Concept Clearance — Cellular Senescence Network (SenNet) Program
Proposal for Continued Common Fund Support

I.   Status Report of the SenNet Program

The three major SenNet initiatives that make up Stage 1 and their accomplishments are as follows:

Tissue Mapping Centers (TMCs; U54s)

Thirteen TMCs serve as the data generators for SenNet and to date have: **(1)** analyzed over 1,000 tissue samples; **(2)** published 650 datasets on the SenNet Data Portal; **(3)** submitted over 350 data sets currently queued for quality assurance and ingestion and **(4)** revealed the extensive heterogeneity of senescent cells with 327 biomarkers covering 15 human organs; **(5)** produced 14 senescence atlases and biology covering eight tissues across the lifespan and **(6)** published over 258 manuscripts and successfully negotiated a *Cell* publication package currently underway.

Technology Development and Application (TDAs; UG3/UH3)

SenNet's 11 TDAs are developing technologies, many of which are published or on their way to publication. Novel technologies include the development of: (1) **^{18}F-PyGal radiotracer** to detect senescent cells *in vivo* using PET/MRI; (2) **Pixel-Seq**, a single-cell spatial transcriptomic and proteomic assay for mapping senescent cells; (3) **Seq-scope**, a high resolution spatial transcriptomics method for detecting rare, senescent cells; (4) **SenoQuant**, an analytic tool to quantitate senescent cells in human tissues; (5) **FICTURE** for resolving segmentation issues that are prevalent in senescence research and (6) **ScResolve** for recovery of single cell expression from data acquired at the multicellular level.

The Consortium Organization and Data Coordination Center (CODCC; U24)

SenNet's organization and data coordinating center is responsible for successfully: **(1)** building the consortium infrastructure; **(2)** organizing two consortium-wide meetings each year; **(3)** organizing and supporting SenNet's ten working groups; **(4)** coordinating and running an internal SenNet data club for members; **(5)** ingesting, securing and storing SenNet's data, protocols and analytical tools; and **(6)** organizing and supporting the cross-consortium benchmarking project.

II.   SenNet Stage 2 Program Proposal

The overarching goal of Stage 2 is to understand the biological consequences of the extensive senescence heterogeneity uncovered in Stage 1, including the identification and characterization of tissue specific senescent cells, or senotypes, in human biospecimens where vulnerabilities can be identified to inform and facilitate the development of effective, precision senotherapeutic strategies that improve health outcomes and mitigate chronic disease conditions. The three initiatives described below are proposed to anchor the Stage 2 of the SenNet consortium.

Overview of Proposed Initiatives and Deliverables

Initiative 1: SenNet Discovery and Validation Centers (DVCs; U54s) will define tissue specific senotypes and their associated biological functions with the ultimate objective of guiding senotherapeutic strategies. Stage 1 efforts in SenNet have extended the landscape of senescence heterogeneity across all 18 tissues examined, setting the stage for Stage 2 DVCs to characterize tissue-specific, pleiotropic senotypes and in doing so provide the following deliverables: (1) Define dynamic, organ-specific senotypes and their function in health and disease conditions and (2) 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) will develop new, innovative tools and technologies that consider the complex nature of senescence uncovered in Stage 1 to facilitate identification, characterization and targeting of senotypes *in vivo.* Deliverables expected from this initiative include: (1) Develop technologies and multi-scale model systems to determine cellular senescence-associated outcomes *in vivo* and (2) 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: SenNet Data Coordination, Integration and Organizational Center (DCIOC; U24 or UM1) will integrate Stage 1 tissue mapping efforts with Stage 2 data to generate Atlases of Senescence incorporating the spatial distribution of senescence biomarkers from Stage 1 with biological and functional data generated in Stage 2 across tissues in health, lifespan and age-associated diseases. The DCIOC will also serve as the organizational hub for SenNet in managing all cross consortium and outreach activities. Deliverables proposed are: (1) Generate and curate searchable Senescence Atlases of healthy and disease state tissues equipped with tools to search and manipulate SenNet data and (2) Initiate, implement and manage all cross-consortium and outreach activities to afford synergistic collaborations, enhance SenNet output, and visibility of SenNet to the broader research community.

Stage 2 BUDGET SUMMARY

	Lead IC	FY26	FY27	FY28	FY29	FY30
Initiative 1 — SenNet Discovery and Validation Centers (DVCs; U54)	NIA	$20M	$20M	$20M	$20M	$20M
Initiative 2 — SenNet Senescence Technology Projects (SenTecs; UG3/UH3)	NCI	$6M	$6M	$6M	$6M	$6M
Initiative 3 — SenNet Data Coordination Integration and Organization Center; (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