to measure senescence markers in human tissue (Mayo)
- **FICTURE:** Resolving segmentation issues that are prevalent in senescence research (UMI) *Nat Methods*. 2024
- **ScResolve:** Recovery of single cell expression from data acquired at the multicellular level (Carnegie Mellon) *Cell Rep Methods*. 2024

Impact of SenNet Stage 1-Publications

288 publications to date



SenNet WG Publications


nature aging

Review article https://doi.org/10.1038/s43587-023-00446-6

Spatial mapping of cellular senescence: emerging challenges and opportunities

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Check for updates

Aditi U. Gurkar[1], Akos A. Gerencser[2], Ana L. Mora[3], Andrew C. Nelson[4], Anru R. Zhang[5], Anthony B. Lagnado[6], Archibald Enninful[7], Christopher Benz[2], David Furman[2,8,9], Delphine Beaulieu[1], Diana Jurk[6], Elizabeth L. Thompson[4], Fei Wu[2], Fernanda Rodriguez[4], Grant Barthel[4], Hao Chen[10], Hemali Phatnani[11], Indra Heckenbach[2], Jeffrey H. Chuang[12], Jeremy Horrell[13], Joana Petrescu[11], Jonathan K. Alder[1], Jun Hee Lee[14], Laura J. Niedernhofer[4], Manoj Kumar[15], Melanie Königshoff[1], Marta Bueno[1], Miiko Sokka[13], Morten Scheibye-Knudsen[2], Nicola Neretti[13], Oliver Eickelberg[1], Peter D. Adams[16], Qianjiang Hu[1], Quan Zhu[17], Rebecca A. Porritt[16], Runze Dong[18], Samuel Peters[4], Stella Victorelli[6], Thomas Pengo[4], Timur Khaliullin[3], Vidyani Suryadevara[15], Xiaonan Fu[18], Ziv Bar-Joseph[10], Zhicheng Ji[5] & João F. Passos[6]


nature reviews molecular cell biology https://doi.org/10.1038/s41580-024-00738-8

Expert recommendation Check for updates

SenNet recommendations for detecting senescent cells in different tissues

Vidyani Suryadevara[1], Adam D. Hudgins[2], Adarsh Rajesh[3], Alberto Pappalardo[4], Alla Karpova[5], Amit K. Dey[6], Ann Hertzel[7,8], Anthony Agudelo[9,10], Azucena Rocha[9,10], Bikem Soygur[11], Birgit Schilling[11], Chase M. Carver[12,13], Cristina Aguayo-Mazzucato[14], Darren J. Baker[13,15], David A. Bernlohr[7,8], Diana Jurk[12,13,16], Dilyana B. Mangarova[1], Ellen M. Quardokus[17], Elizabeth Ann L. Enninga[18], Elizabeth L. Schmidt[7,8], Feng Chen[5], Francesca E. Duncan[11,19], Francesco Cambuli[20], Gagandeep Kaur[21], George A. Kuchel[22,23], Gung Lee[12,13], Heike E. Daldrup-Link[1], Helene Martini[12,13], Hemali Phatnani[20,24], Iman M. Al-Naggar[22], Irfan Rahman[21], Jia Nie[25], João F. Passos[12,13], Jonathan C. Silverstein[26], Judith Campisi[11,47], Julia Wang[5], Kanako Iwasaki[14], Karina Barbosa[3], Kay Metis[26], Kerem Nernekli[1], Laura J. Niedernhofer[7,8], Li Ding[5], Lichao Wang[22,23], Lisa C. Adams[1], Liu Ruiyang[5], Madison L. Doolittle[12,13,27], Marcos G. Teneche[3], Marissa J. Schafer[12,13,16], Ming Xu[22,23], Mohammadjavad Hajipour[1], Mozhgan Boroumand[6], Nathan Basisty[6], Nicholas Sloan[28], Nikolai Slavov[10,29,30,31], Olena Kuksenko[28], Paul Robson[32,33], Paul T. Gomez[12,13], Periklis Vasilikos[34], Peter D. Adams[3], Priscila Carapeto[14], Quan Zhu[35], Ramalakshmi Ramasamy[32], Rolando Perez-Lorenzo[4], Rong Fan[26], Runze Dong[27,38], Ruth R. Montgomery[26], Sadiya Shaikh[21], Sanja Vickovic[20,39,40,41], Shanshan Yin[3], Shoukai Kang[37], Sonja Suvakov[12,42], Sundeep Khosla[12,13,27], Vesna D. Garovic[16,42], Vilas Menon[24,43], Yanxin Xu[44,45,46], Yizhe Song[5], Yousin Suh[2,34], Zhixun Dou[44,45,46] & Nicola Neretti[9,10]

Stage 2 Planning Activities

Focus group surveys involving Consortium PIs and NIH WG members
External Experts meetings
Program Consultants meetings

Executive Summary

- Define biological relevance of senescence heterogeneity with mechanistic understanding of cellular senescence to guide senotherapeutic strategies
- Develop and expand pre-clinical model systems for validation and understanding of senescence physiology and pathology
- Need to study senescence in the context of disease
- Develop cutting-edge tools including AI/ML for senescence signature prediction, validation and therapeutic approaches
- Enhance data integration and interactions between SenNet and other single-cell consortia including HTAN, HuBMAP, and SMaHT

Stage 2 Planning Activities-Portfolio Analysis (2015-2024)

SenNet Stage 1 topics Senescence, single-cell spatial tissue mapping	**29 awards (22 SenNet)**
SenNet Stages 1 & 2 topics Senescence, single cell biomarker heterogeneity	**17 awards (7 SenNet)**
SenNet Stage 2 topics Senescence, single cell biomarker heterogeneity and animal *or* preclinical models	**5 awards (2 SenNet)**
SenNet Stage 2 topics Senescence, single-cell heterogeneity and computational models *or* artificial intelligence	**2 awards**

Continued SenNet Investment is Needed

- To understand the extent of heterogeneity and the biology of senescence at the single-cell level for normal and disease states
- To uncover and validate biomarkers/molecular targets for senotherapeutics in relevant pre-clinical models
- To develop novel tools, technologies, including harnessing the predictive power of AI/ML to accelerate the discovery of senescence targets
- To integrate Stage 1 tissue mapping efforts with Stage 2 data to generate searchable Atlases of Senescence

SenNet Stage 2 Goals and Initiatives

SenNet Stage 2 Goals

- Understand the biological relevance of senescence heterogeneity
- Identify and validate diverse senescence signatures in human biospecimens
- Inform senotherapeutic strategies for human health

SenNet Stage 2 Initiatives

Initiative 1: Discovery, Mapping and Validation Centers (DMVCs; U54)

Initiative 2: Senescence Technology Projects (SenTecs; UG3/UH3s)

Initiative 3: Data Coordination Integration and Organizational Center (DCIOC; U24 or UM1)

Initiative 1
Discovery, Mapping and Validation Centers (DMVCs; U54)

Leverage state-of-the-art, spatial, single-cell technologies to identify and functionally characterize tissue-specific senotypes in health and disease conditions

Deliverables

- Define dynamic, organ-specific senotypes and their function in health and disease conditions
- Advance pre-clinical model systems to test and validate senotherapeutic strategies to improve health and alleviate disease conditions

Initiative 2
Senescence Technology Projects (SenTecs; UG3/UH3)

Employ an integrated systems biology approach that leverages several scientific disciplines to address the new complexity of senescence to advance current understanding of the biological relevance of senescence heterogeneity

Deliverables

- Develop technologies and multi-scale model systems to determine cellular senescence-associated outcomes *in vivo*
- Develop computational tools, including AI/ML to identify, characterize and predict the outcomes of modulating levels of senescent cells in both aging and age-associated conditions *in vivo*

Initiative 3
Data Coordination Integration and Organizational Center (DCIOC; U24 or UM1)

Integrate Stage 1 tissue mapping efforts with Stage 2 data to generate dynamic, searchable Atlases of senotypes representing the spatial distribution of senescence signatures across tissues and lifespan, and in health and disease conditions

Deliverables

- Generate and curate Senescence Atlases of healthy and diseased tissues with tools to search and manipulate SenNet data
- Initiate, implement and manage cross-consortium and outreach activities for synergistic collaborations and enhance SenNet output and visibility to the broader research community

SenNet Stage 2 Proposal Meets Common Fund Criteria

- **Novel:** Biological and computational approaches to interrogate the functional outcomes of senescence heterogeneity in a multi-tissue, multi-center and multi-technology setting
- **Transformative:** Potential for paradigm shifting senescence research and senotheropeutic strategies
- **Catalytic:** Advances will accelerate tissue- and organ-specific senescence research across human lifespan and in disease conditions
- **Goal-driven:** Dynamic, searchable atlases of senotype biology across human lifespan, innovative pre-clinical model systems, multi-scale and computational tools and methods, and cross-consortium and outreach activities to enhance SenNet impact
- **Synergistic:** Advance the missions across NIH ICOs in multiple diseases and conditions

Proposed SenNet Stage 2 Budget

	Lead IC	FY26	FY27	FY28	FY29	FY30
Initiative 1 – SenNet Discovery, Mapping and Validation Centers (~8 DMVCs; U54)	NIA	$20M	$20M	$20M	$20M	$20M
Initiative 2 – SenNet Technology Projects (~8 SenTecs; UG3/UH3)	NCI	$6M	$6M	$6M	$6M	$6M
Initiative 3 – SenNet Data Coordination Integration and Organization Center; (1 DCIOC; U24 or UM1)	NCI	$3.4M	$3.4M	$3.4M	$3.4M	$3.4M
RMS – for NIH staff salary and travel; NIH-organized workshops		$0.6M	$0.6M	$0.6M	$0.6M	$0.6M
TOTAL		**$30M**	**$30M**	**$30M**	**$30M**	**$30M**

Anticipated Deliverables

- Curated, searchable atlases of senotype biology in health and disease
- Improved animal and relevant pre-clinical models to accelerate senotherapeutic interventions
- Innovative tools and technologies including AI/ML approaches to predict the biological outcomes of senescence heterogeneity and modulation of senescent cells *in vivo*

Council Action:
Vote for approval of the concept for Cellular Senescence Network (SenNet) Continuing Program

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