

Extending healthy lifespan by elimination of senescent cells

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Keio University

Kyushu University

Jyuntendo University

Kyoto University

University of Tokyo

University of Tokyo

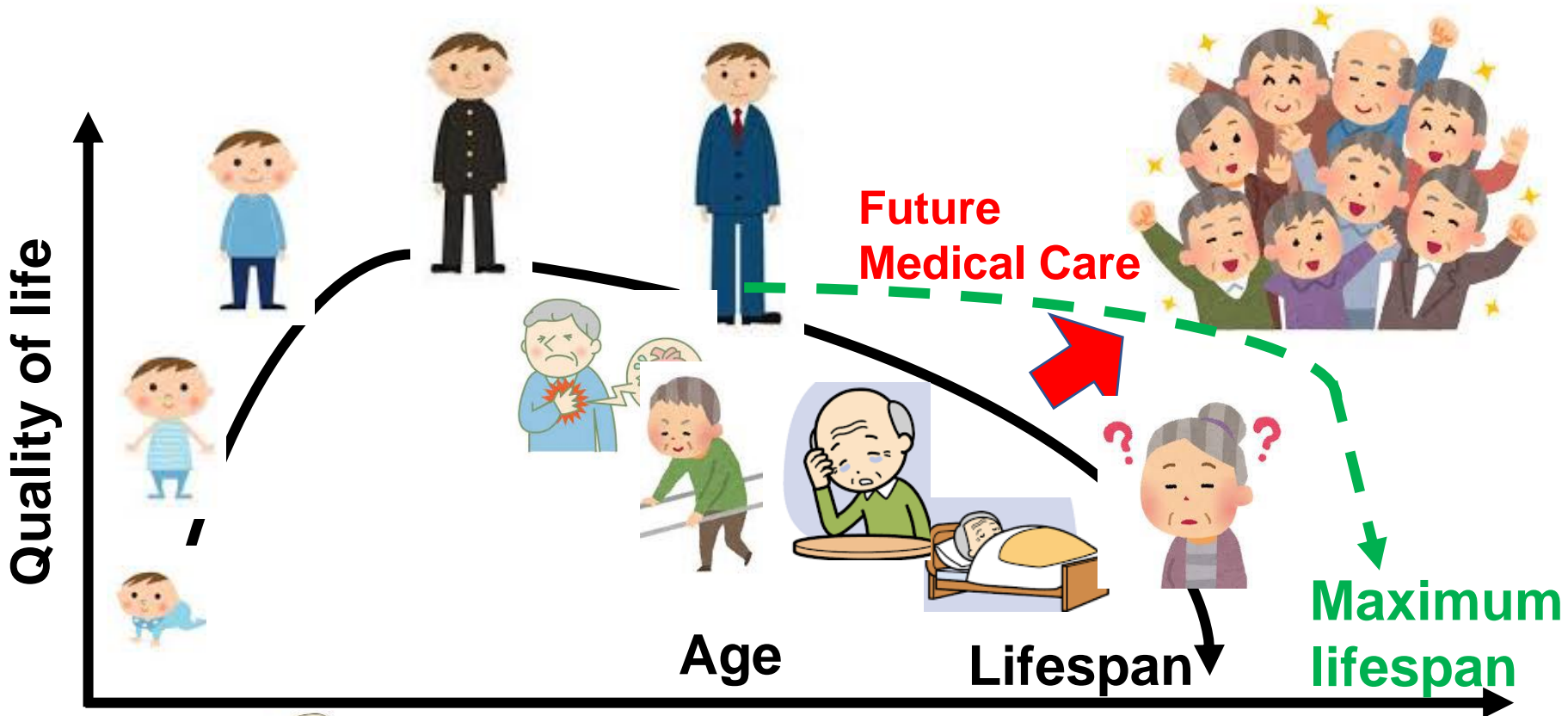
University of Tsukuba

QST

Keio University

The Program's Vision of Society in 2040

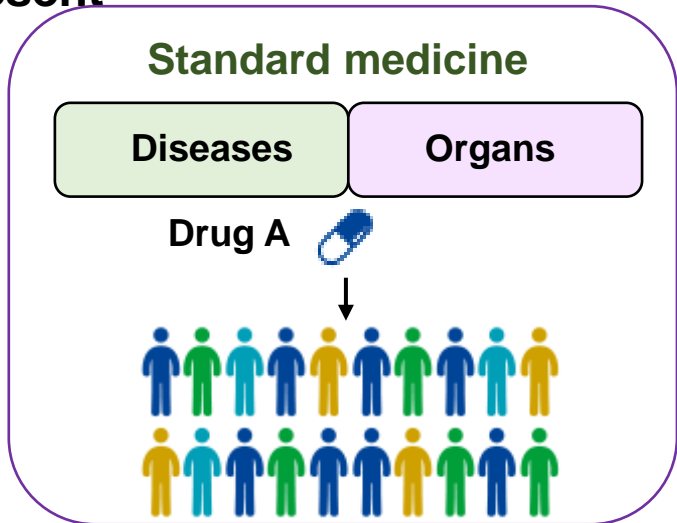
A society where everyone leads healthy lives up to maximum lifespan



Everyone can take diagnostic examinations for determining their rate and degree of aging

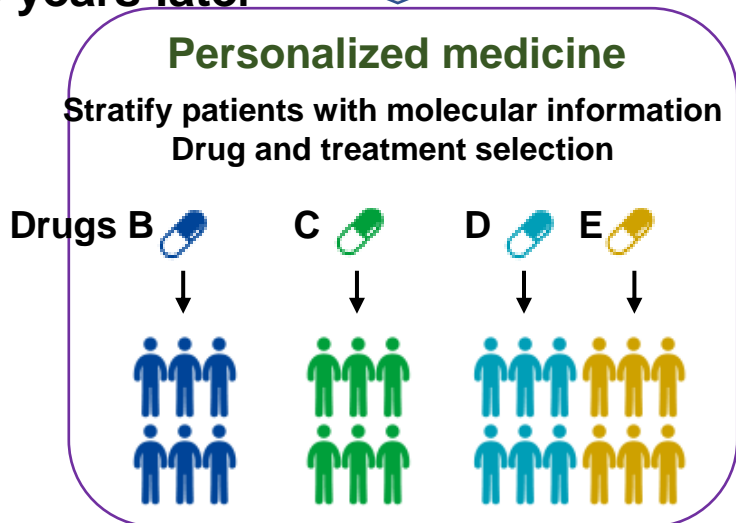
The Program's Vision of Society in 2040

Present

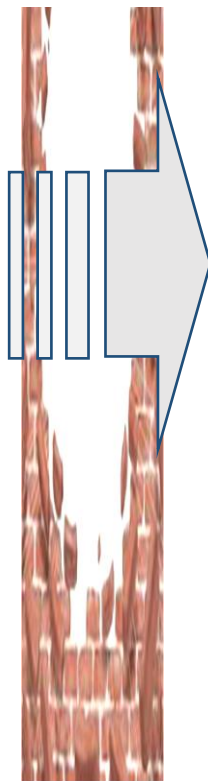


Subdivision of diseases at the protein and gene level

5 years later



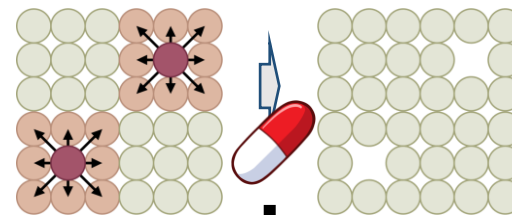
Year 2040



Almighty medicine



Targets inflammation-induced cells



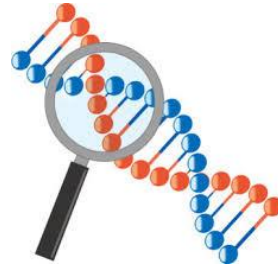
The same drugs for all patient with many different diseases

Aging diagnosis technologies in 2040

Everyone can easily measure the degree and speed of aging and for prevention of diseases.



Blood test



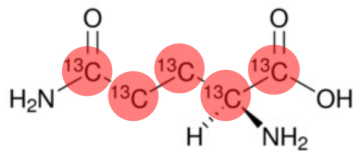
Genome analysis



Radioactive probes



PET analysis



Exhalation analysis



Diagnosis of individual degree and speed of aging



Ultimate preventive medicine

Stable isotope labeled glutamine

Understanding and overcoming aging

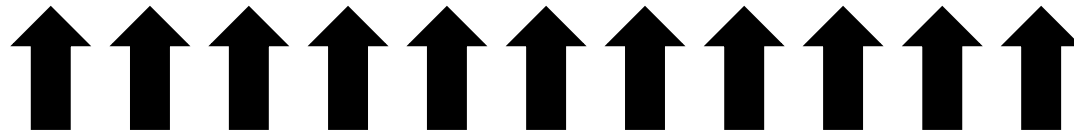
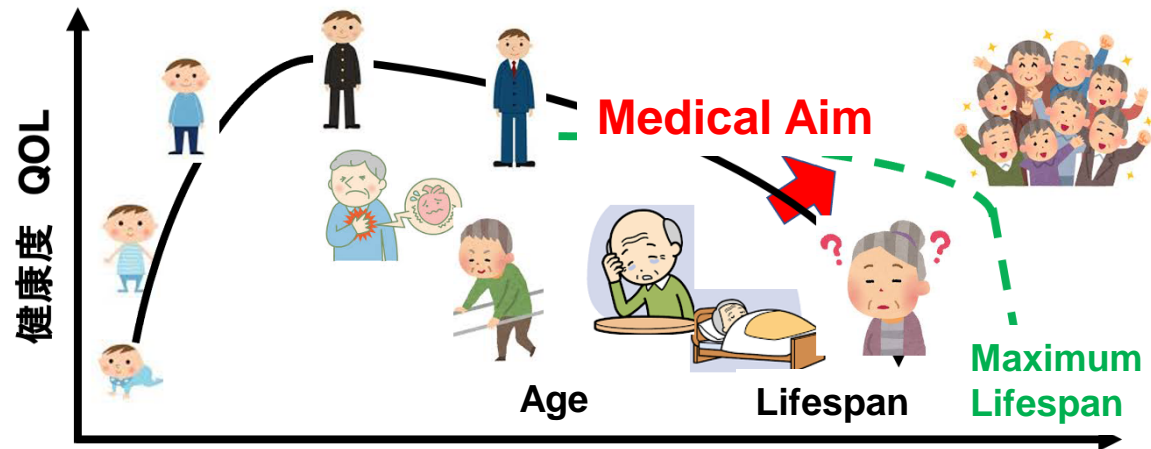
Achieved by FY2030

Build a society where everyone can live a healthy and vigorous life up to the maximum life span

Senolysis

Aging improvement evaluation

Diagnose of aging



Research on human aging based on organ function

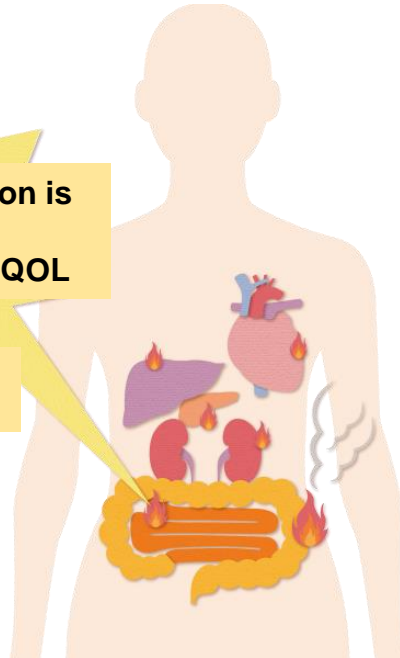
Tissue microinflammation is a major cause of age-associated decrease of QOL

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

Atherosclerosis

Liver diseases

DM



Inflammation inducing cells

Immune cells

**M Φ , T cells,
Leukocytes**

Necessary for
immune response

Non-immune cells

Senescent cells

Age-dependent
accumulation

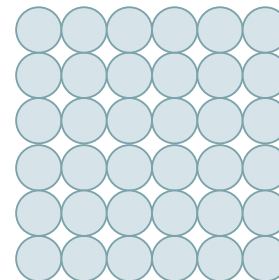
Non-immune cells

Inflammation inducing cells

Cells with lysosome dysfunction

Senescent cells

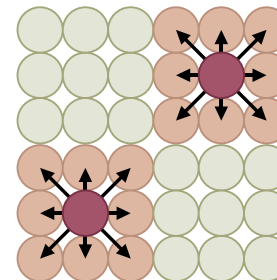
Young



QOL high

Aged

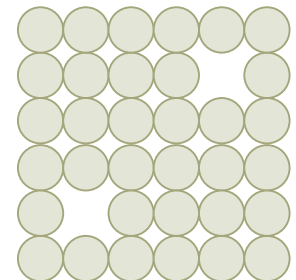
Accumulation of
senescent cells



QOL Low

Aged

Elimination of
senescent cells

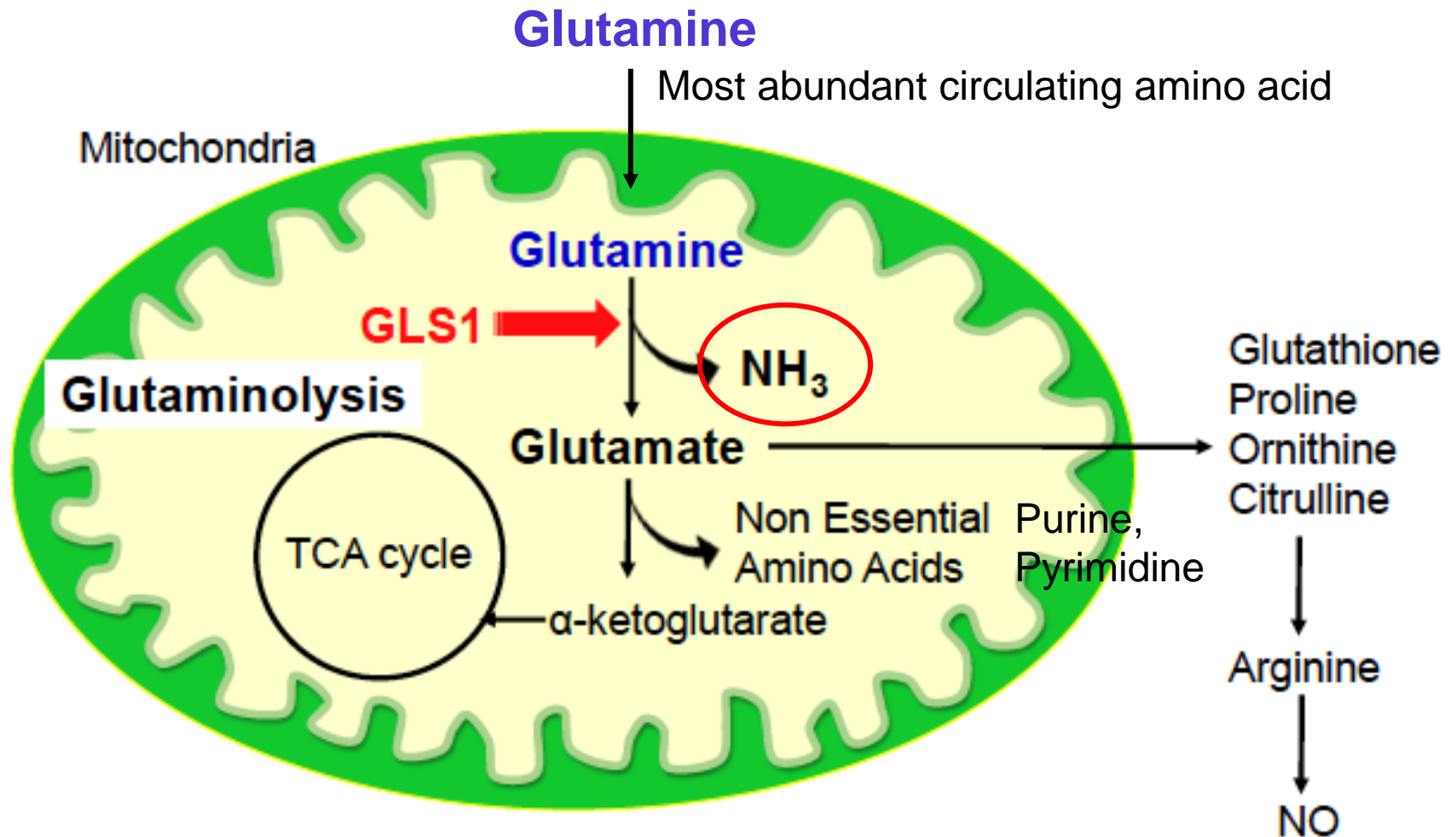


QOL high

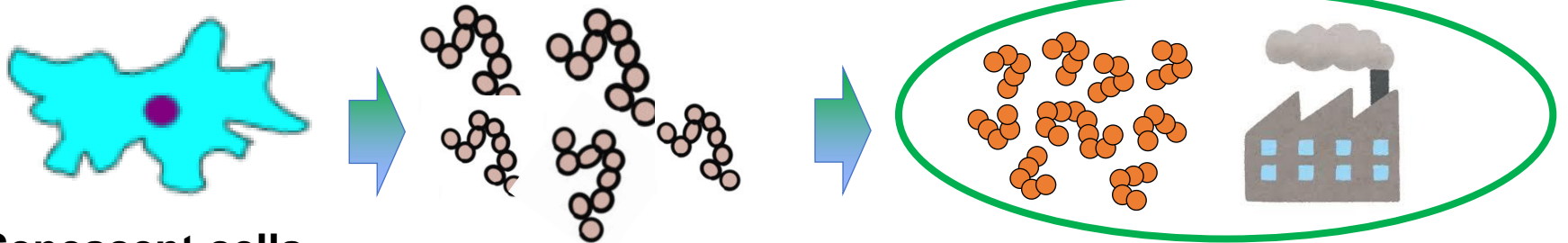
Research background

**Improvement of aging by
senolysis**

GLS1 is essential for senescence survival



A mechanism of senolysis by GLS1 inhibitor

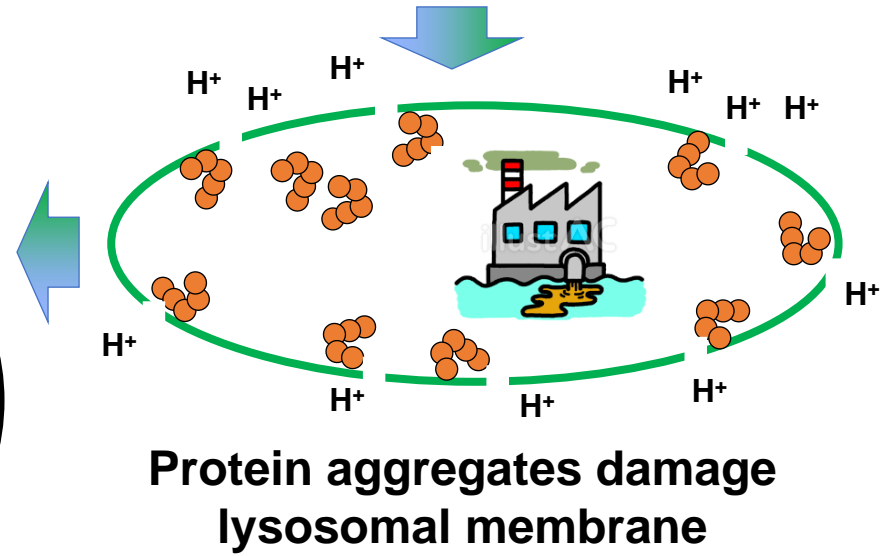
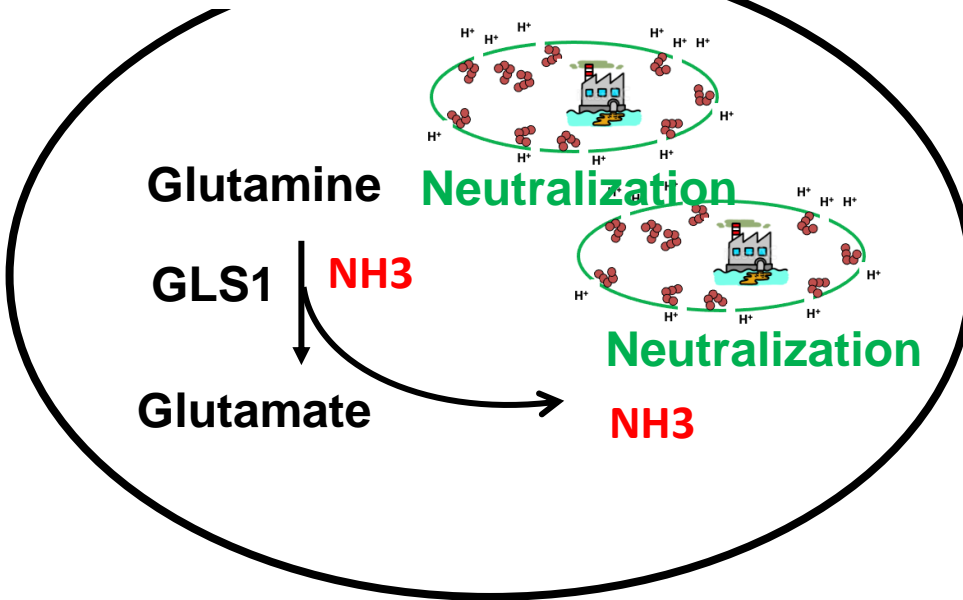


Senescent cells possess twice DNA amount than normal

Excess protein synthesis

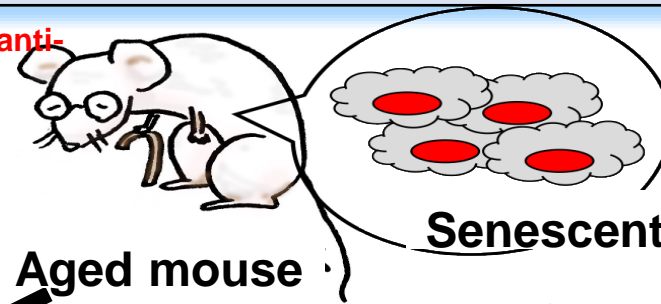
Accumulation of misfolded proteins in lysosomes

Senescent cells



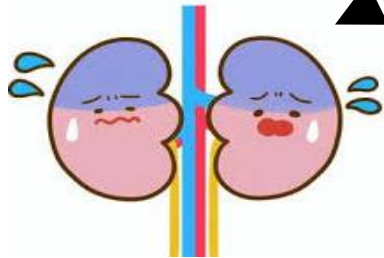
Amelioration of age-associated disorders by GLS1 inhibitor in vivo

GLS1 inhibitors are in development as anti-cancer drugs targeting cancer cells
No significant side effects
When targeting senescent cells, the dosing regimen can be devised

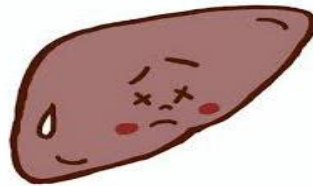


Planned clinical trials for unmet medical needs such as chronic renal failure, fatty hepatitis, and frailty

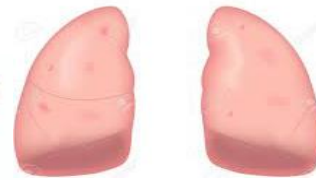
Elimination of senescent cells by GLS1 inhibitor



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

Current Status of GLS1 Inhibitors into Clinical Application:.

IPN60090 In development in the U.S. for the treatment of solid tumors Phase I KEAP1/NFE2L2 mutant cancer 60% efficacy

CB-839 In development in the U.S. for PIK3CA mutant colorectal cancer Phase I
Little significant side effects

Research progress and future plans

Summary of progress of projects over the past year

Development of technology to improve aging and diseases by removing inflammation-induced cells

2040

Elucidation of the mechanism of carcinogenesis prevention by removal of inflammation-induced cells

- Development of innovative cancer therapies targeting cancer stromal senescent cells

Elucidation of the mechanism of improvement of organ function by removal of inflammation-induced cells

- Rejuvenation of immune aging
- Rejuvenation by immune checkpoint inhibition
- Improvement of chronic renal failure by CD153 signaling inhibition
- Improvement of chronic renal failure by GLS1 Inhibition

Development of technology to remove inflammation-induced cells

- Remove senescent cells using immune system
- Development of vaccines against senescent cells
- Development of GLS1 inhibitors

Organ and stem cell dysfunctions due to excessive inflammation

- Aging acceleration in senescence accumulation mice
- Identification of epigenomic signatures of aged hematopoietic stem cells

Comprehensive identification of inflammation-inducing cells

- Elucidation of inflammation induction in lysosome-deficient cells
- Creation of in vivo senescent cell atlas

2020

Summary of progress of projects over the past year

Development of technologies for predicting and measuring the degree of aging

2040

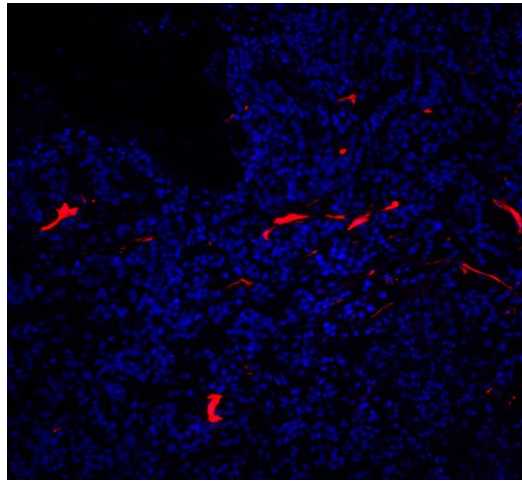
Prediction of measurement of aging degree by genomics, PET, and liquid biopsy

- Identification of lifespan associated genes
- Establishment of PET technologies for quantification of inflammation and senescent cells in vivo and its application to humans
- Development of technologies for quantification of senescent cells in vivo using exhaled gas

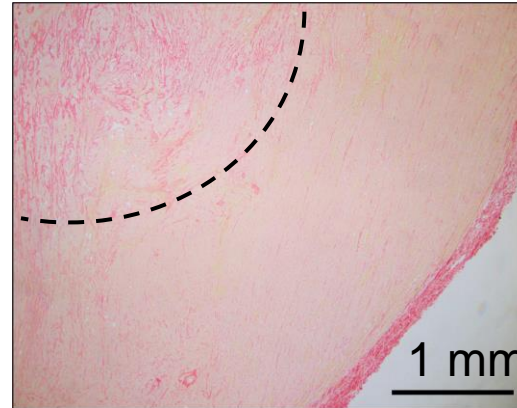
2020

Cancer as an unmet medical need

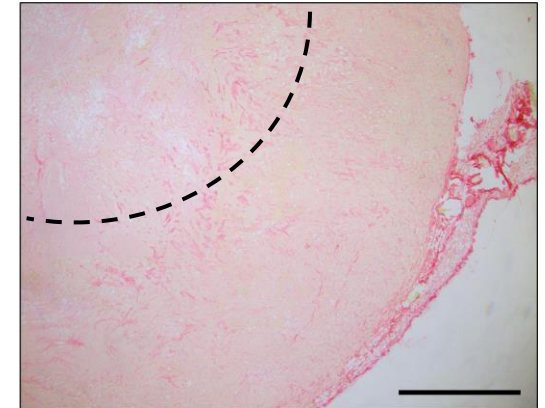
Cancer stromal senescent cells



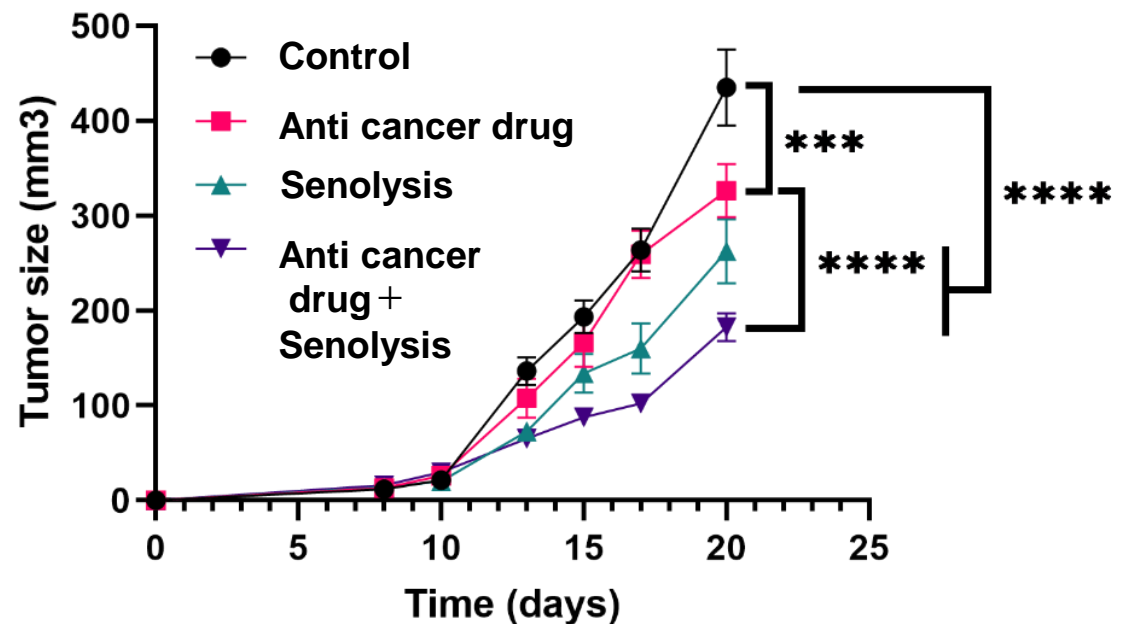
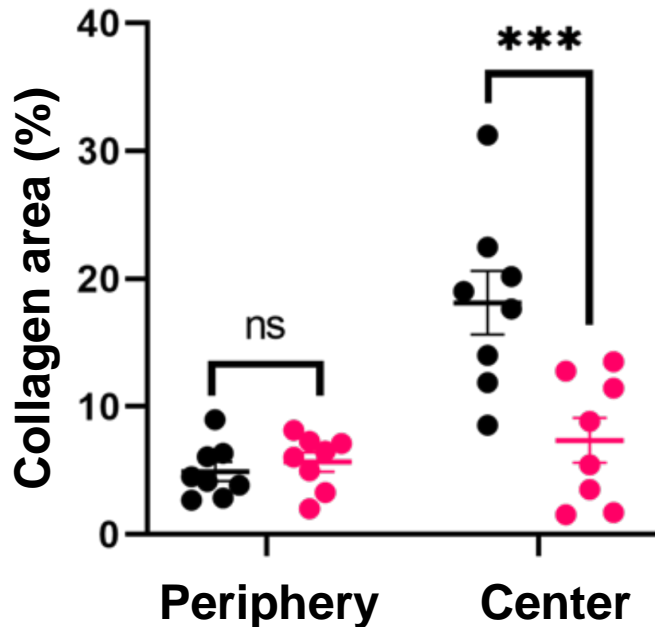
Control



Removal of senescent cells



Tumor growth

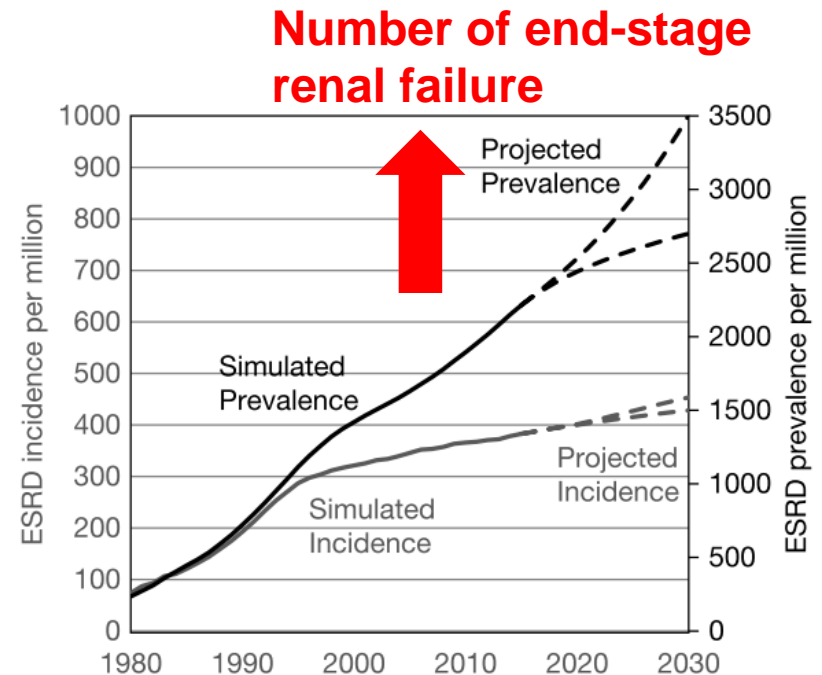


Chronic kidney disease as an unmet medical need

- Definition : Abnormal kidney structure or function for more than 3 months
- End-stage renal failure, requiring dialysis therapy or kidney transplantation
- **eGFR < 60 ml/min/1.73m²**
- World : **13.4%**、 Japan : About 13.3 million: CKD, 330,000 : RRT
- CKD→End-stage will increase **11-18% from 2015-2030**
- RRT: **540 million in 2030**

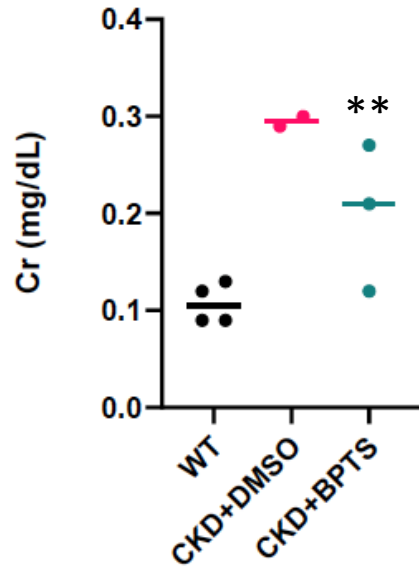
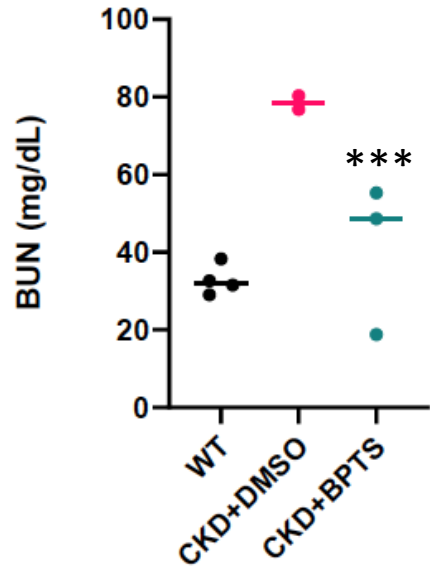
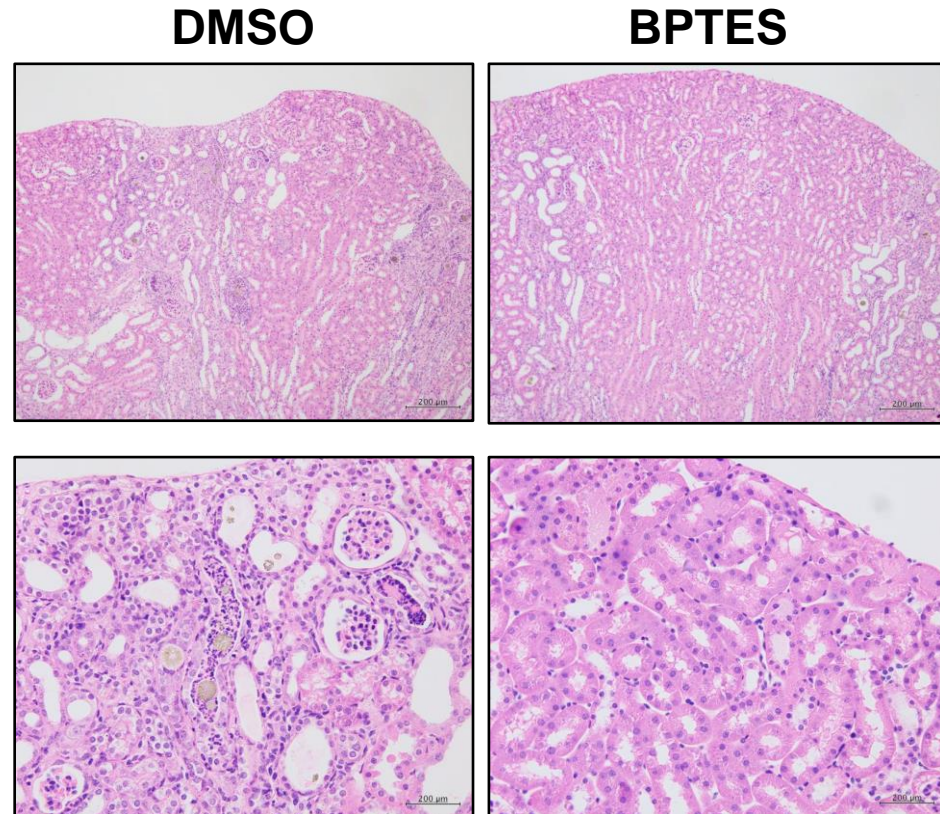
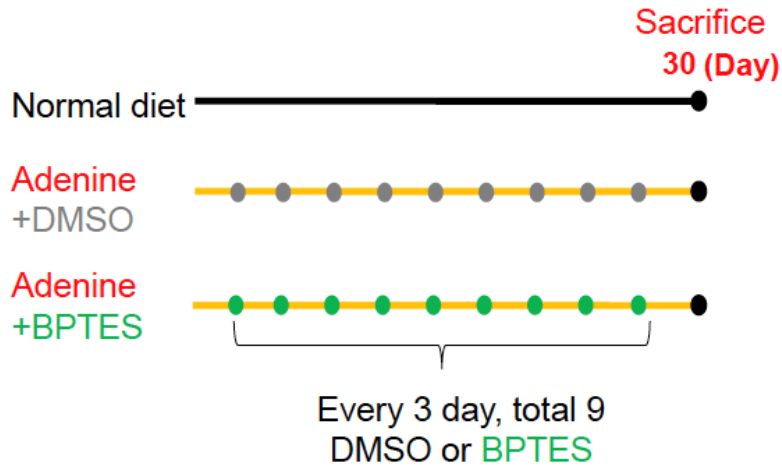


- 2012 KDIGO guideline
- GBD Chronic Kidney Disease Collaboration. Lancet. 2020.
- Hill, N.R et al. PLoS ONE. 2016.

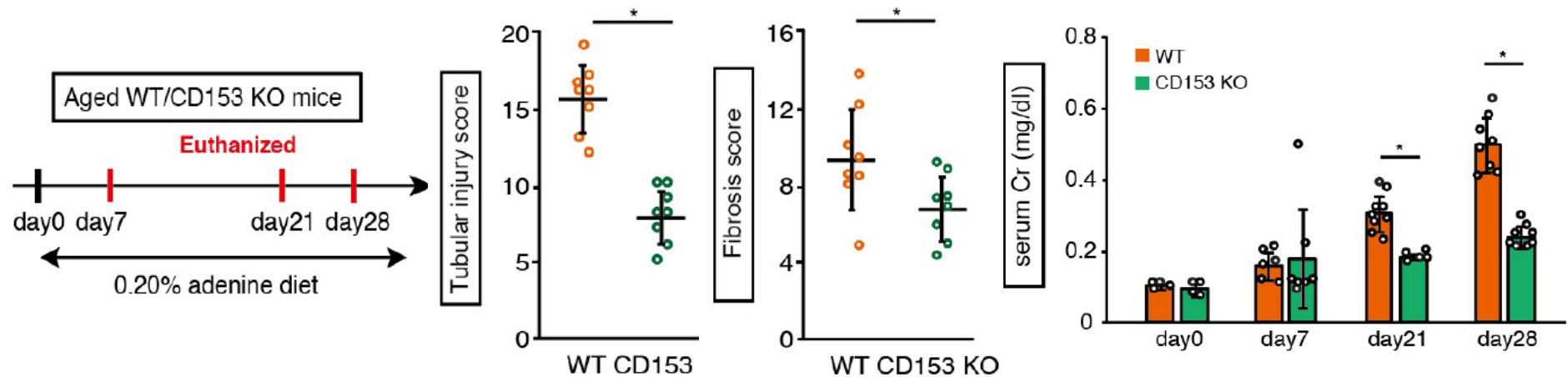
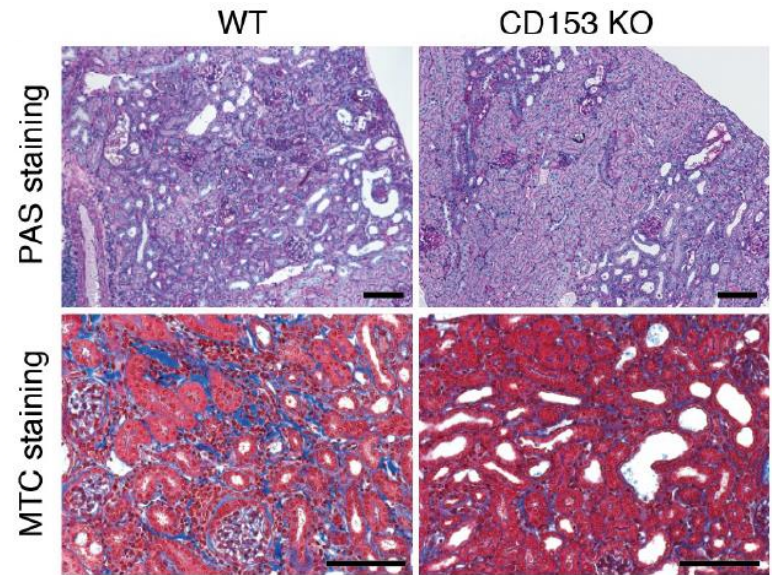
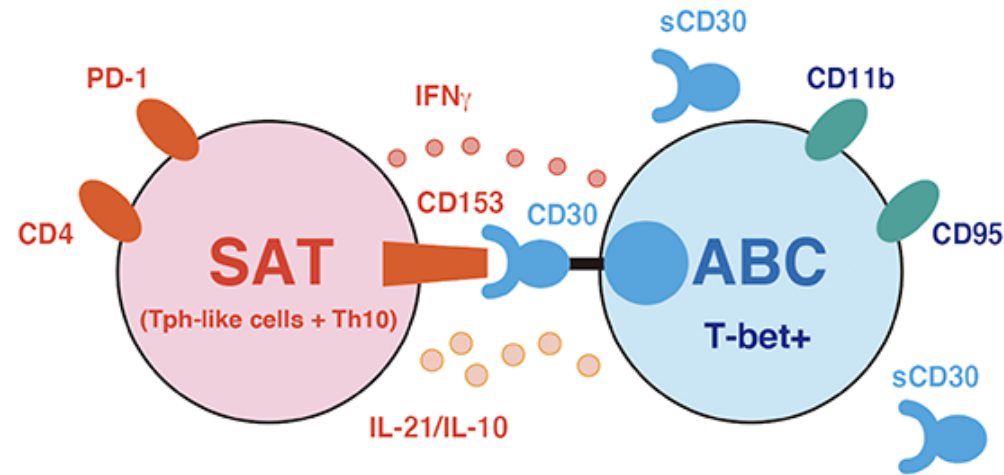


Improvement of CKD by GLS1 inhibitor

Age; 2 month



Improvement of CKD by suppression of CD153 signal



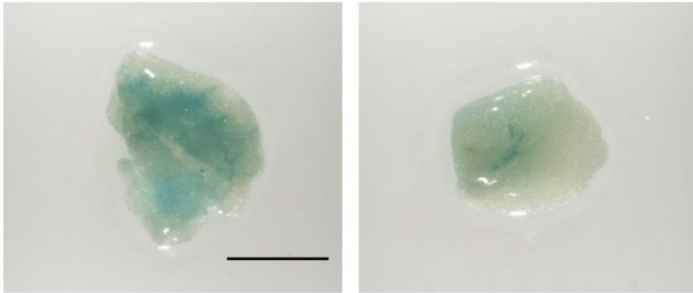
Development of senolytic vaccine

Effects of the senescence vaccine on obese mice

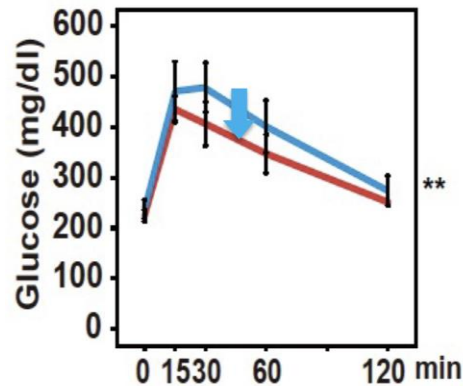
SA- β gal staining (細胞老化染色)

Cont vac

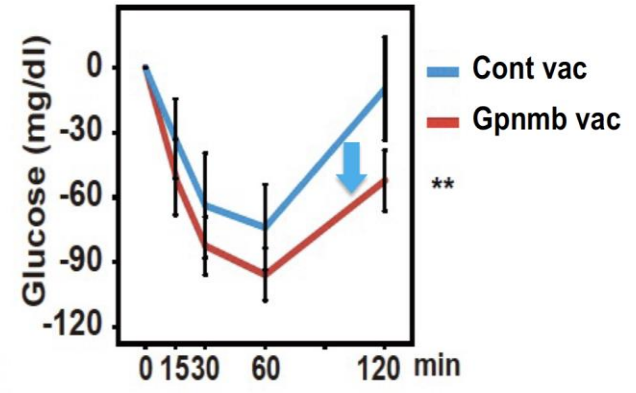
Gpnmb vac



Glucose tolerance test

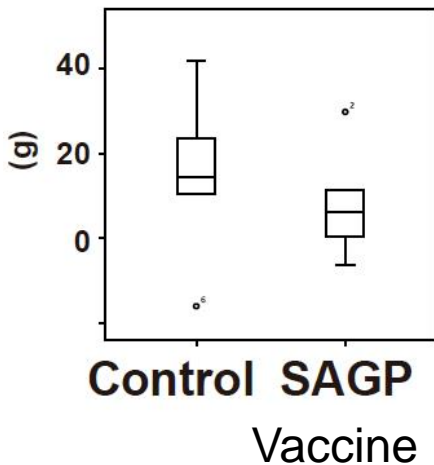


Insulin tolerance test

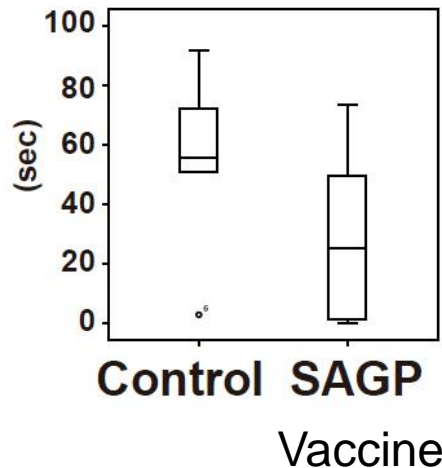


— Control
— SAGP Vaccine

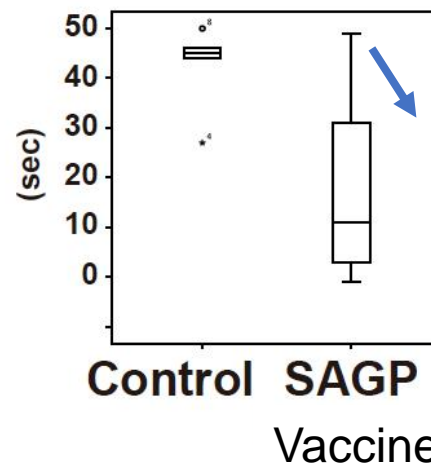
Grip strength



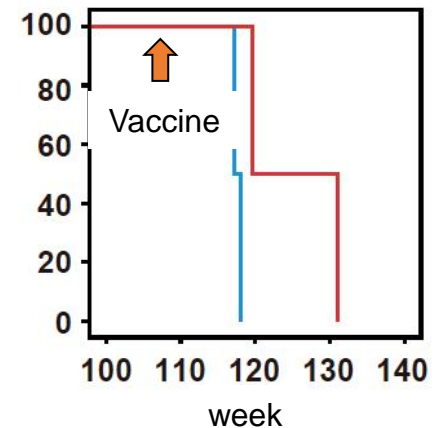
Motor function



Muscle power



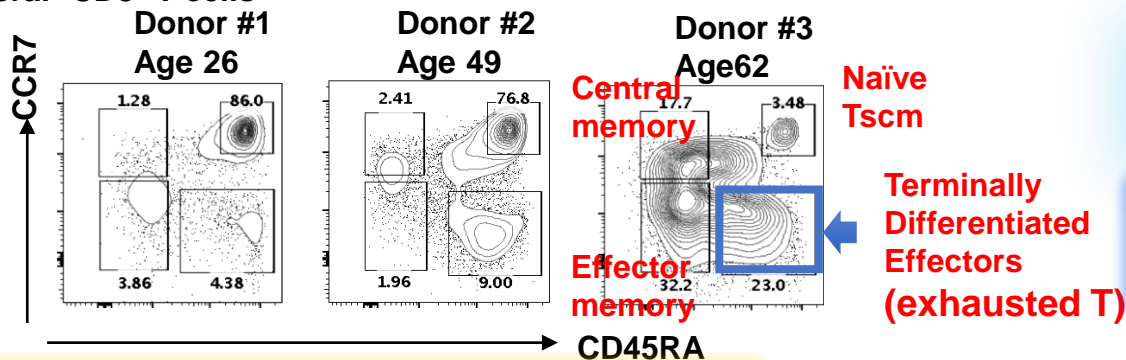
Survival



Rejuvenation of exhausted T cells

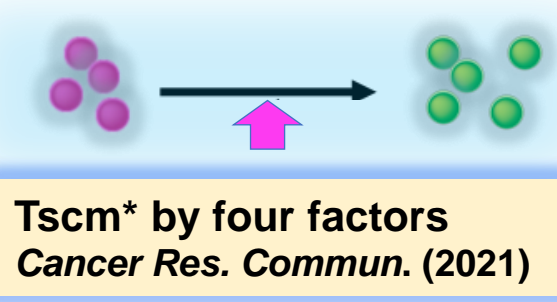
Age-dependent increase in exhausted T cells

Peripheral CD8⁺ T cells



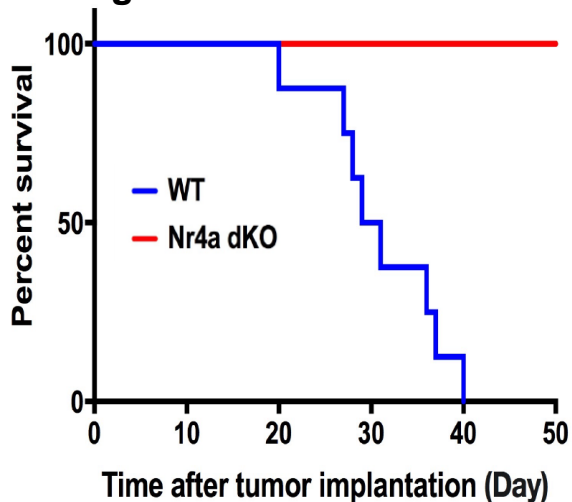
Exhausted T cells

CAR-iTscm



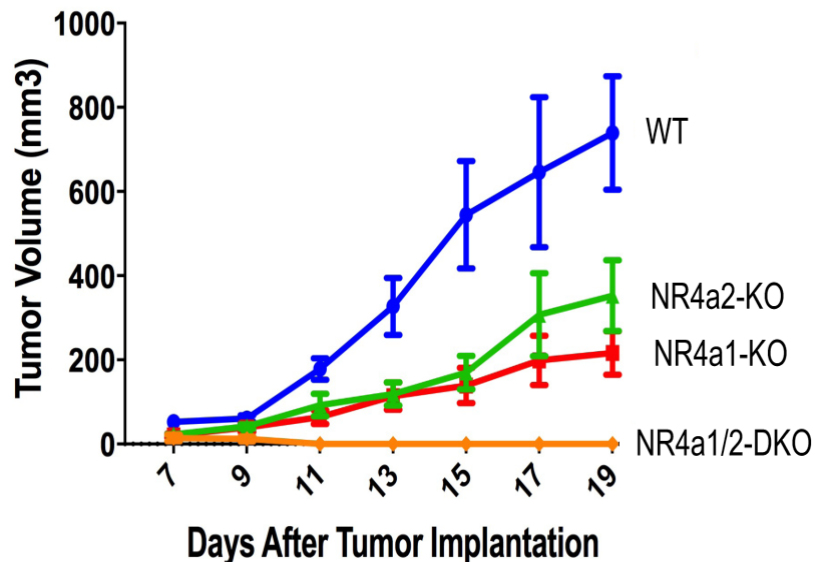
Identification of NR4a as a factor for exhausted and senescent T cells

Strong resistance to tumors

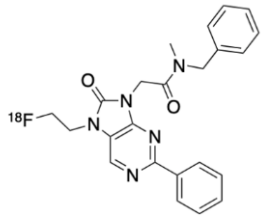


* Tscm is the youngest T cells

Tumor Growth Curve (B16)

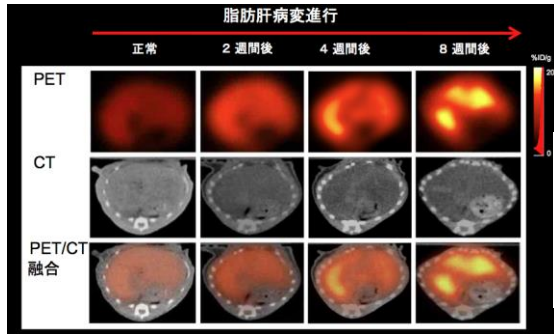


Quantification of senescent cells and diagnosis of aging with PET



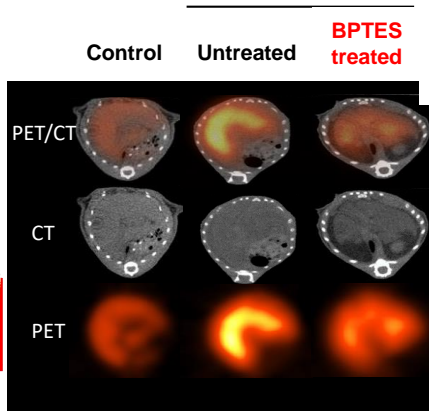
[¹⁸F]FEDAC

TSPO-PET probe
developed by QST

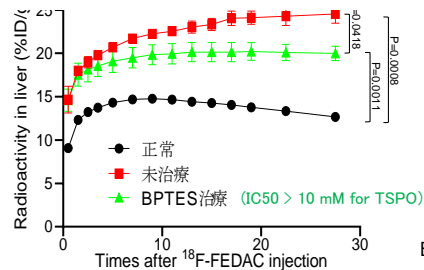


Xie et al, J Hepatol, 2012

Fatty liver

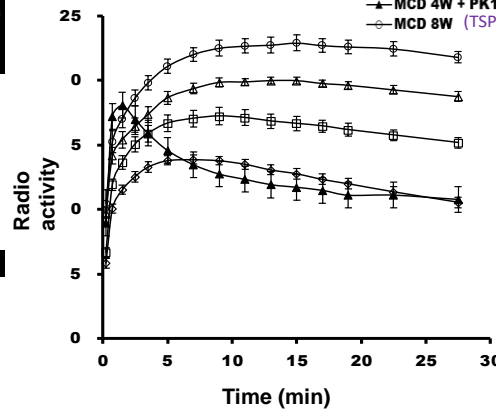


Quantification of radio activity in liver

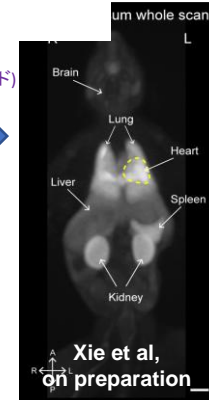


Dose-dependent effectを確認

Quantification of radio activity in liver



Monkey PET

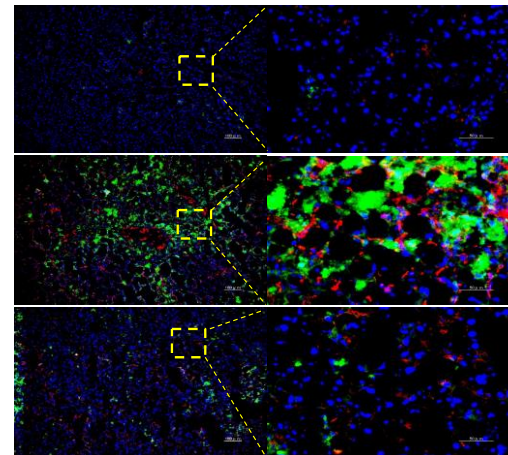
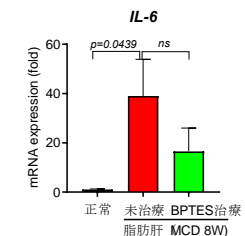
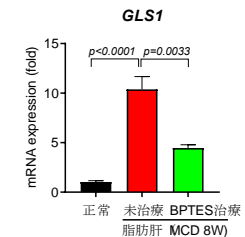
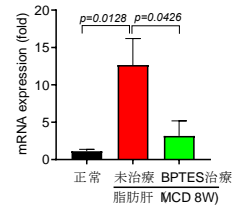


First-In Human PET Study

Safety confirmed

Patients

TSPO



DAPI/TSPO/SA-β-gal

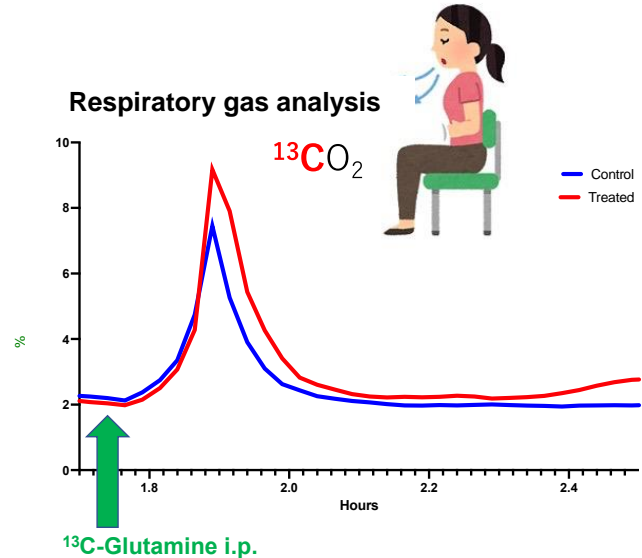
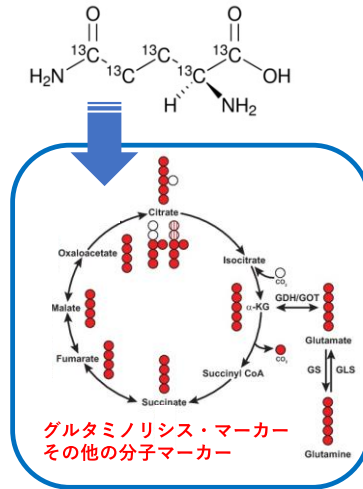
Xie et al, on preparation

TSPO-PET can image senescent cells and evaluate the effects of anti-aging drugs

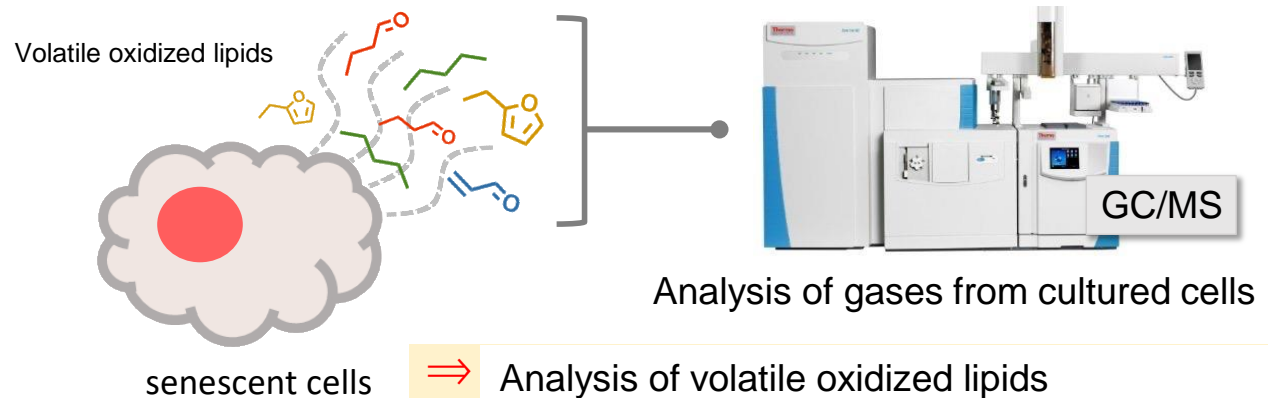
Establishment of diagnostic methods for aging using respiratory gas

Respiratory gas analysis

Development of glutaminolysis markers

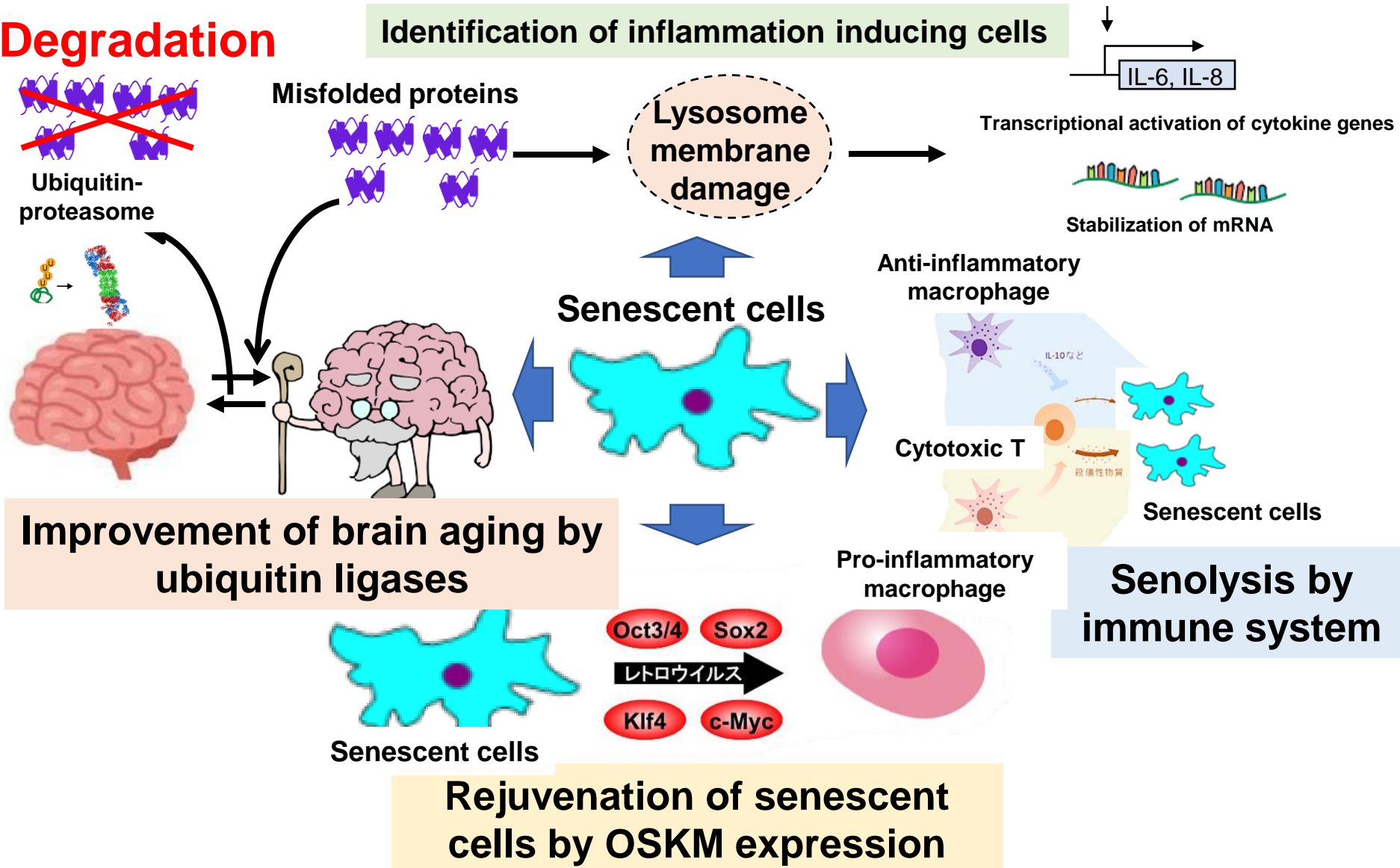


Analysis of volatile oxidized lipids released by inflammation-induced cells



Ongoing projects

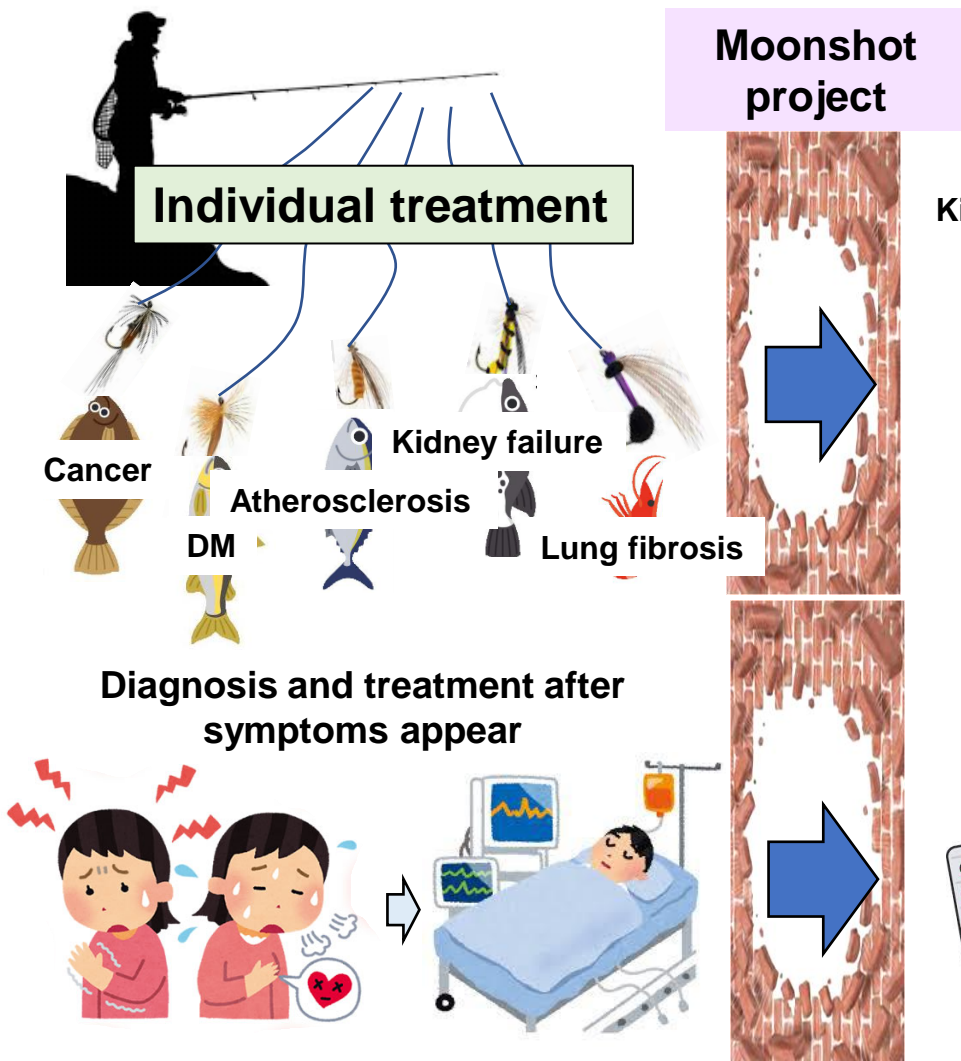
Degradation



The reason why our project can be categorized as a moonshot

Present

Individual treatment for each disease



The 2040s

One treatment for all geriatric diseases

