Extending healthy lifespan by elimination of senescent cells

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Researchers

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Tohru Minamino, MD/PhD	Jyuntendo University
Motoko Yanagita, MD/PhD	Kyoto University
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Yoichiro Kamatani, MD/PhD	University of Tokyo
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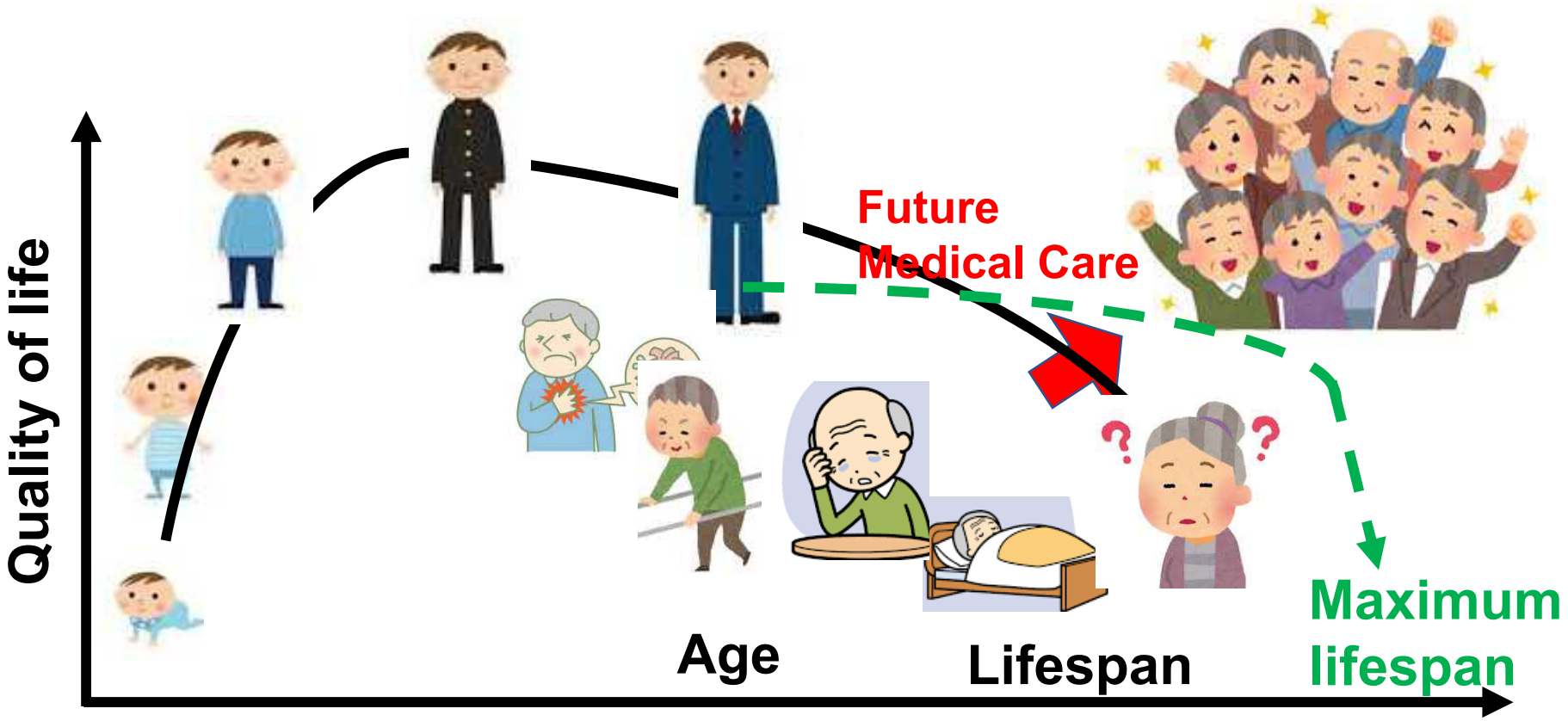
Yuki Sugiura, PhD	Keio University

Aiming for a healthy society through our moonshot project in the 2040s-1

A society where everyone leads healthy lives up to maximum lifespan



Aiming for a healthy society through our moonshot project in the 2040s-2

Present

Standardized medicine

Diseases | Organs

Medicine A

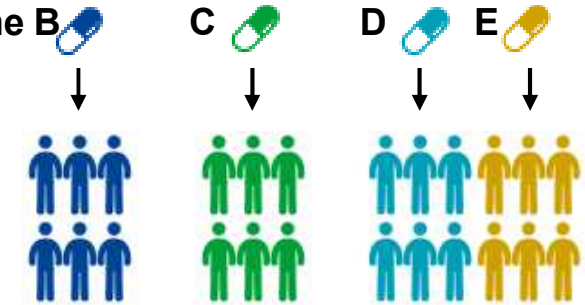
Subdivision of diseases

5 years later

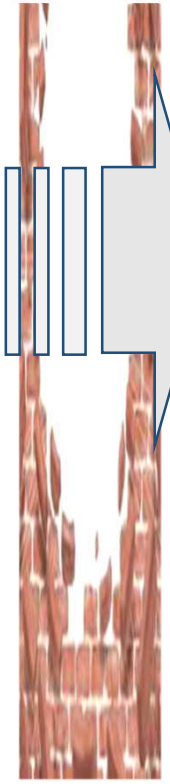
Precision medicine

Subdivision of diseases by omics
Selection of medical care

Medicine B C D E

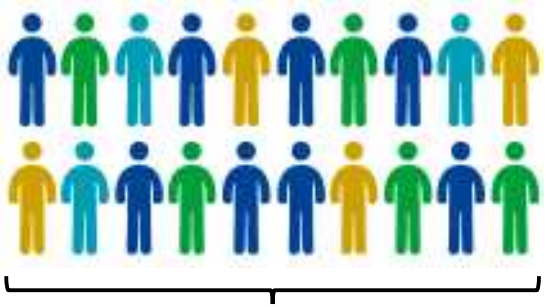


MOONSHOT
RESEARCH & DEVELOPMENT PROGRAM

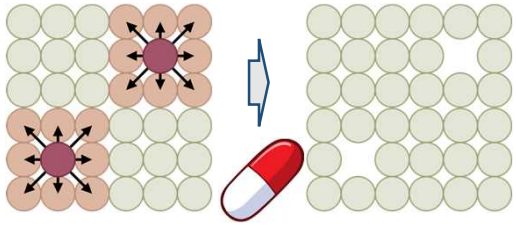


The 2040s

Almighty medicine



Targeting inflammation-inducing cells

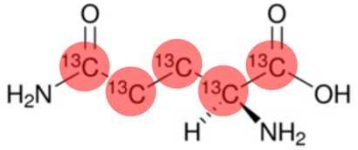


Aiming for a healthy society through our moonshot project in the 2040s-3

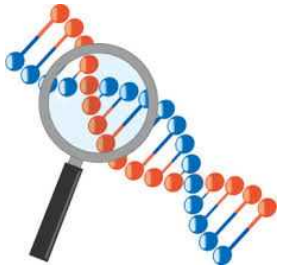
Everyone can take diagnostic examinations for determining the progression of aging

Blood sample

Radio probes detecting inflammation



Glutamine labeled with stable isotope



Genome analysis

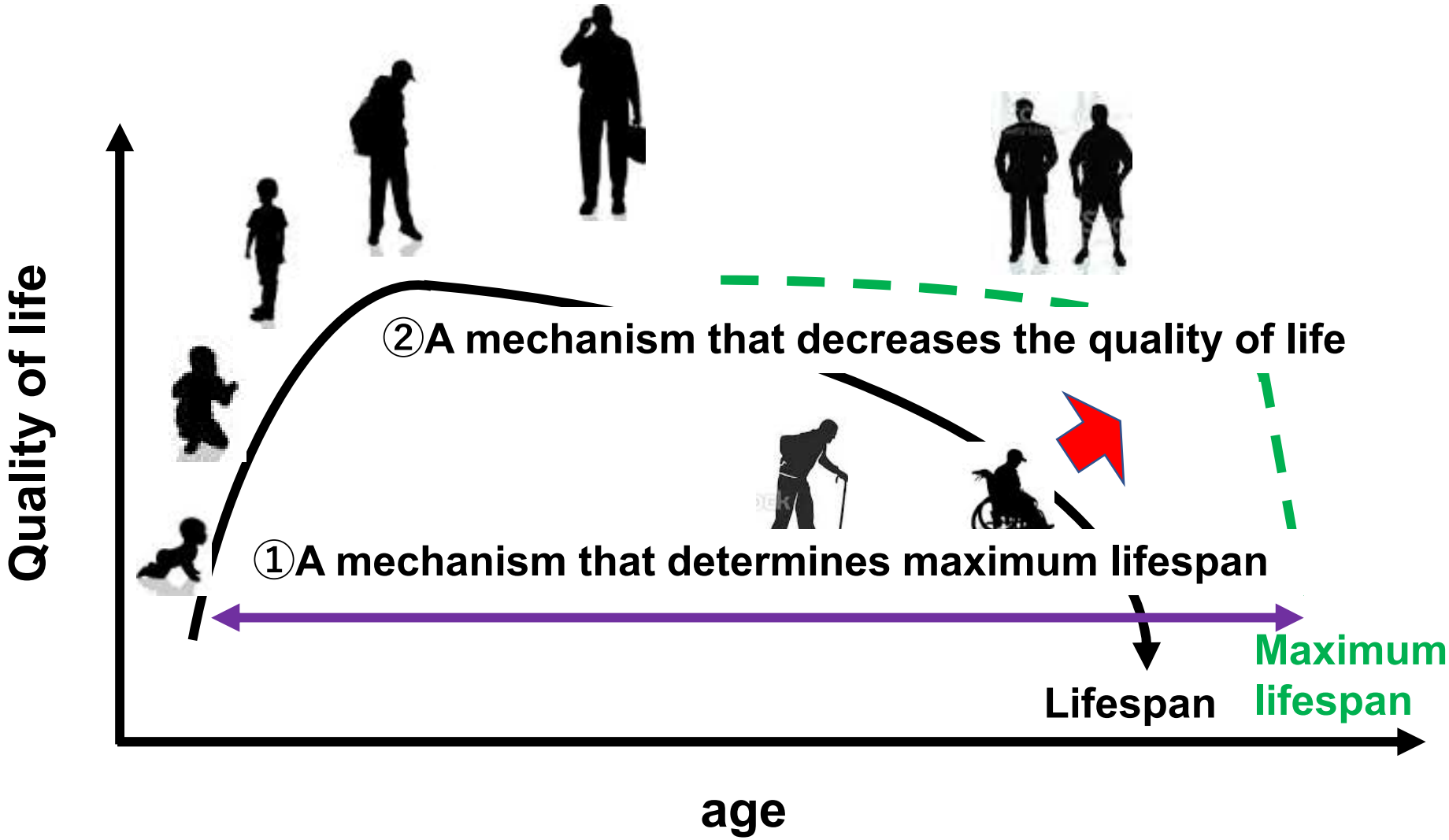
PET analysis

Gas analysis

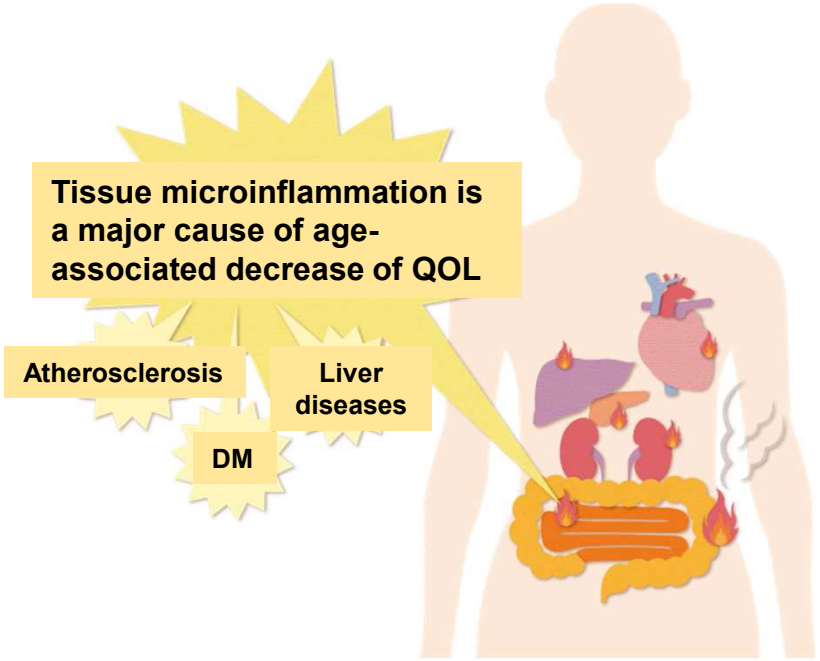
Diagnose the individual progression of aging

Ultimate preventive medicine

Two independent mechanisms regulating aging processes

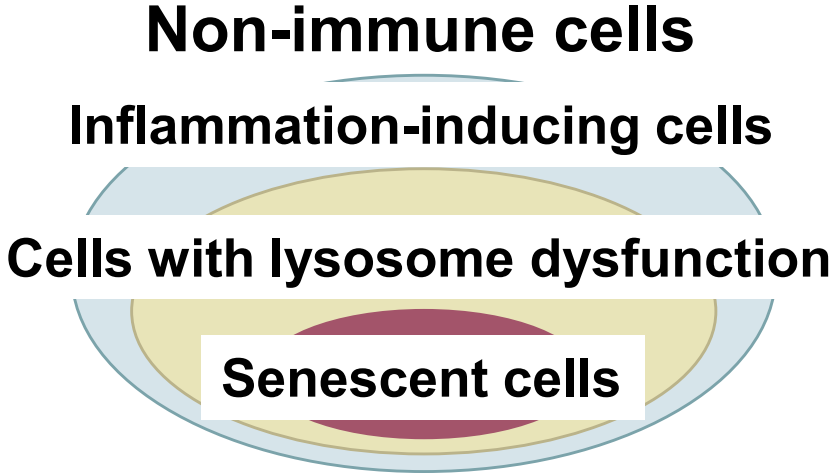


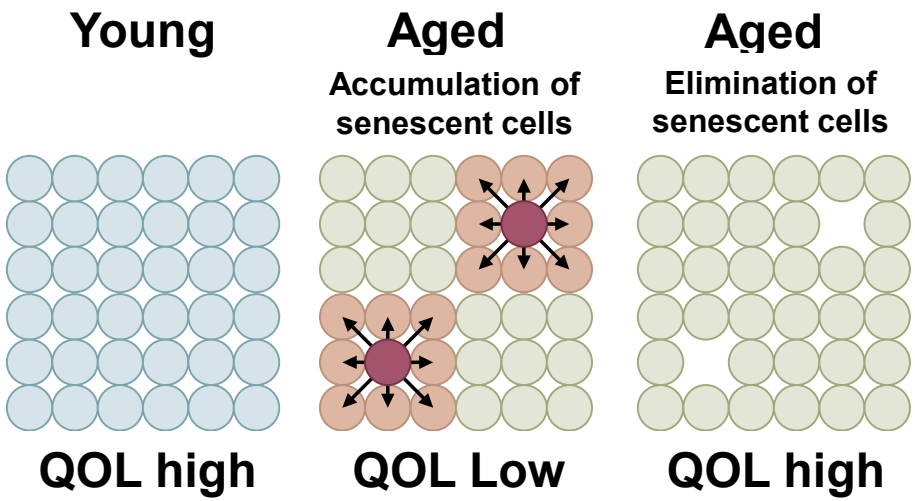
Tissue microinflammation is a major cause of age-associated decrease of QOL



Inflammation-inducing cells

Immune cells	Non-immune cells
MΦ,T cells, Leukocytes Necessary for immune response	Senescent cells Age-dependent accumulation





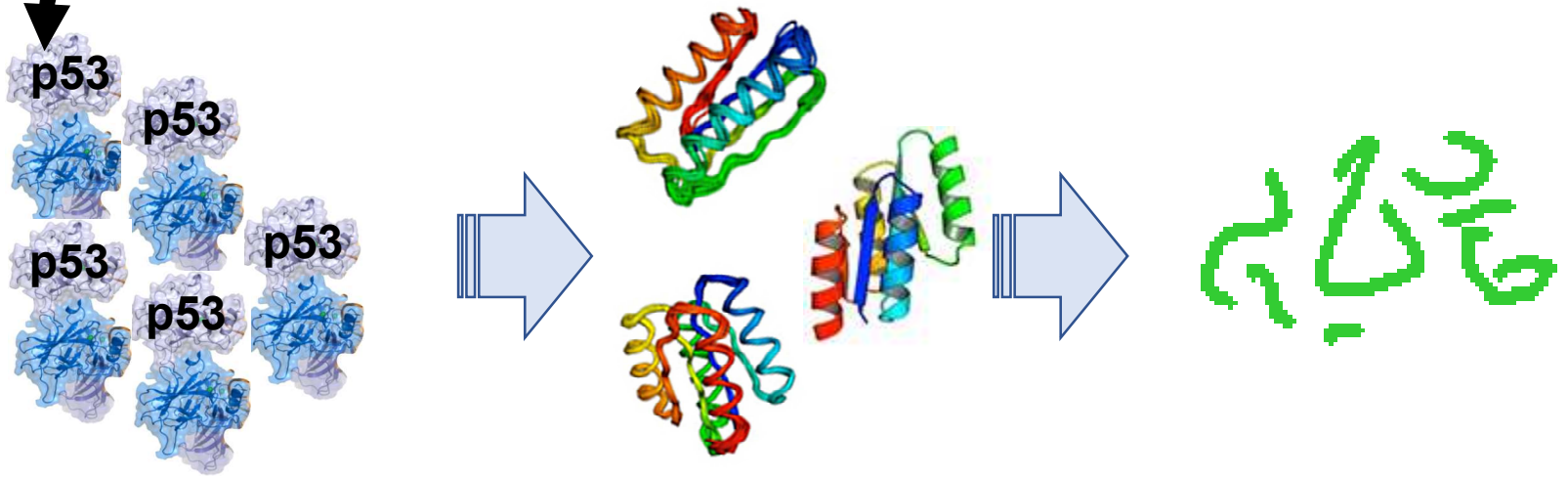
Research background-1

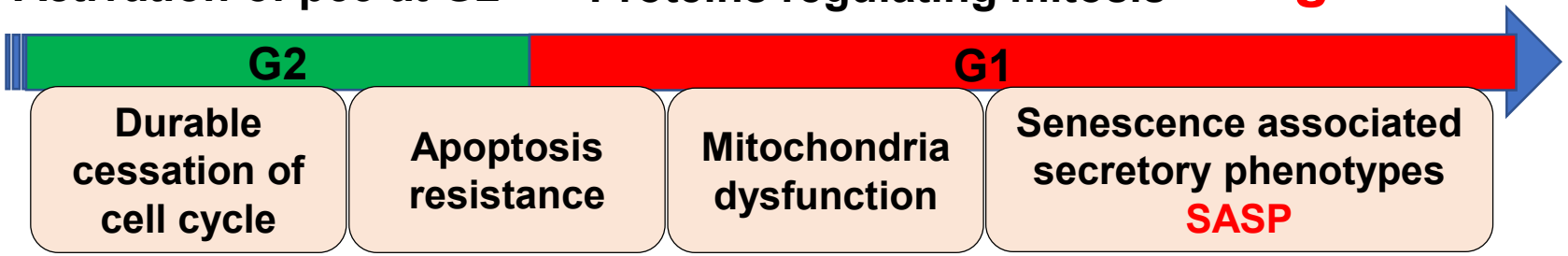
What is senescence？

Cellular senescence and a mechanism of its induction

Telomere dysfunction	Oxidative stress	DNA damage	Oncogene activation	Mitochondria dysfunction

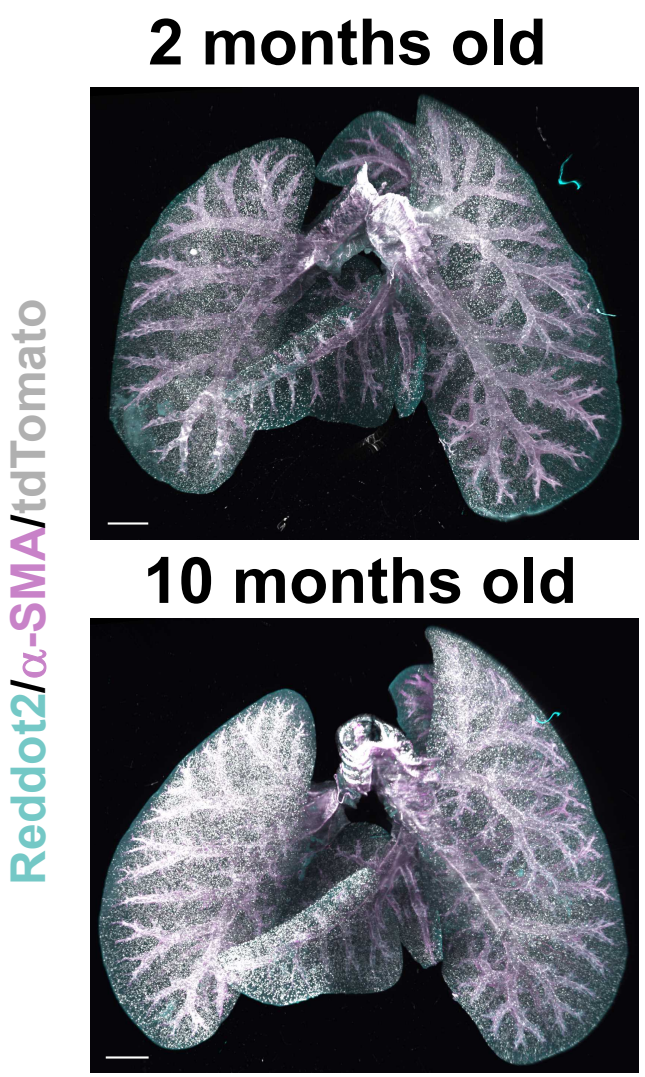
Activation of DNA damage responses

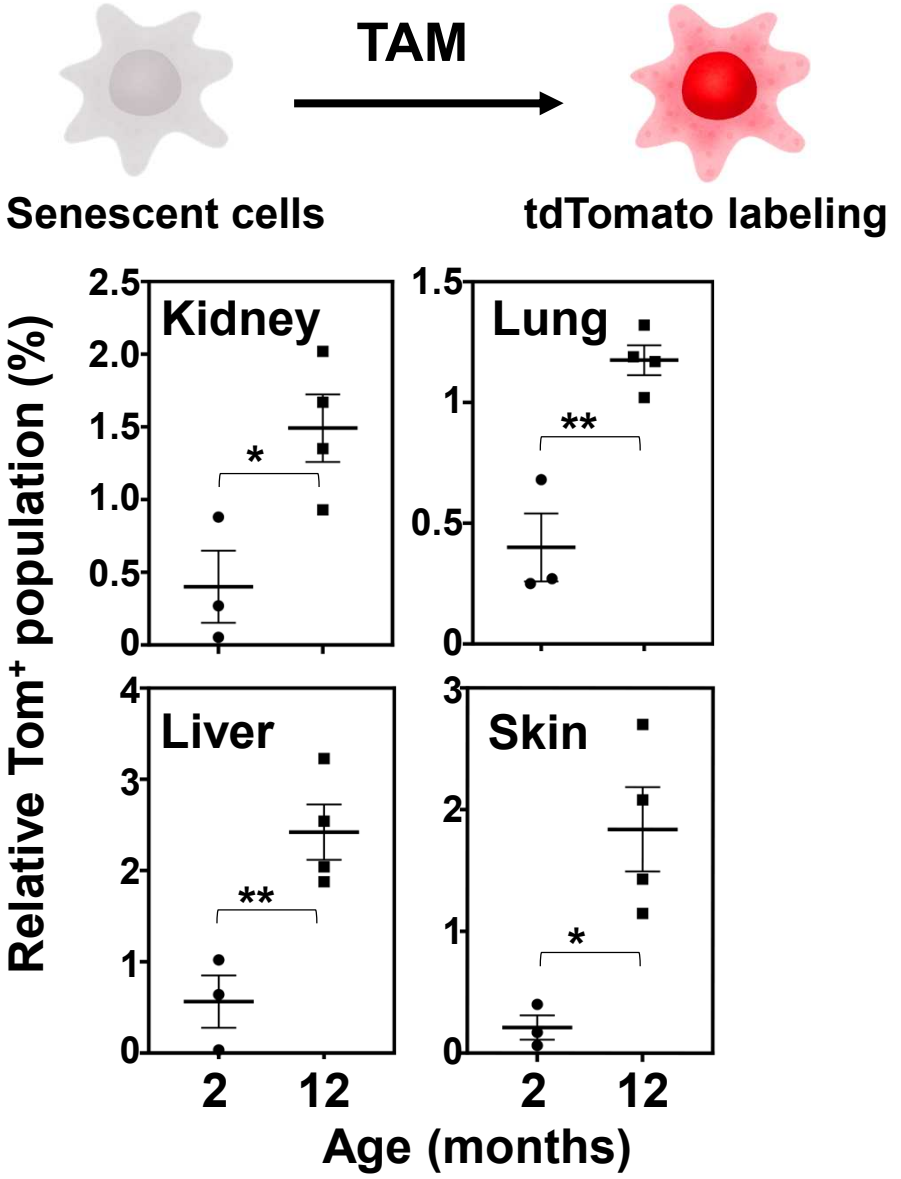




Johmura et al. *Mol Cell* 2014

Accumulation of senescent cells with age





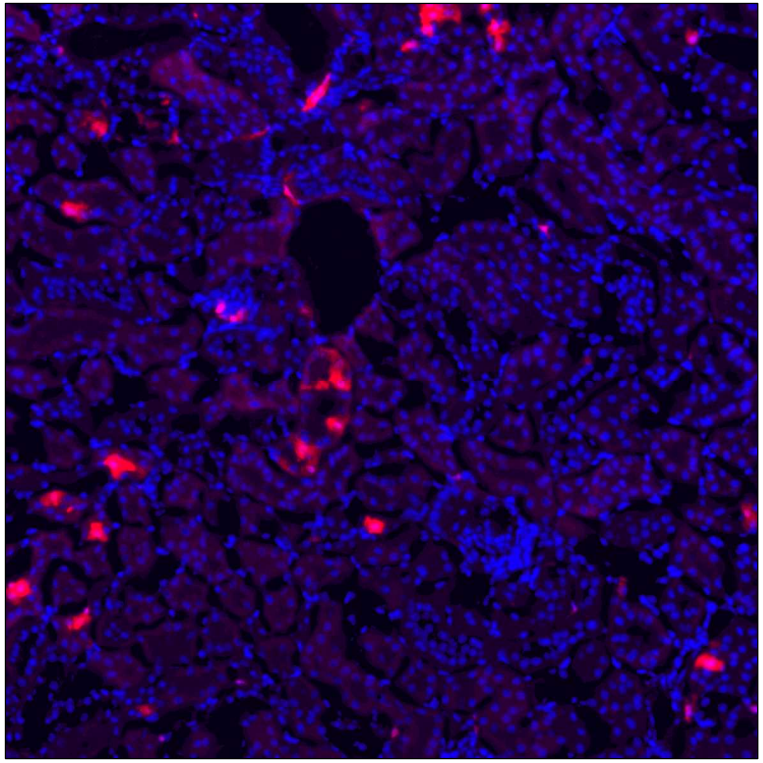
Omori et al. *Cell Metab* 2020

Senescent cells associate with age-associated kidney dysfunction *in vivo*

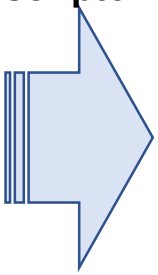
p16-positive senescent cells in distal tubule

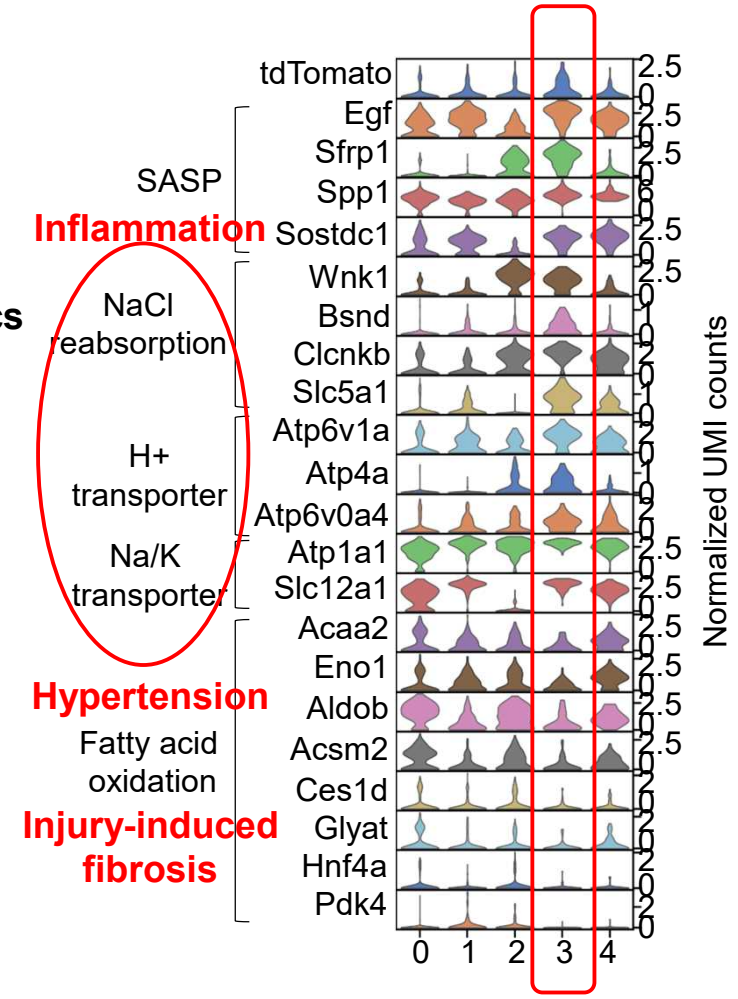
Kidney

tdTomato/DAPI



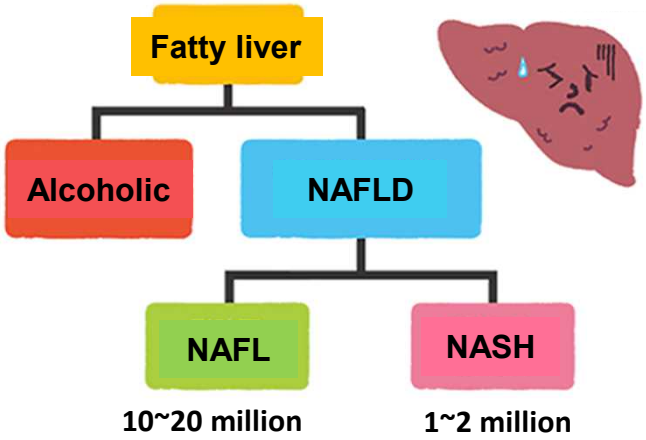
Single cell transcriptomics

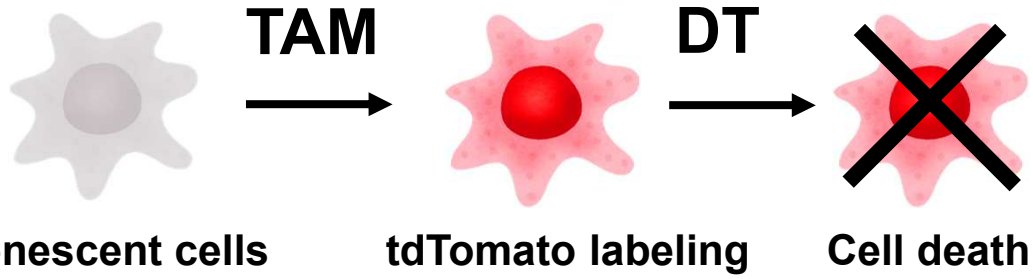


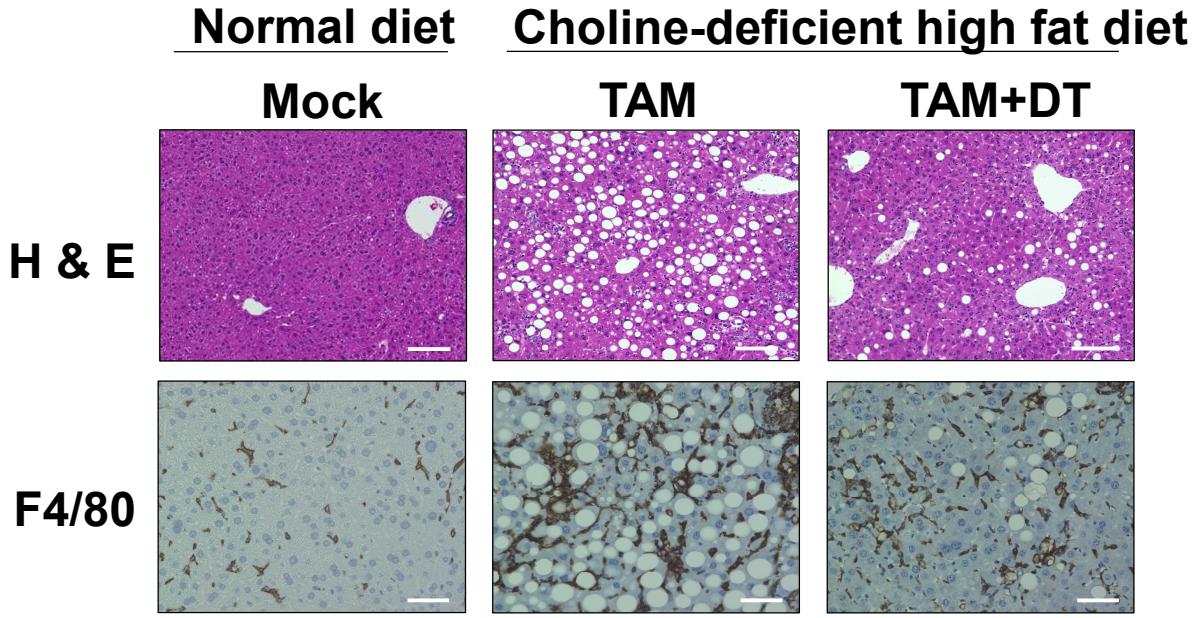


Omori et al. *Cell Metab* 2020

Improvement of NASH pathogenesis by elimination of senescent cells



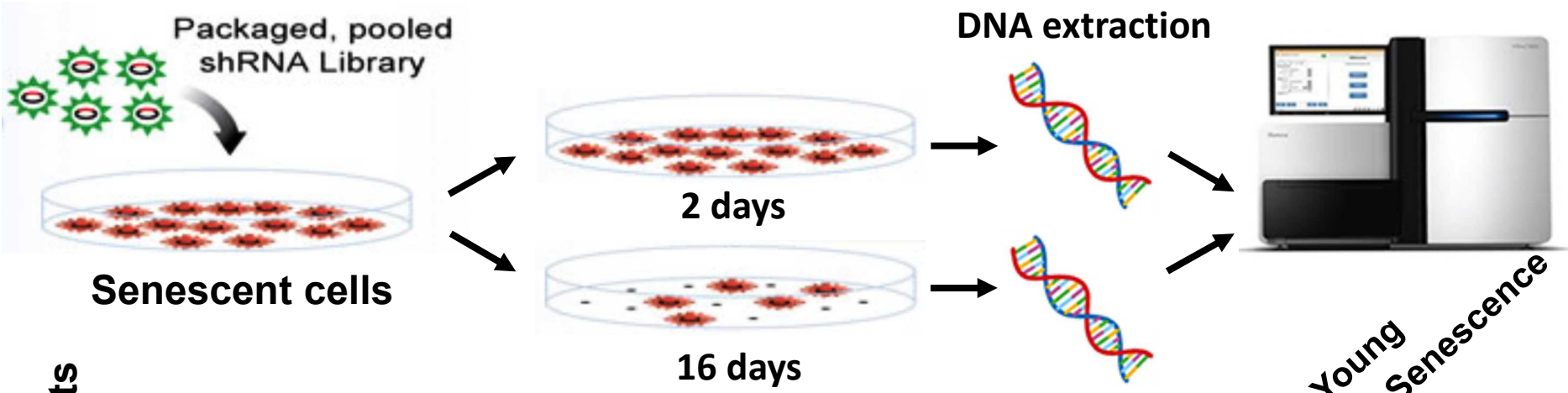


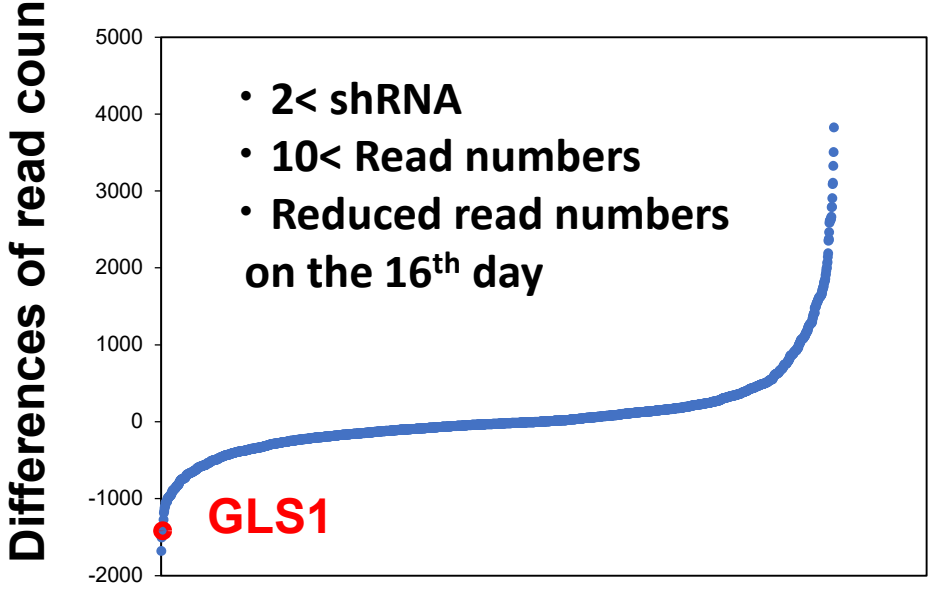


Research background-2

Improvement of age-related disorders by senolysis

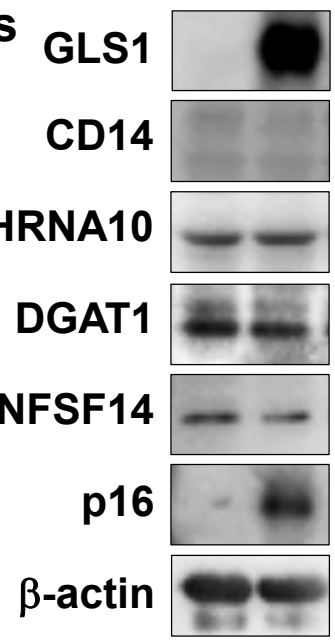
GLS1 is essential for senescence survival





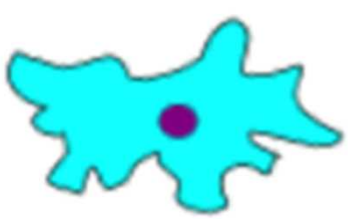
Top 5 candidates

1. DGAT1
2. TNFSF14
3. CHRNA10
4. GLS1
5. CD14

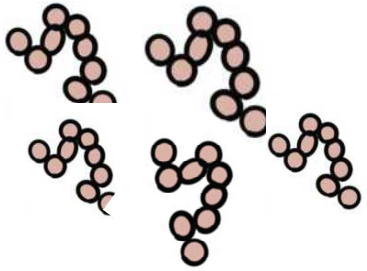


Johmura et al. *Science* 2021

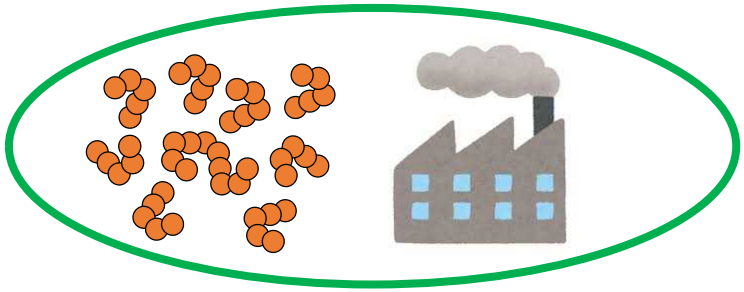
A mechanism of senolysis by GLS1 inhibitor



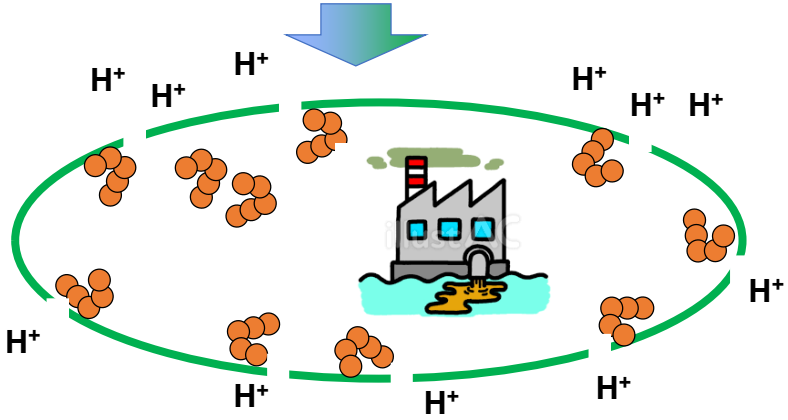
Senescent cells



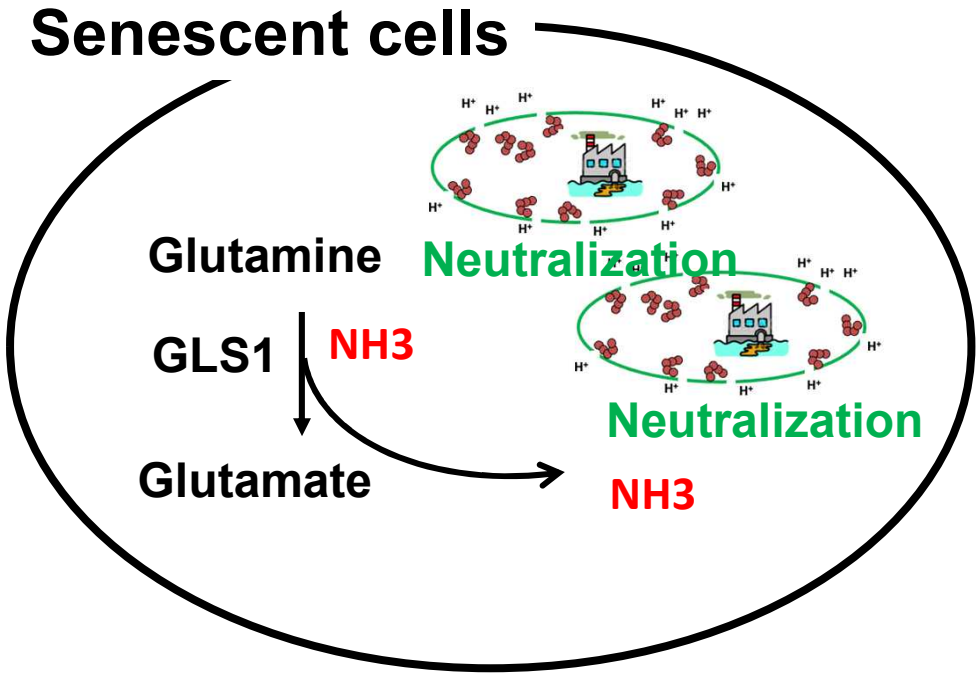
Excess protein synthesis



Accumulation of misfolded proteins in lysosomes

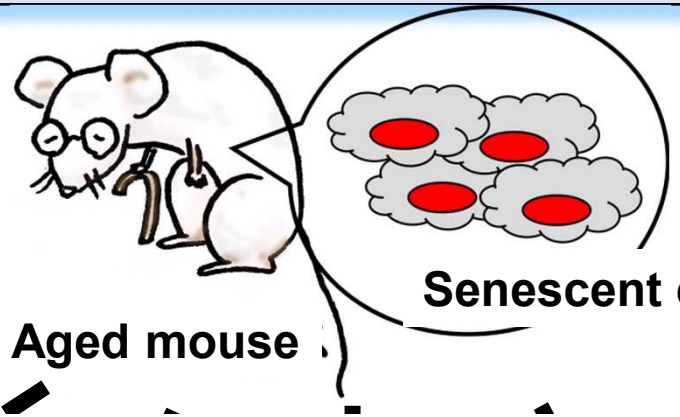


Protein aggregates damage lysosomal membrane

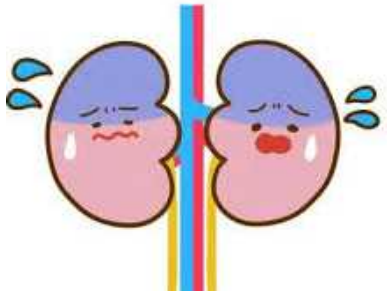


Johmura et al. *Science* 2021

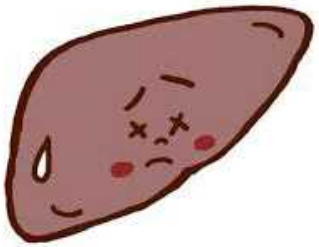
Amelioration of age-associated disorders by GLS1 inhibitor in vivo



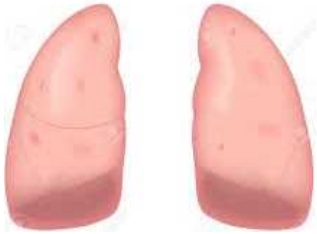
Elimination of senescent cells by GLS1 inhibitor



Improvement of glomerulosclerosis kidney functions



Improvement of liver inflammation liver functions



Improvement of lung fibrosis

Improvement of sarcopenia

Improvement of atherosclerosis

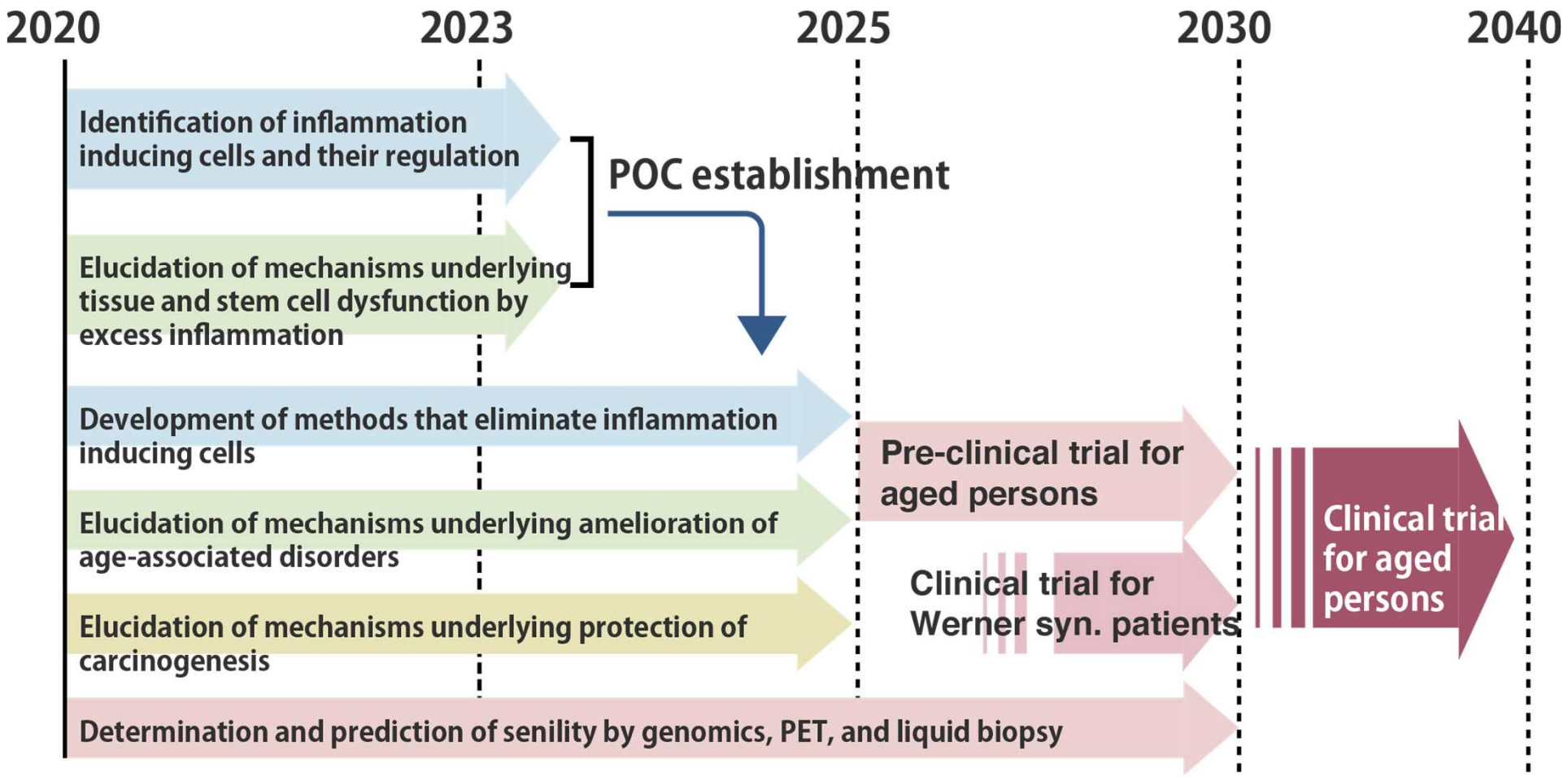
Johmura et al. *Science* 2021

Research plans and scenario

Overview and scenario

- Development of methods that eliminate inflammation-inducing cells and elucidation of molecular basis underling age-associated organ dysfunction by excess inflammation

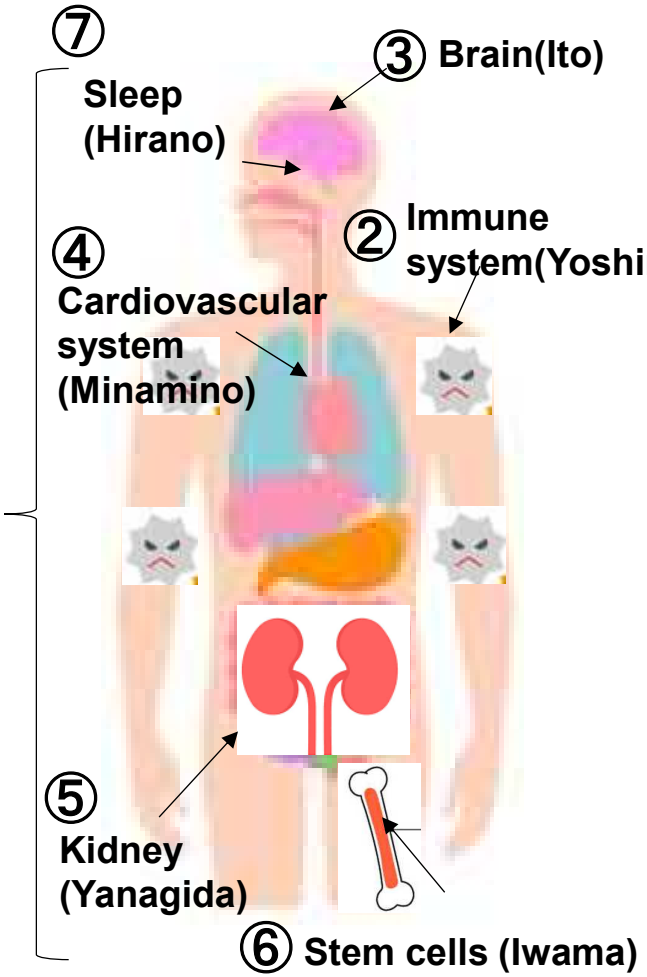
- Development of technologies that determine and predict aging



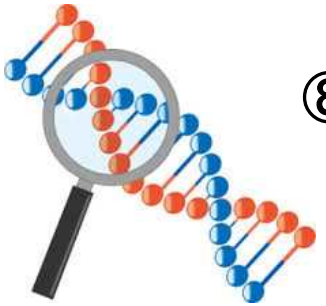
Research plans and researchers

Aging mechanisms and improvement of age-associated disfunction by elimination of inflammation-inducing cells

① Technologies for elimination of inflammation-induing cells and age-associated organ networks (Nakanishi)



Development of technologies by which the progression of aging are determined



⑧ Genome (Kamatani)

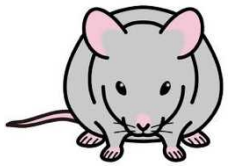
⑨ PET (Zhang)

⑩ Aging markers (Sugiura)

① Elimination of inflammation-inducing cells and age-associated organ networks

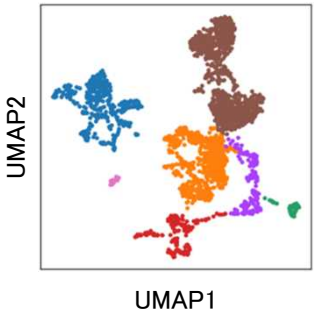
Nakanishi
Univ.
Tokyo

Identification and analyses of inflammation-inducing cells



・Visualizing inflammation -inducing cells

Single cell analyses



Development of methods that eliminate inflammation-inducing cells

Lysosome membrane damage

Secretion of inflammatory factors

Intracellular acidosis

Stabilization of GLS1 mRNA by HuC

Activation of glutaminolysis

Neutralization by NH_3

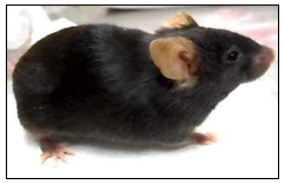
Inflammation-inducing cells

・Targeting all processes

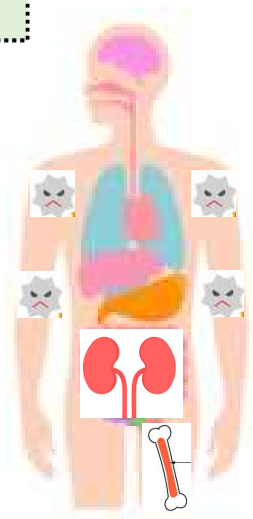
・Clinical application of most effective targets

Elucidation of organ networks during aging

Mock

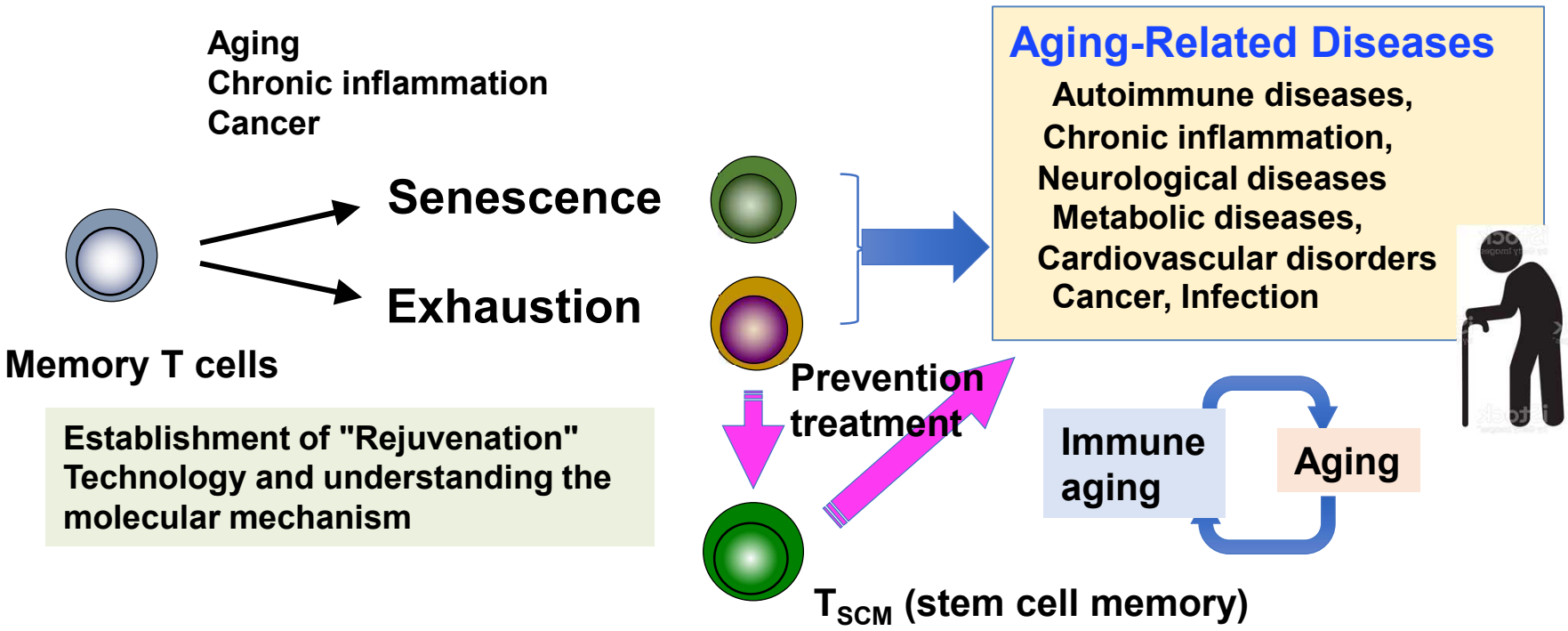


Accumulation of senescent cells



② Immune aging and its improvement

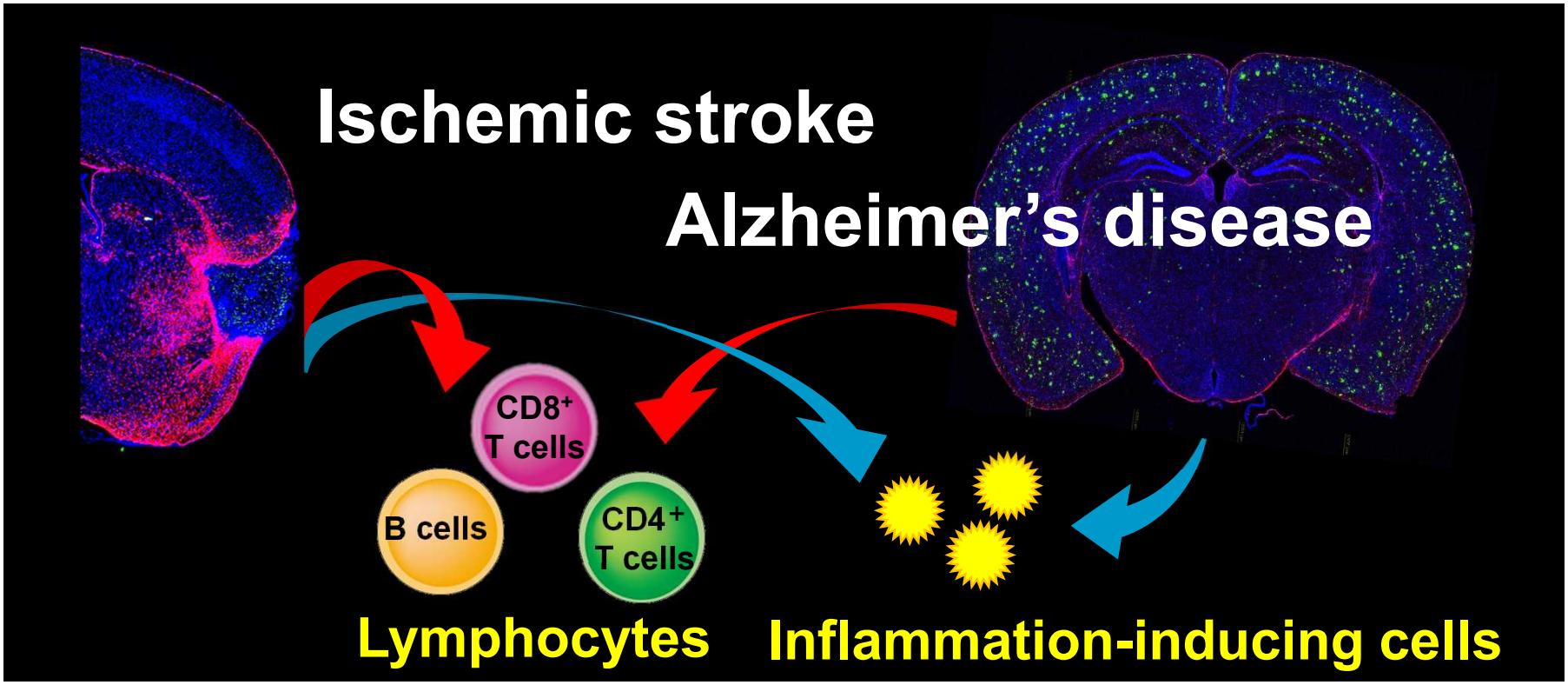
Yoshimura
Keio Univ



- Elucidate the mechanism of T-cell senescence and exhaustion at the molecular level and develop a method to convert to young memory cells.
- Prevent and cure aging-related diseases by eliminating or rejuvenating senescent T cells.

③ Brain inflammation by immune aging and its improvement

Ito
Kyushu
Univ.



Aging of the brain's immune system

Regulation of brain function by lymphocytes in the brain and their dysregulation by immune aging.

Eliminating tissue inflammation-inducing cells

Elucidation of the recognition and elimination mechanisms of abnormal inflammation-inducing cells induced by inflammation in the brain.

④ Aging of cardiovascular system and its improvement

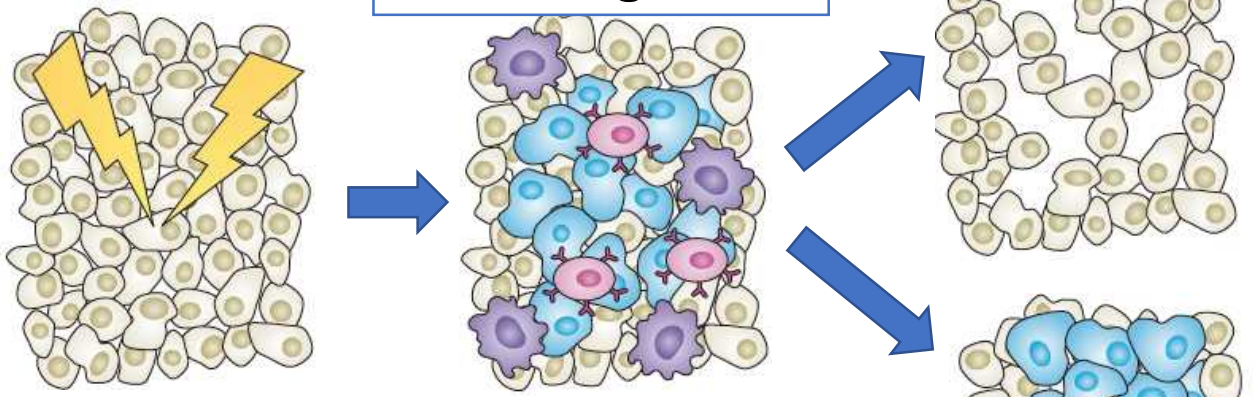
Minamino
Juntendo
Univ.

(1) Anti-senescence therapy by targeting seno-antigens

Elimination of inflammation-inducing cells

Accumulation of inflammation-inducing cells

Age/Stress



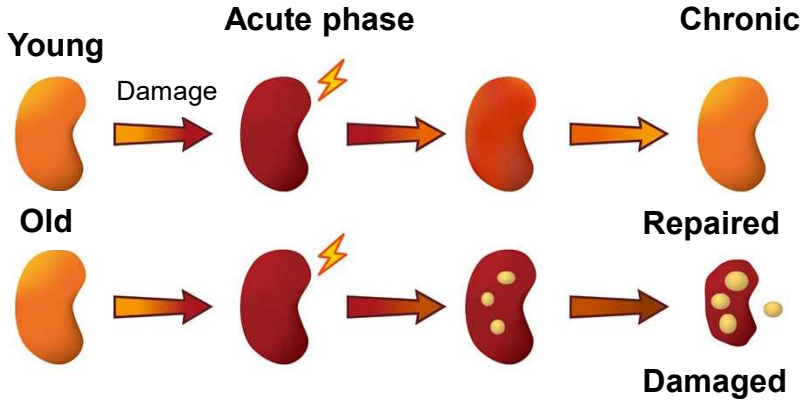
(2) Mechanism of accumulation of inflammation-inducing cells in cardiovascular system

Prolonged accumulation of inflammation-inducing cells

⑤ Kidney aging and its improvement

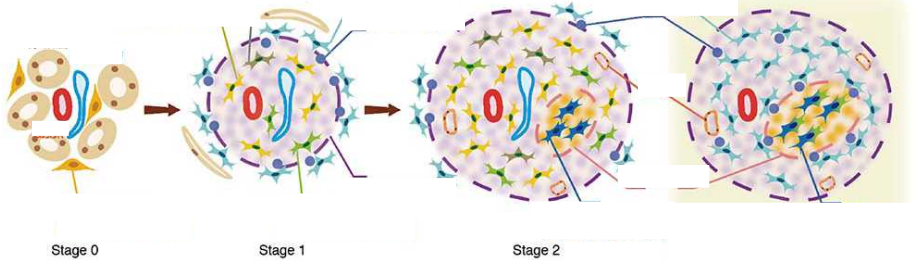
Yanagita
Kyoto
Univ.

The reasons of insufficient repair in aged kidney are unclear

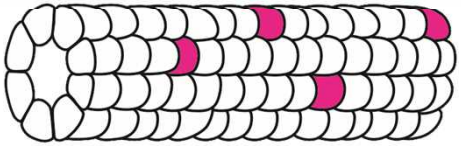


Aging & Inflammation

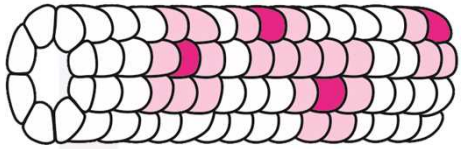
Formation of age-associated TLT



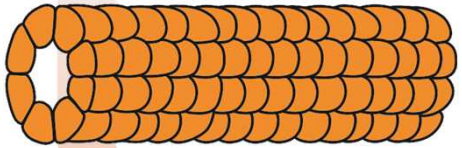
Mouse **Human**



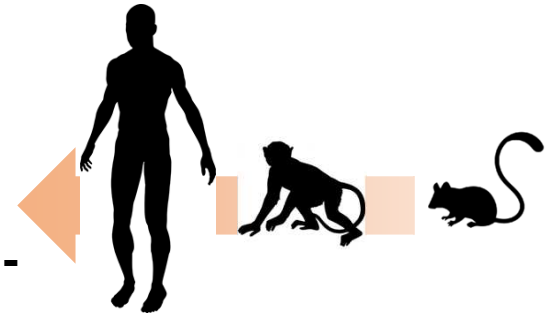
Identify inflammation-inducing cells and analyze their regulatory mechanisms



Elucidate the effects of inflammation-induced cell accumulation on the kidney



Compare kidney with inflammation-induced cell accumulation and aged kidney

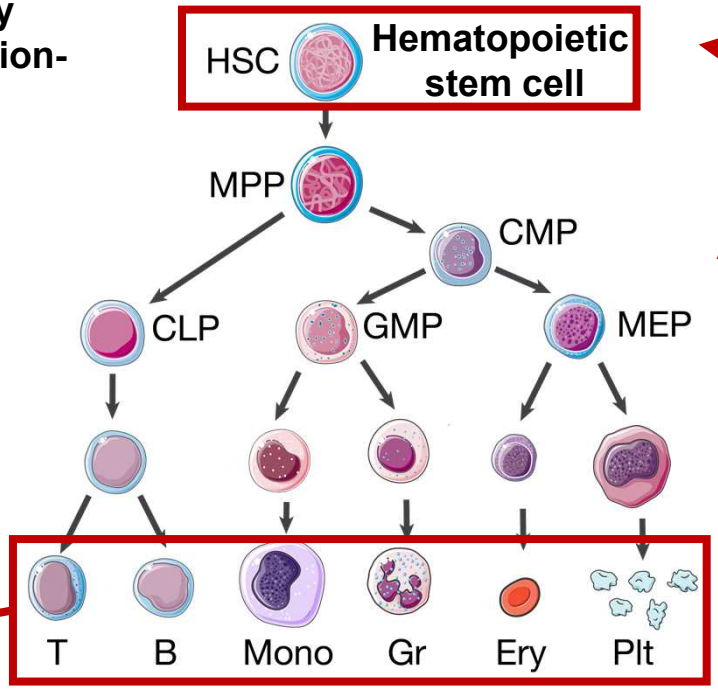


Therapeutic trials targeting inflammation-inducing cells

⑥ Stem cell aging and its improvement

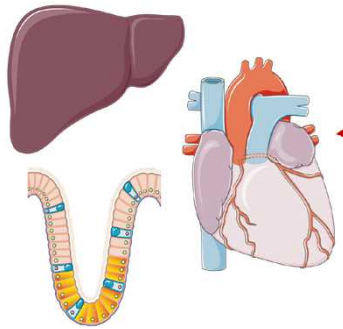
Iwama
Univ.
Tokyo

① Impaired stem cell function in hematopoietic system by accumulation of inflammation-inducing cells

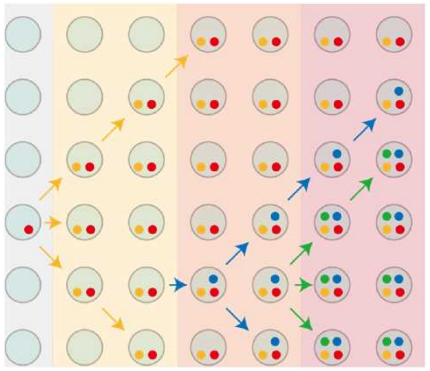


④ Elimination of inflammation-inducing cells

Accumulation of inflammation-inducing cells



③ Promotion of aging of other organs by hematopoietic stem cell aging

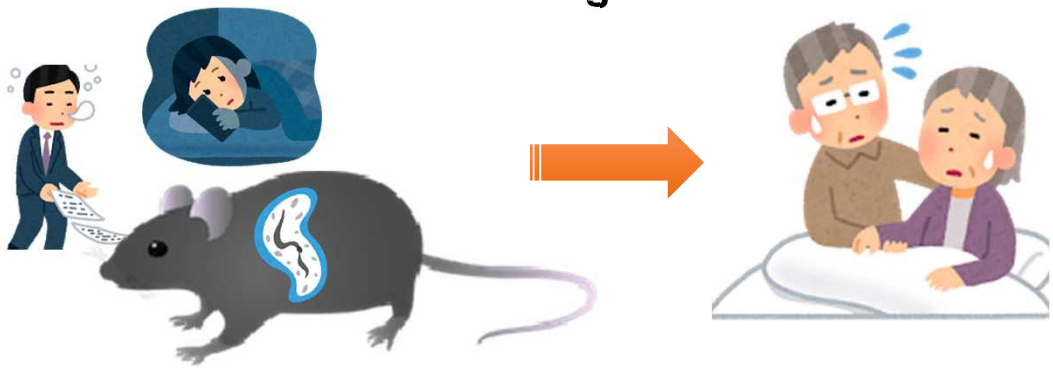


② Progression of clonal hematopoiesis by accumulation of inflammation-inducing cells

⑦ Aging process in circadian rhythms and sleep disorders

Hirano
Univ.
Tsukuba

Accumulation of inflammation-inducing cells？

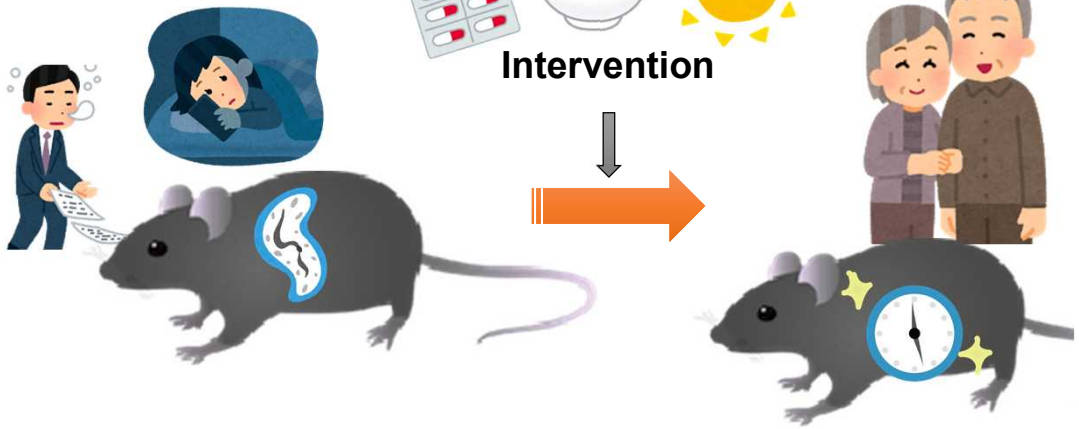


Mechanism of aging in the circadian rhythm/sleep disorder

Rhythm/sleep disorder model mice

Prevention of increase in the number of inflammation-inducing cells and anti-aging?

Intervention

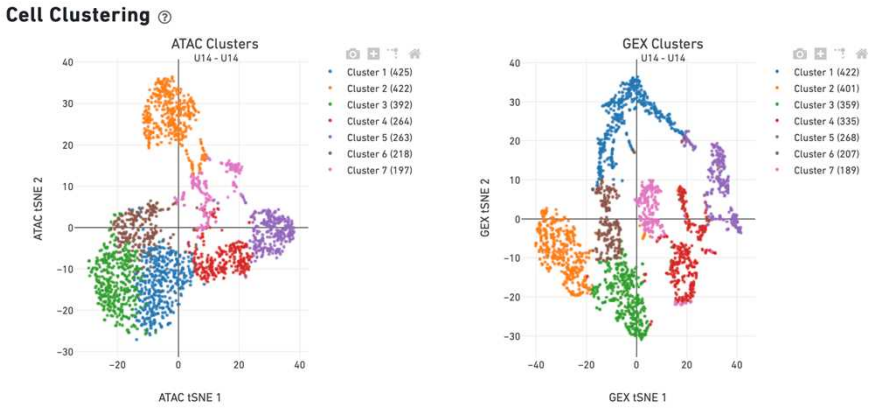


Aiming to prevent aging by treatment of the rhythm/sleep disorder

⑧ Diagnostic methods using genomics that predict the progression of individual aging

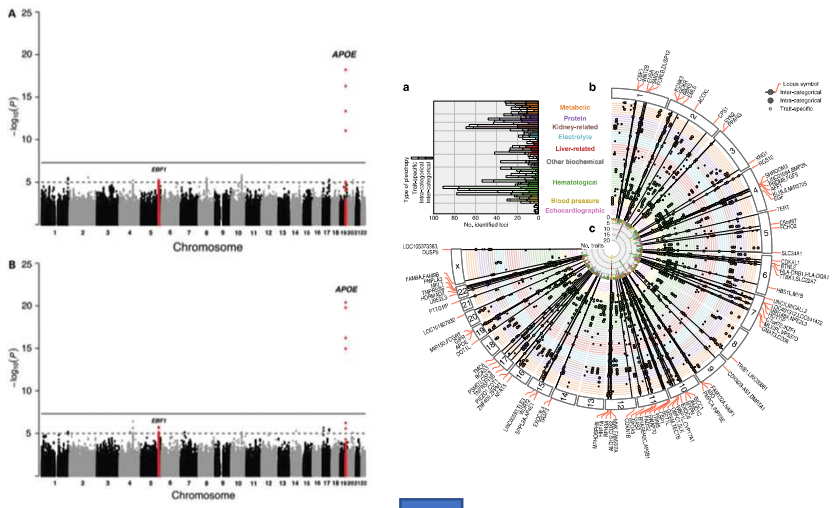
Kamatani
Univ.
Tokyo

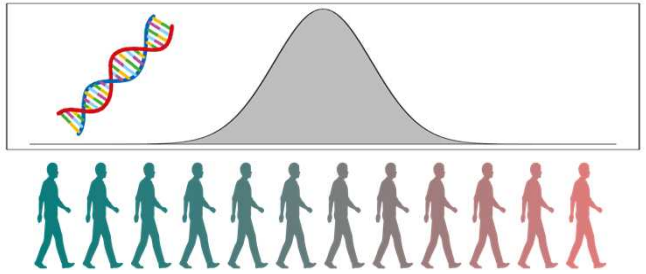
Genome omics of Werner syn. patients



Age-associated changes in epigenomes and transcriptomes in Werner syn. patients

Investigation of biomarkers by genetic and biochemical analyses using large genome and omics data





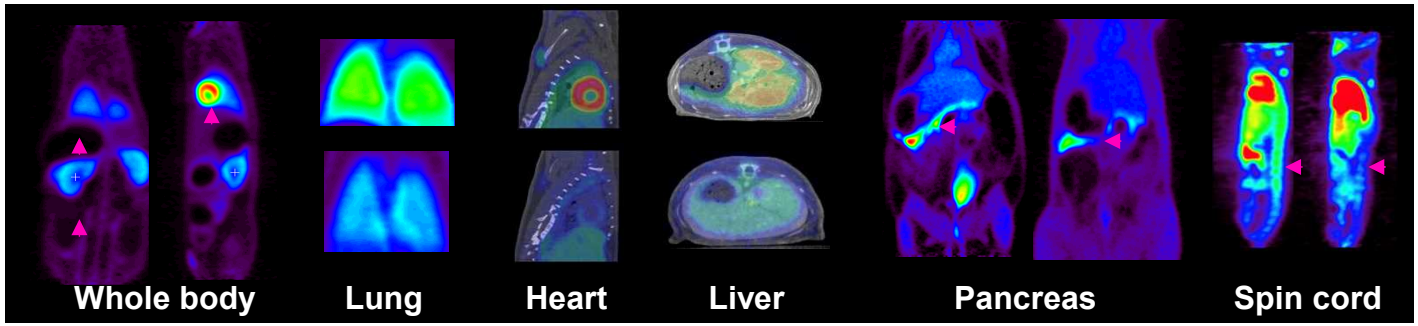
Polygenic analyses of aging and inflammation using GWASs of inflammation, aging and lifestyle diseases, and mosaic mutations

⑨ Quantification of inflammation-inducing cells and diagnosis of aging with PET

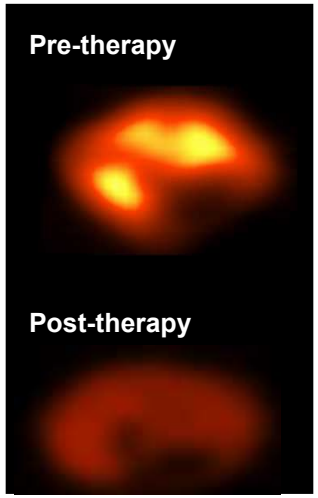
Zhang
QST

Quantification of inflammation-inducing cells and diagnosis of aging with PET using novel probes

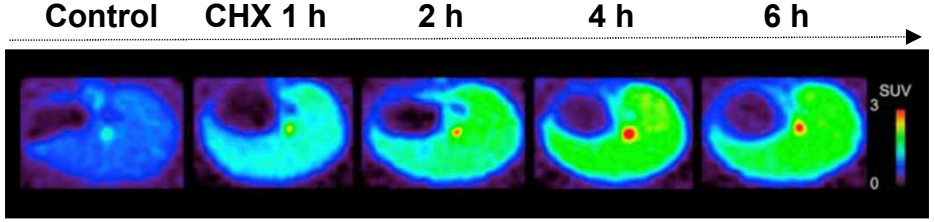
(1) Evaluation of PET probes

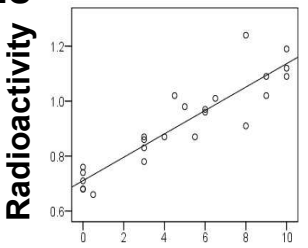


(2) Deleting inflammation-inducing cells



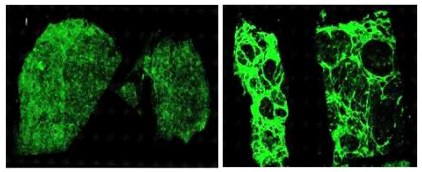
(3) Quantification of inflammation-inducing cells





Inflammation-inducing cells

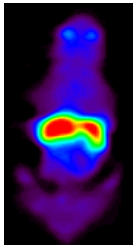
Validation on human tissues



Clinical use

GMP production

Safety and Toxicity



Human

⑩ Diagnostic methods for accumulation of inflammation-inducing cells *in vivo*

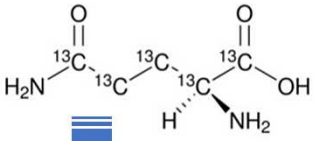
Sugiura
Keio
Univ.

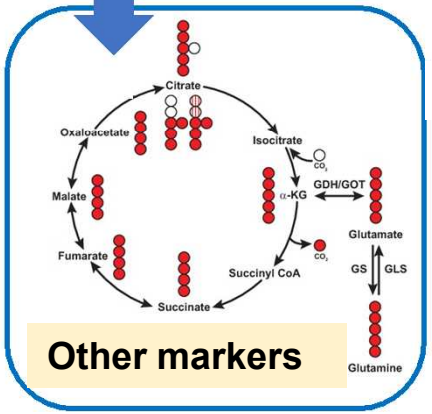
Background

Glutaminolysis is upregulated in inflammation inducing cells

On-going Projects

Stable isotope (non-radioactive) **labeled glutamine administration**



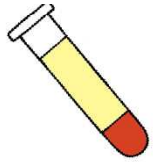


Respiratory gas analysis

$^{13}CO_2$

$^{15}NH_4$

Serum/Urine analysis



^{13}C Organic acids

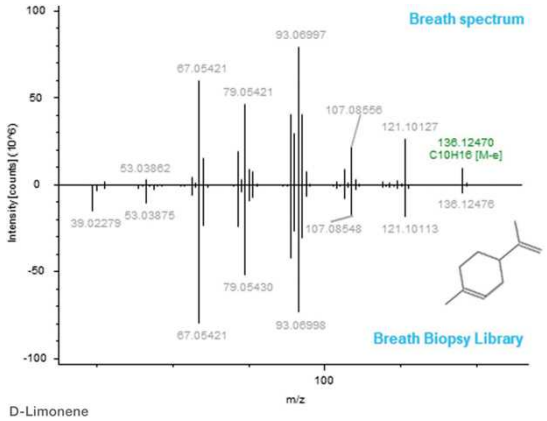
^{15}N Amino acids

Future Projects

Toward minimally invasive daily monitoring of senescent cell accumulation by mass spec.

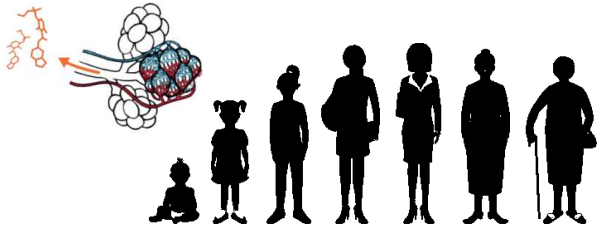
(1) Establishment of easy breath biopsy method

(2) Identification of novel breath biomarkers



D-Limonene

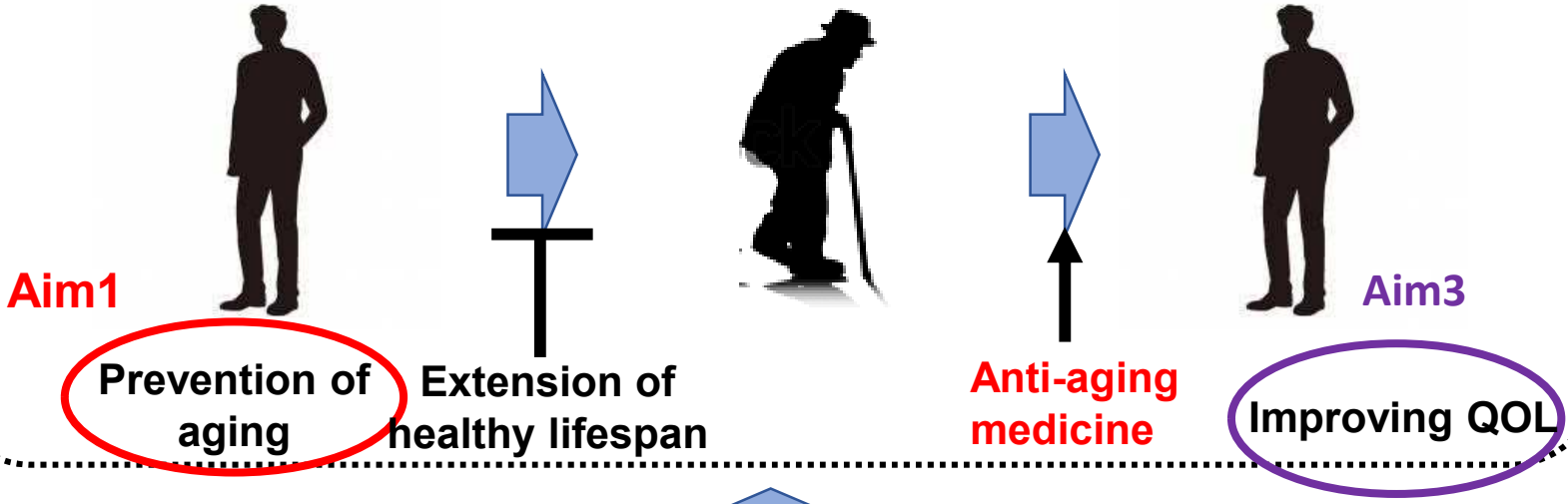
(3) Demonstration of aging indicator markers in a large population



Establishing non-invasive methods for routinely monitoring inflammation-inducing cells

The goal of our project after 10 years

Practical implementation of an innovative medicine by which various age-associated disorders are simultaneously improved through elimination of inflammation inducing cells



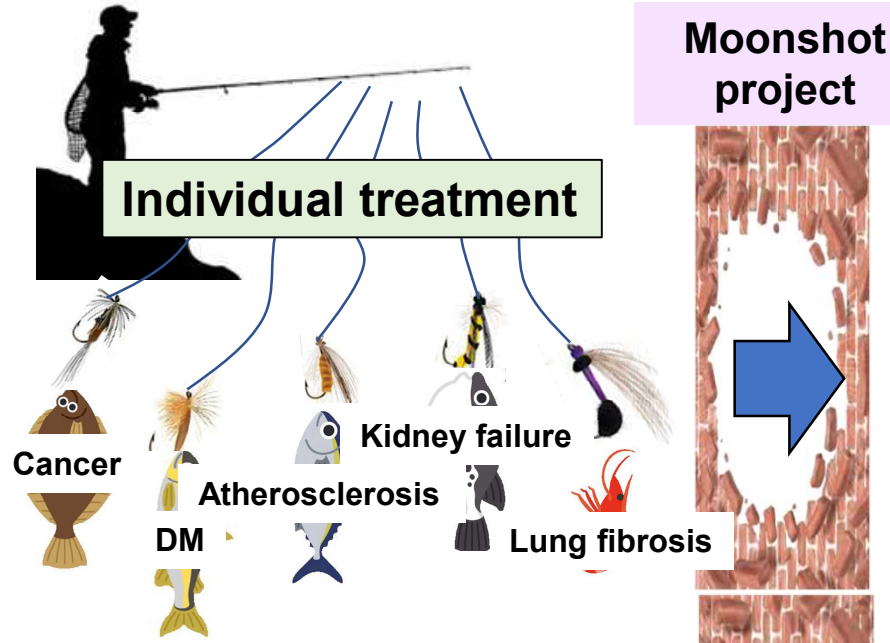
Development of diagnostic technologies using inflammation inducing cells by which the progression of aging is determined

Everyone can determine the progression of aging by minimally invasive and ongoing examinations anywhere in the world

The reason why our project can be categorized as a moonshot

Present

Individual treatment for each disease

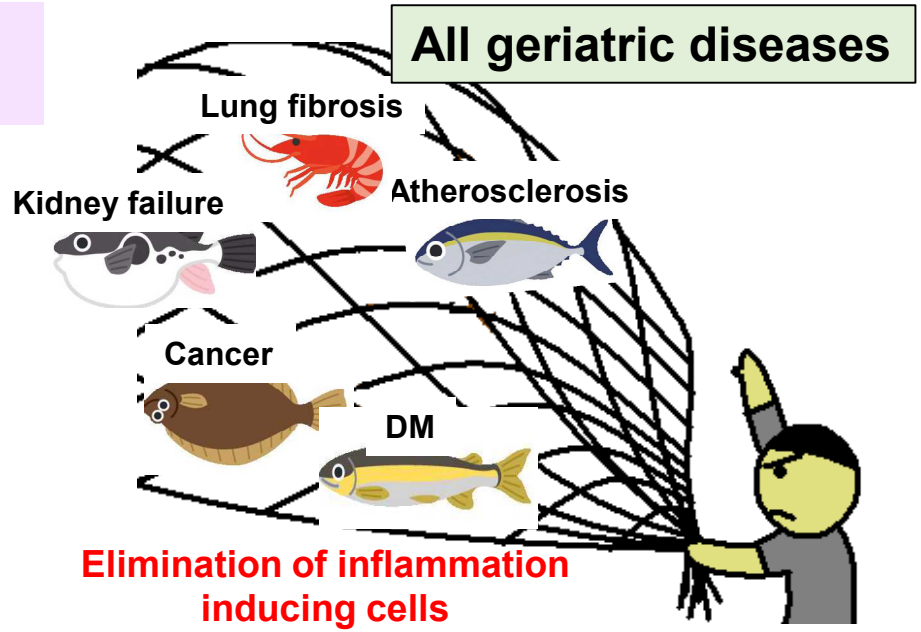


Diagnosis and treatment after symptoms appear

Moonshot project

The 2040s

One treatment for all geriatric diseases



Elimination of inflammation inducing cells

Prevention before symptoms appear

Establishment of examinations that determine the progression of aging