CELLULAR SENESCENCE NETWORK (CSN)--A COMMON FUND PROPOSAL

Background. Senescence is a programed cellular response to damage. While senescent cells can have beneficial consequences in some contexts, the accumulation of senescent cells with age is thought to underlie a variety of chronic diseases. Thus, senescent cells – and their regulation – have received substantial attention recently. Elimination of senescent cells holds a significant promise for betterment of human health. In addition, characterizing cellular senescence in tissues and cells can offer insights on human health, disease, and lifespan, including the known influence of sex/gender and social determinants. However, the considerable heterogeneity of senescent cells represents an important barrier for the development of universal interventions.

Program Goal. To identify and functionally characterize the heterogeneity of senescent cells across multiple tissues in human health.

Proposed Initiatives: The proposed initiatives are based on the input and recommendations gathered from Request for Information (RFI) responses and targeted workshops.

- 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. The primary objective is acquisition and characterization of biospecimens at high resolution state-of-the-art molecular, cellular, and tissue-levels, to construct tissue maps of cellular senescence, both at the cellular and secretome levels for at least 2 tissues and paired biofluids, with respect to variables including developmental stage, healthy aging, sex and gender, nature of senescence inducer (if known), and relevant interventions.
- 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.
- Consortium Organization and Data Coordination Center (CODCC): The Center will serve as an organizational hub for the consortium. It will also develop controlled access workspaces for consortium working groups as well as a public portal for access by the scientific community to consortium generated resources. *An overriding priority for the CODCC is to leverage the existing standards and analysis pipelines of a suitable single cell atlas data platform to ensure interoperability and sustainability.*

Deliverables:

1. Atlas of cellular senescence and the Senescence Associated Secretory Phenotype in multiple human tissues, under a variety of physiological and developmental conditions;

2. Development of novel tools, technologies & biomarkers to identify heterogenous senescent cells into discreet subtypes and unite the field with a common taxonomy/terminology.

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.

Budget: The total requested phase 1 budget for 5 years is $**144.25M**.

Cellular Senescence Network (CSN)	Lead IC	FY22	FY23	FY24	FY25	FY26	Total
Initiative 1: Tissue Mapping Centers (6 Awards)	**TBD**	**18**	**18**	**18**	**18**	**18**	**90**
Initiative 2: Technology Development Projects (5-10 awards)	**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**