

# Aging, Cancer-Initiating Cells, and Cancer Development

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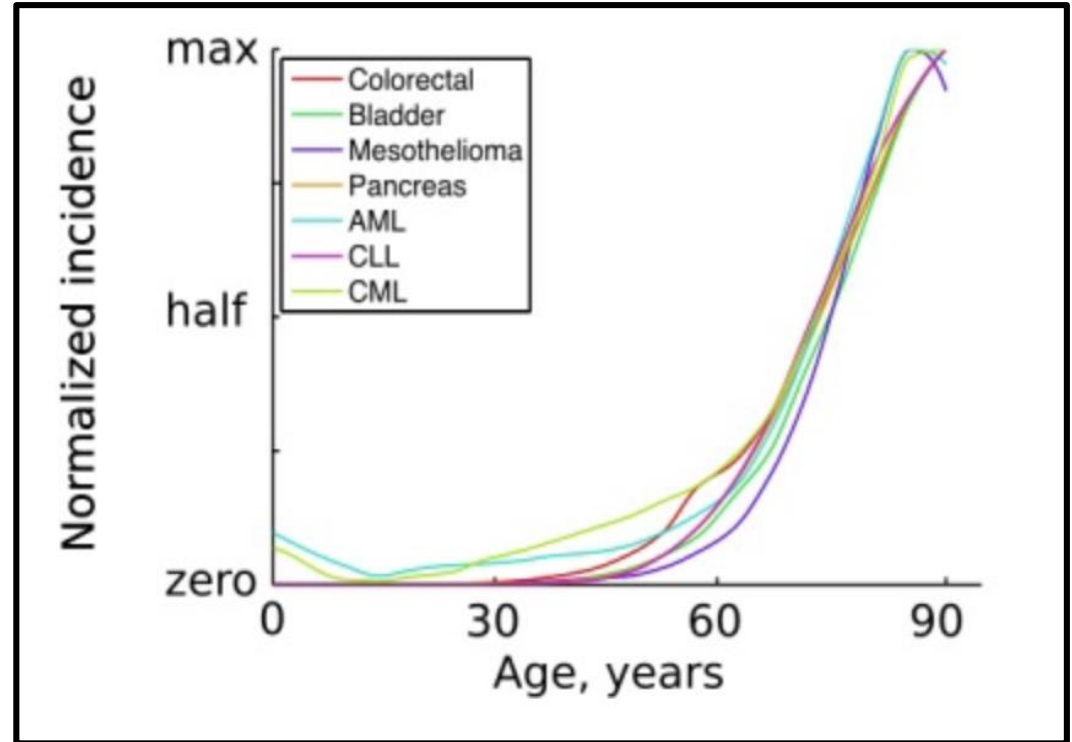
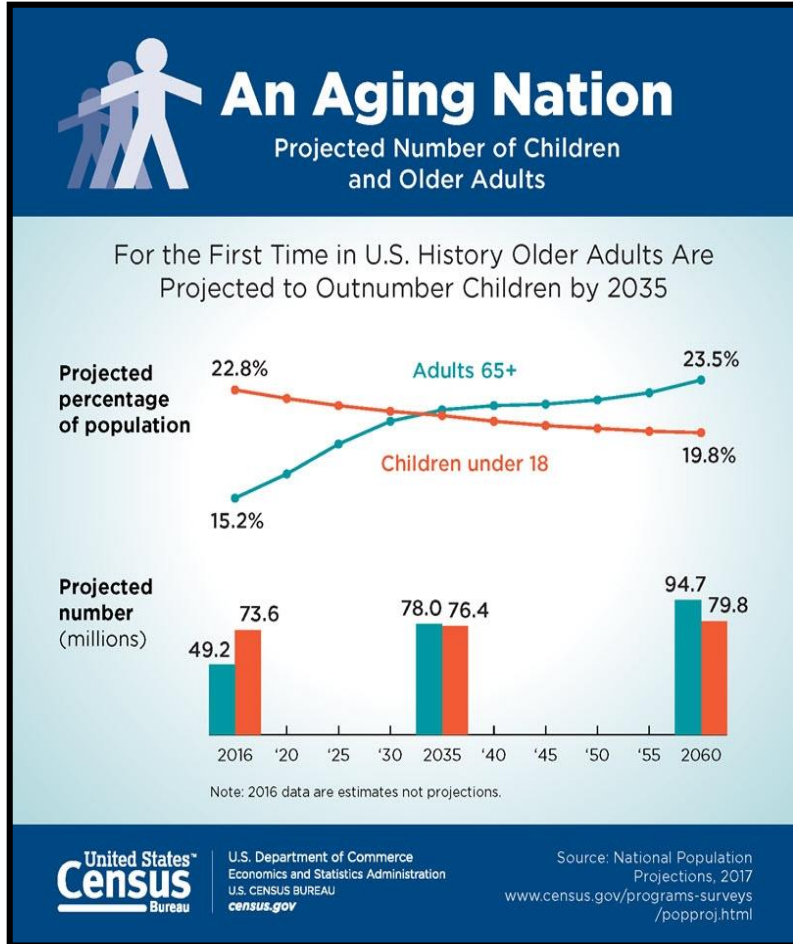
*Rebecca Fuldner*

The **overarching goal** of this joint NCI-NIA concept is to support collaborative studies, between cancer and aging researchers, that address limited understanding of mechanistic factors and cellular interactions during aging that contribute to cancer initiation

**This Concept Proposes:**

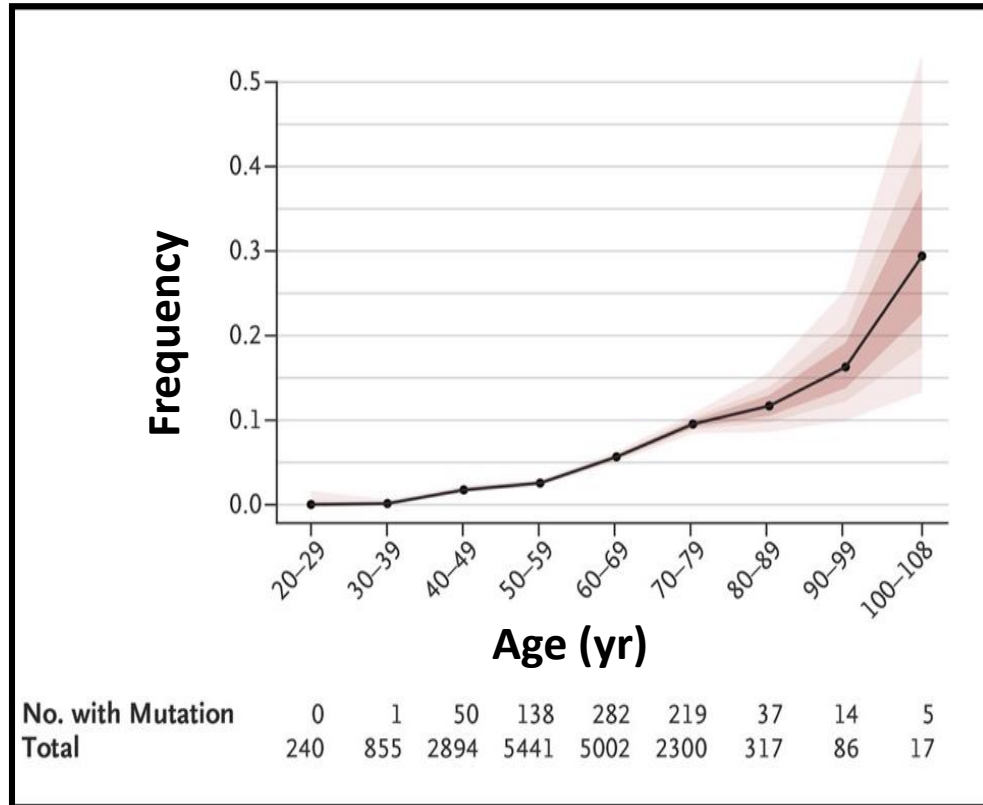
- RFA – NCI set aside \$2M/year, 3-4 applications
- Cooperative Agreement U01 grant mechanism
- Joint NCI-NIA program (paired funds)

# Significance



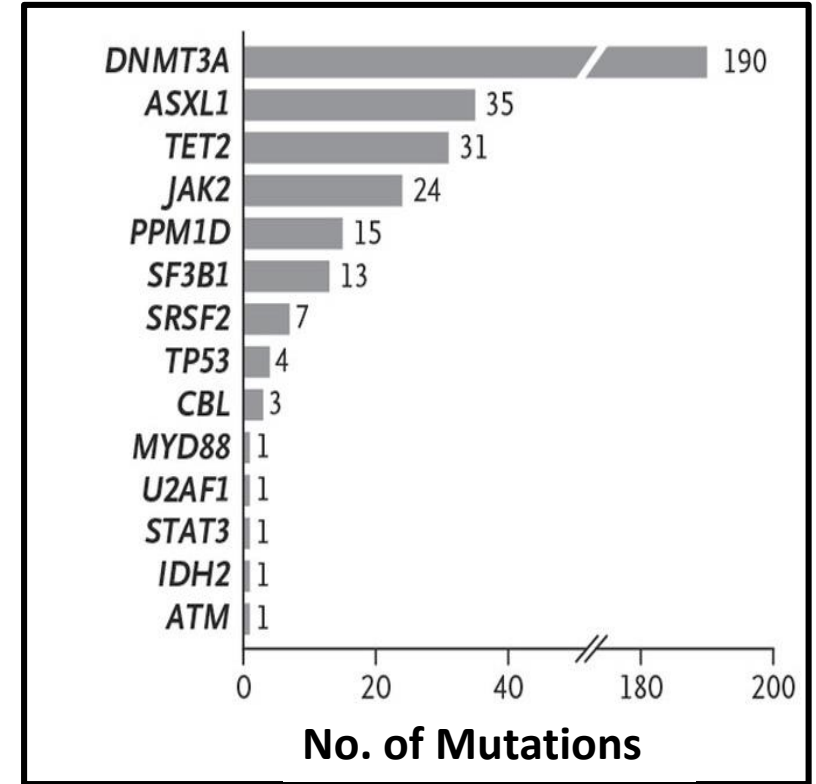
Rozhok&DeGregori, eLife 2019

# Age-related somatic mutations in adult cells are common



Jaiswal S et al., N Engl J Med 2014

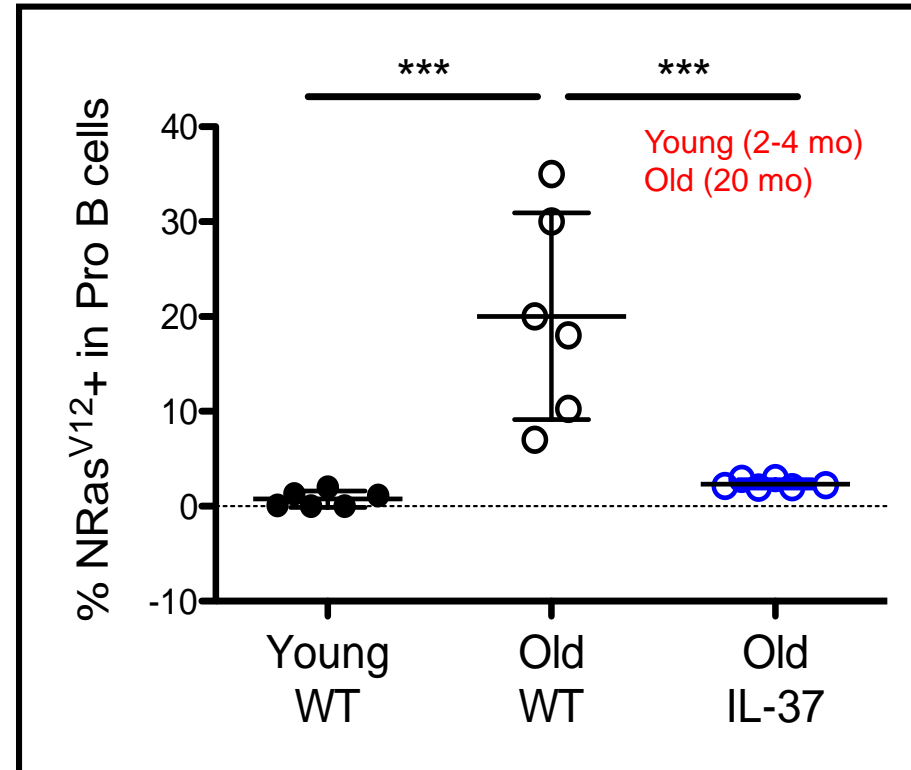
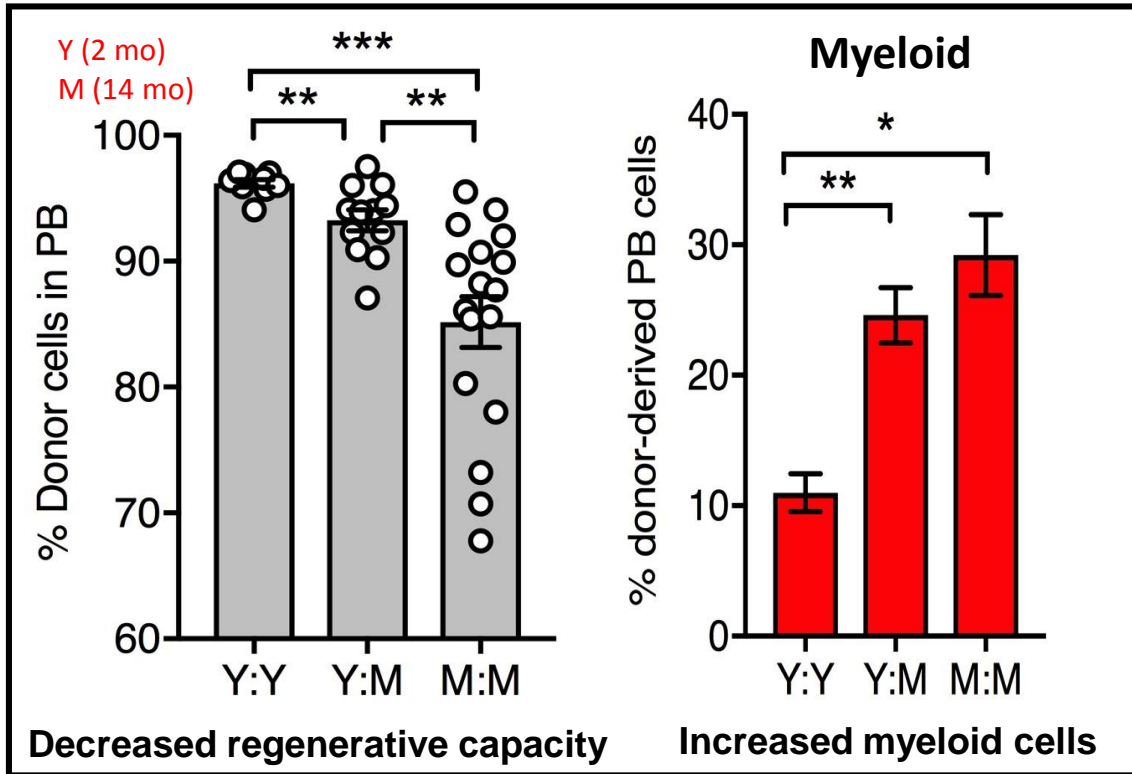
n=17,000



Genovese G et al.; N Engl J Med 2014

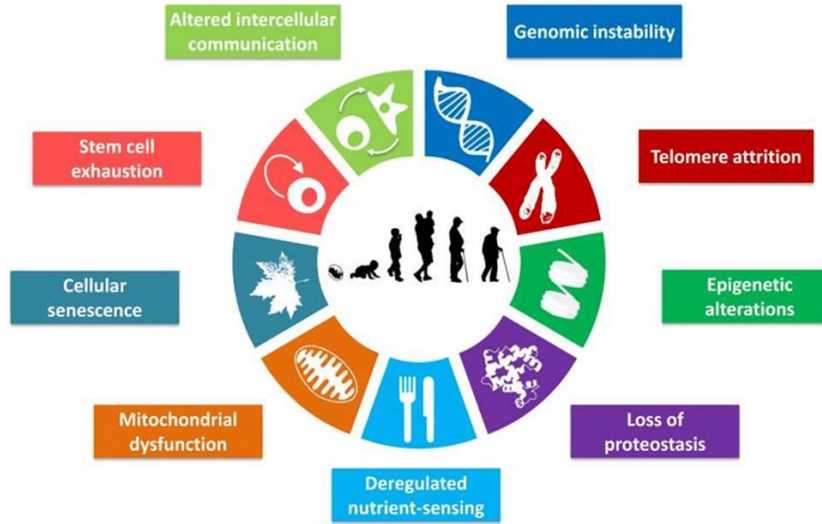
n=13,000

# Age impacts adult stem cells clonal expansion and cancer initiation

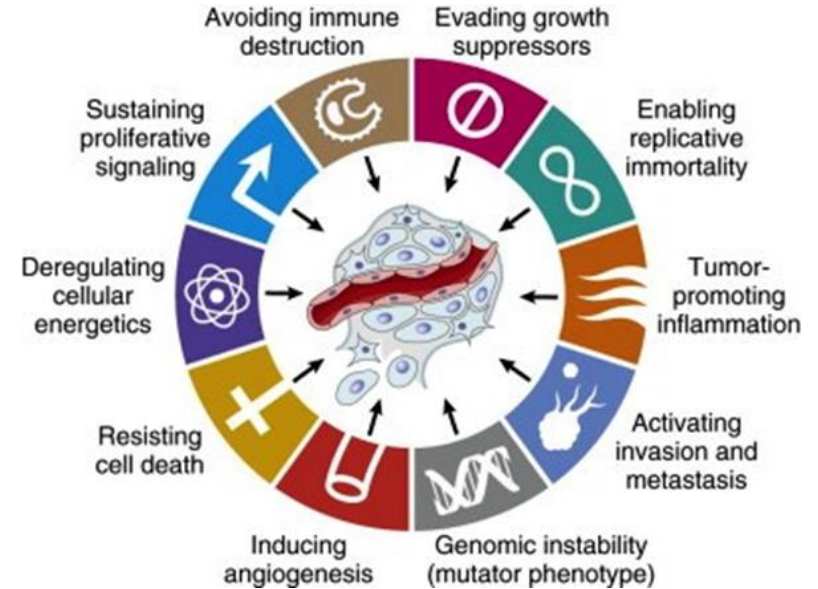


# “Onco-Aging” and cancer initiation

## Hallmarks of Aging



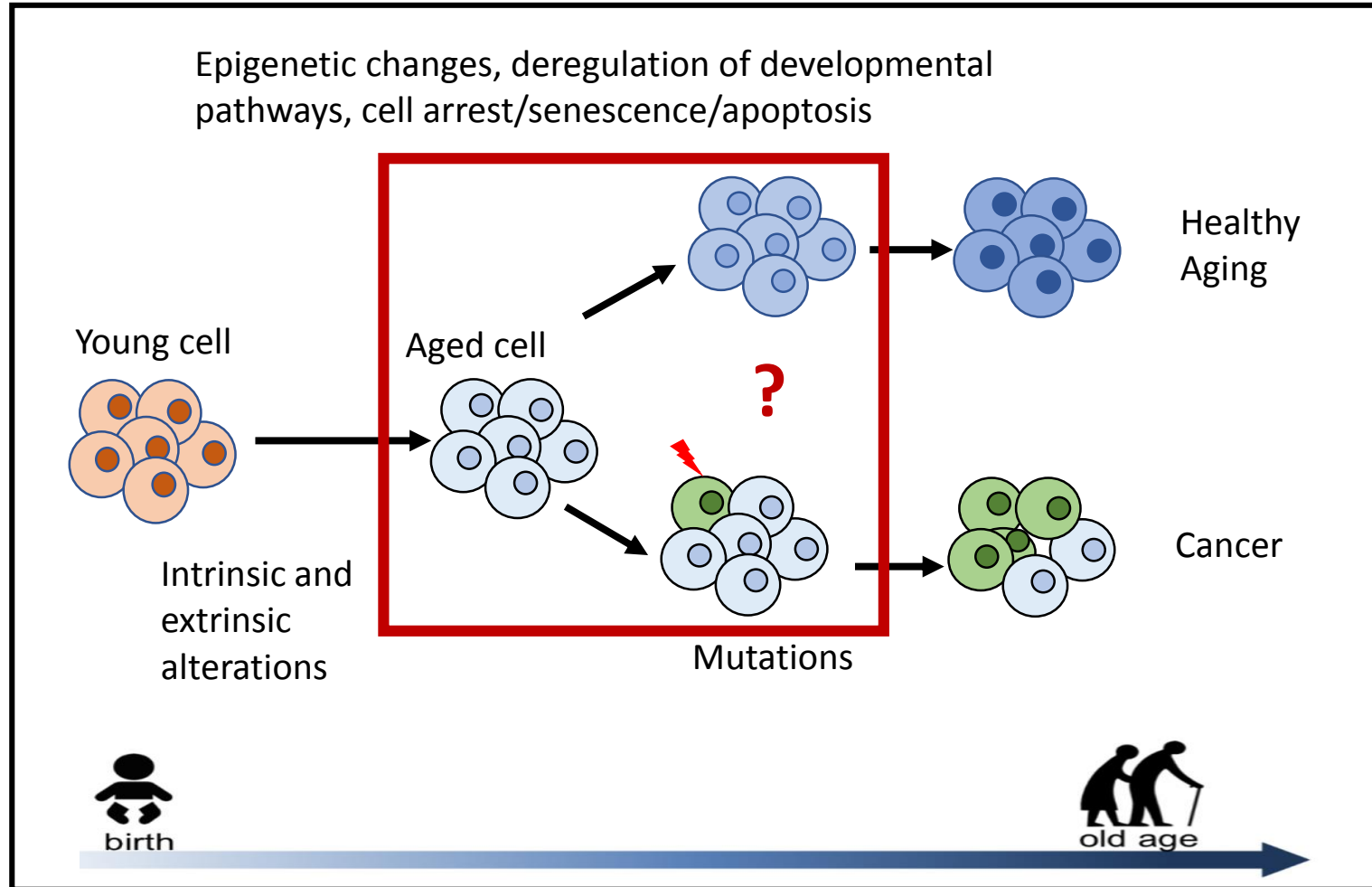
## Hallmarks of Cancer



### Common

- Metabolism/Mitochondrial Dysfunction
- Deregulated Energetics
- Altered Proteostasis
- Inflammation
- Epigenetic Alterations
- Genomic Instability
- Cellular Senescence/Resisting Cell Death

# Concept Overview: what is the mechanism of cancer initiation in an aged cell?



# Portfolio Analysis

- A recent portfolio analysis (from FY2010-FY2020) using “cancer,” and “aging” as keywords identified 251 awarded RO1 grants (NCI -134, NIA -117)
- Majority of NCI grants are focused on investigating mutations, DNA damage and inflammation while NIA grants are more focused on longevity, homeostasis, senescence and metabolism
- Only a small portion (11 NCI, 4 NIA) is relevant to this proposal and focused on mechanisms of aging and cancer development
- There is no current FOA supporting grants or supplements for this research focus



# Cancer and Aging Forums - Assessing Gaps and Needs -

- Workshop: Joint NIA/NCI Aging and Transformation in Stem Cells, May 1-2, 2019
- Roundtable Discussion: American Association for Cancer Research meeting (AACR) March 29 - April 3, 2019
- Symposium: Stem Cells and Regenerative Medicine hosted by the National Academy of Sciences (NAS) March 14, 2019

## Identified gaps and needs:

- Lack of collaboration between cancer and aging investigators
- Limited understanding of how aging leads to cancer development
- Need to establish appropriate models and standards for this field
- Difficult access to aged specimens

# Purpose of the RFA

## Opportunity:

Develop close scientific interactions between aging and cancer researchers that can help identify the aging mechanisms that promote cancer initiation

## Goal:

- Expand our limited understanding of age-driven mechanistic factors and cellular interactions that contribute to cancer initiation in aged cells
- Establish standards for assays
- Develop new or improved aging models to study cancer initiation

# Examples of research areas

Multidisciplinary projects must be focused on the mechanistic understanding of the aged-related factors contributing to cancer initiation

- Identifying novel age-related genes and proteins, epigenetic modifications and/or metabolomic changes that promote cancer initiation
- Identifying roles of senescence and novel age-related nonautonomous factors including those of the niche and inflammaging that regulate cancer initiation
- Understanding how age-related factors are interrelated
- Developing new or unique age-related cancer models to study aging and their niches that lead to oncogenesis. Studies may include cell models developed from aging tissues such as organoids, induced pluripotent stem (IPS) cells from aging tissues, and others

# Implementation plan

## Mechanism

- RFA using U01 cooperative agreement mechanism
- Awardee PIs and NIH Staff will form consortium to:
  - develop best practices, novel approaches and model systems
- Up to 5 years of funding can be requested
- Each application must include model of aging and cancer
- U01 applications, will be solicited for two receipt dates
- Review will be conducted by an NCI SEP to assure both aging and cancer expertise

# Implementation plan

## Budget

NCI plans to fund 3-4 U01 projects

- NCI Set Aside for 01 Year: \$2M TC
- Estimated NCI Cost for Total Project Period: \$10M TC

NIA will fund an additional 5-6 U01 projects

- NIA Set Aside for 01 Year: \$3M TC
- Estimated NIA Total Cost for Total Project Period: \$15M TC