Moonshot Goal 7 (AMED)

Healthy longevity through improved mitochondrial function

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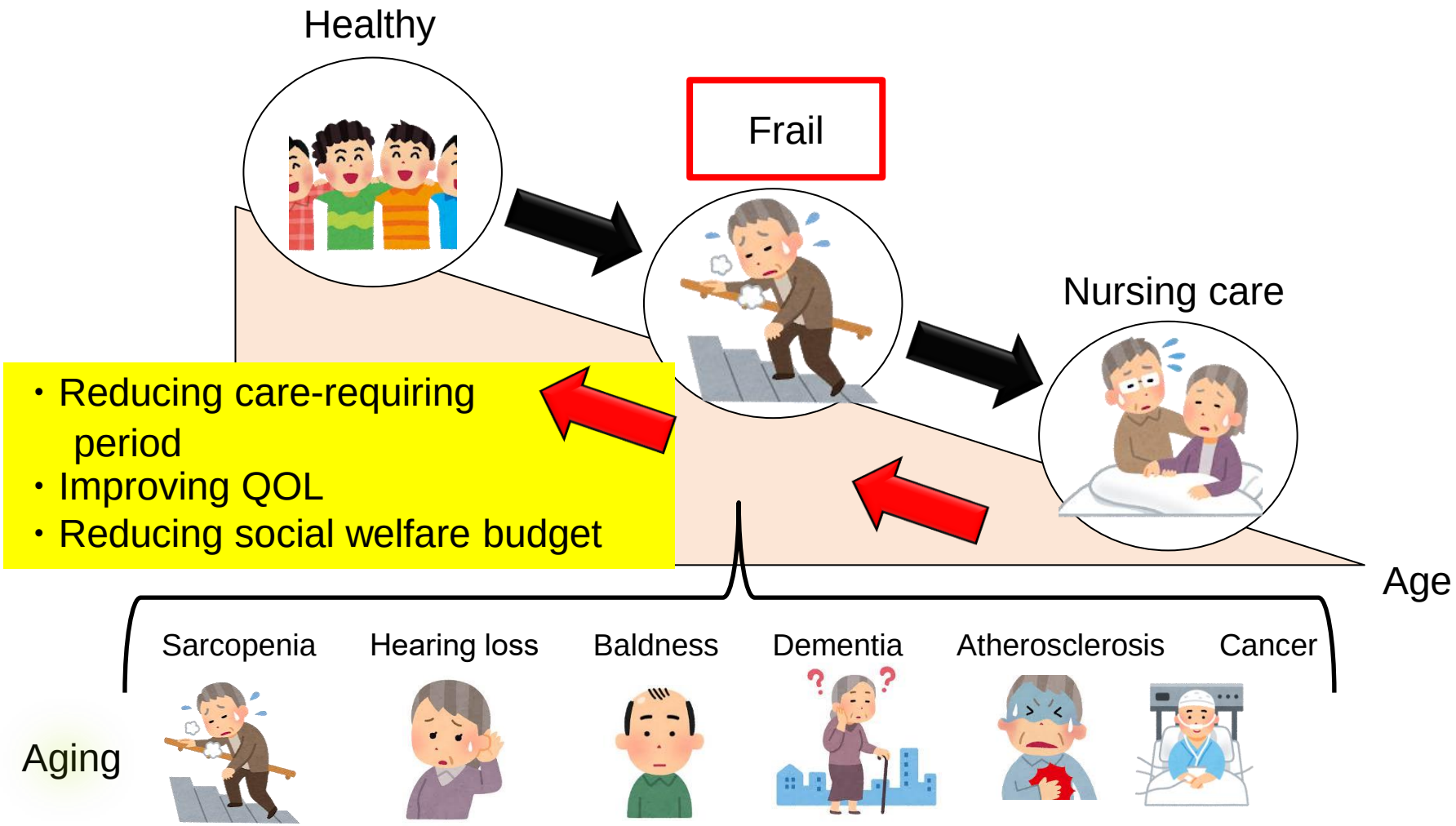
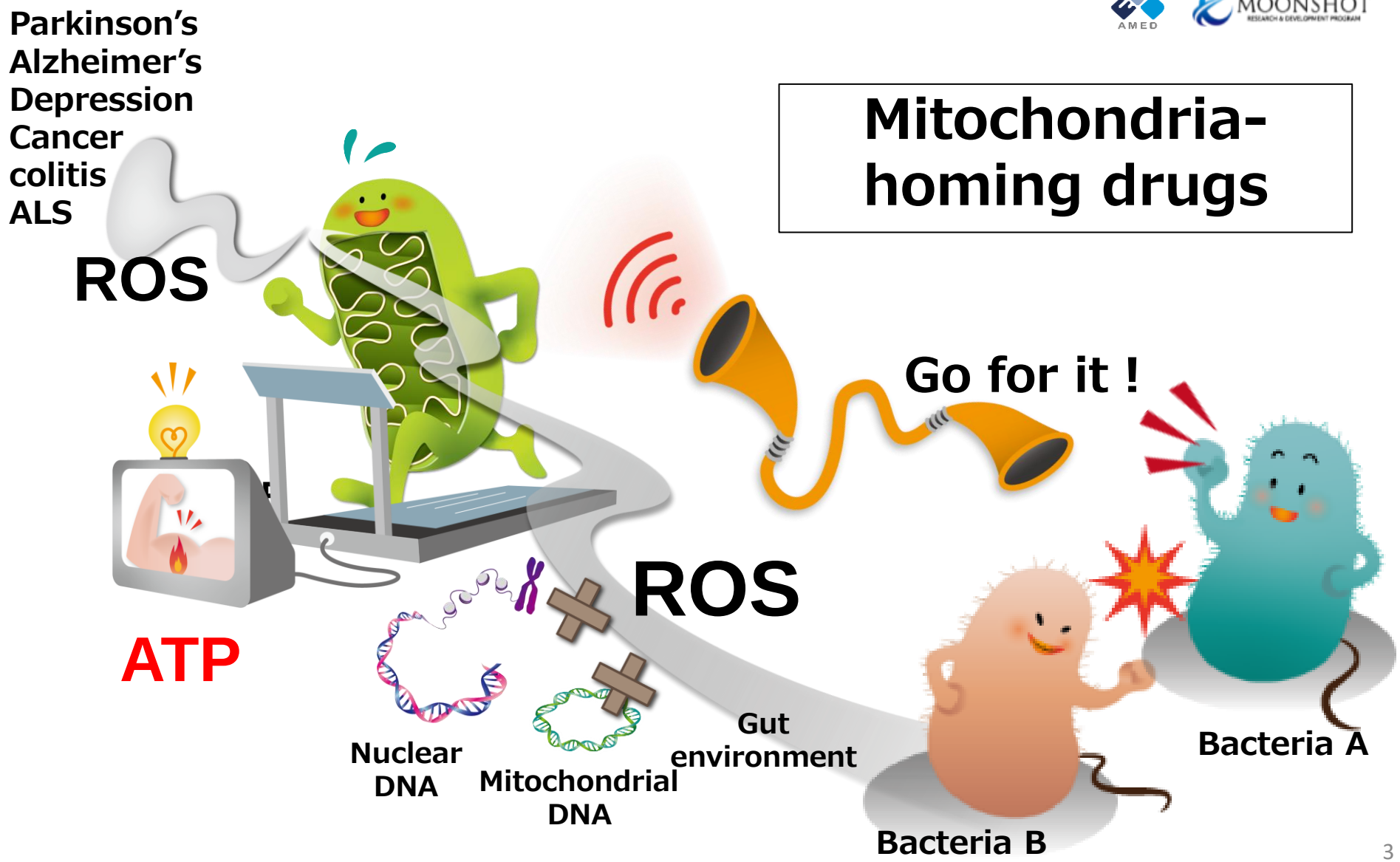
Symposium for Moonshot Goal 7: July 16, 2022

Japan has the problem of aging and the intervention is urgently required



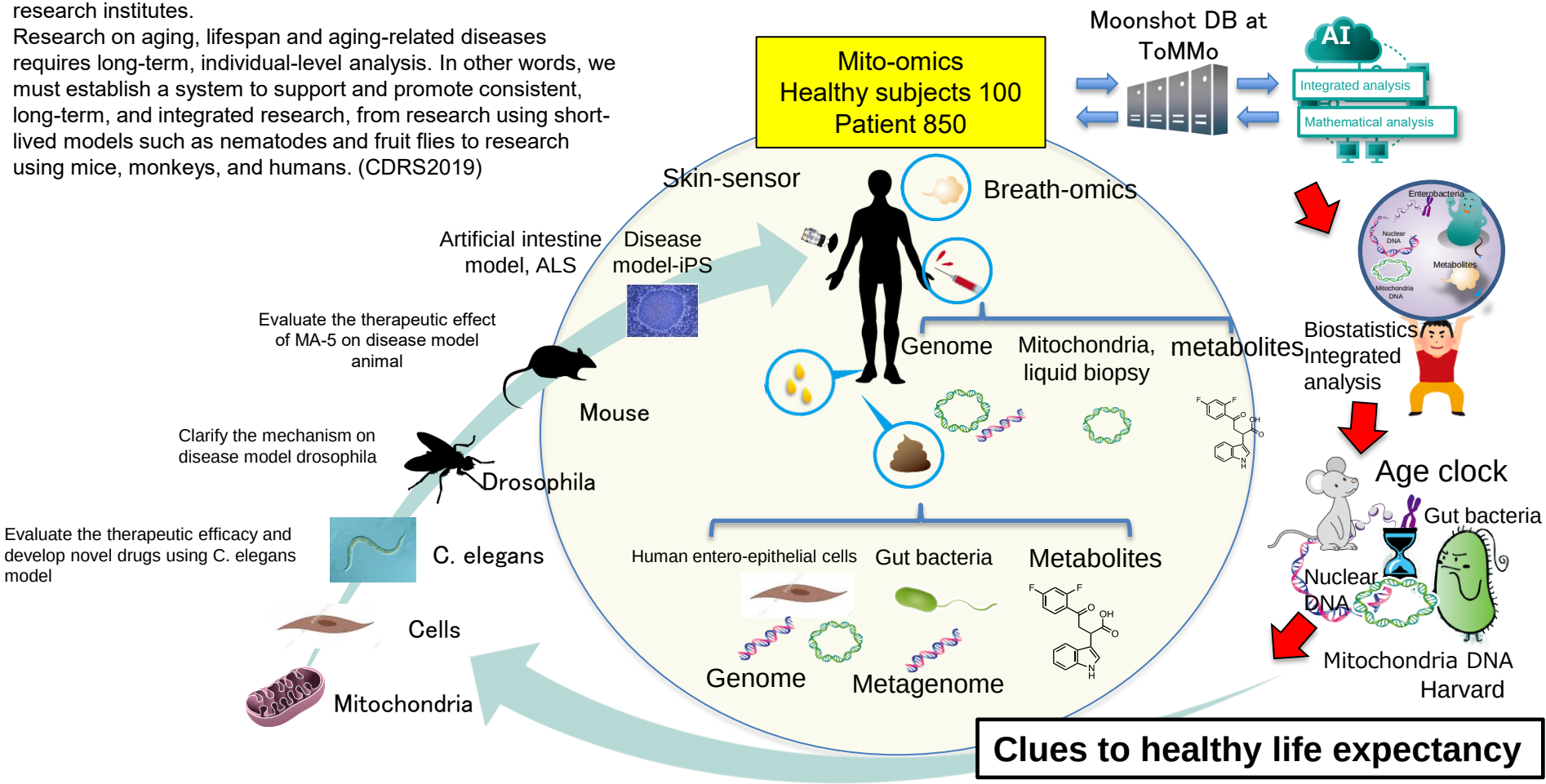
Mitochondria-gut microbiota relation (Human)



Aim of this project (Mitochondrial Medicine)

Centralized analysis of aging in this study

The world is competing to establish and focus on aging research institutes.
Research on aging, lifespan and aging-related diseases requires long-term, individual-level analysis. In other words, we must establish a system to support and promote consistent, long-term, and integrated research, from research using short-lived models such as nematodes and fruit flies to research using mice, monkeys, and humans. (CDRS2019)



- We should establish a system to support and promote long-term, integrated research using cultured cells, nematodes, Drosophila, mice, pigs, human iPS cells, intestinal bacteria, and human trials. Unified elucidation of mitochondrial function regulation mechanisms and aging for rehabilitation, food development, and drug discovery.
- We will immediately verify the findings obtained from basic research in animal experiments to promote research on aging and lifespan through a cycle of exploration of fundamental principles and realize a healthy and long-lived society ahead of the rest of the world.

Mito-omics

＜Hypothesis＞ ＜Confirmation＞ Mitochondrial Medicine

ALS/Mitochondrial Disease 80 cases

IBS 150 cases

Dementia 150 cases

Cancer 450 cases

ATP↓

ROS

Aging clock・Sensor

(NGS)

Blood

Urine

Feces

(NGS)

Data Integration

Drugs

MA-5 etc.

Nuclear DNA

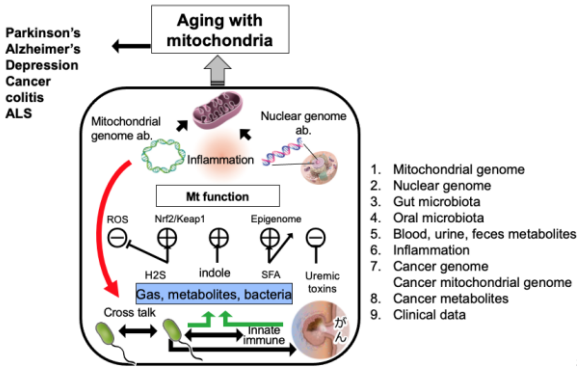
micro biota

Metabolite

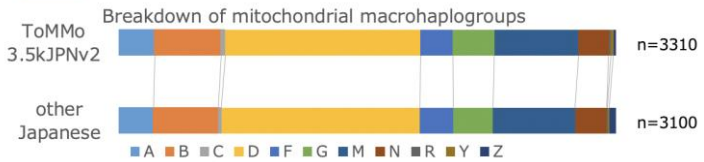
Mitochondrial DNA

Marker
Sensor
Drugs

Data & Sample distribution

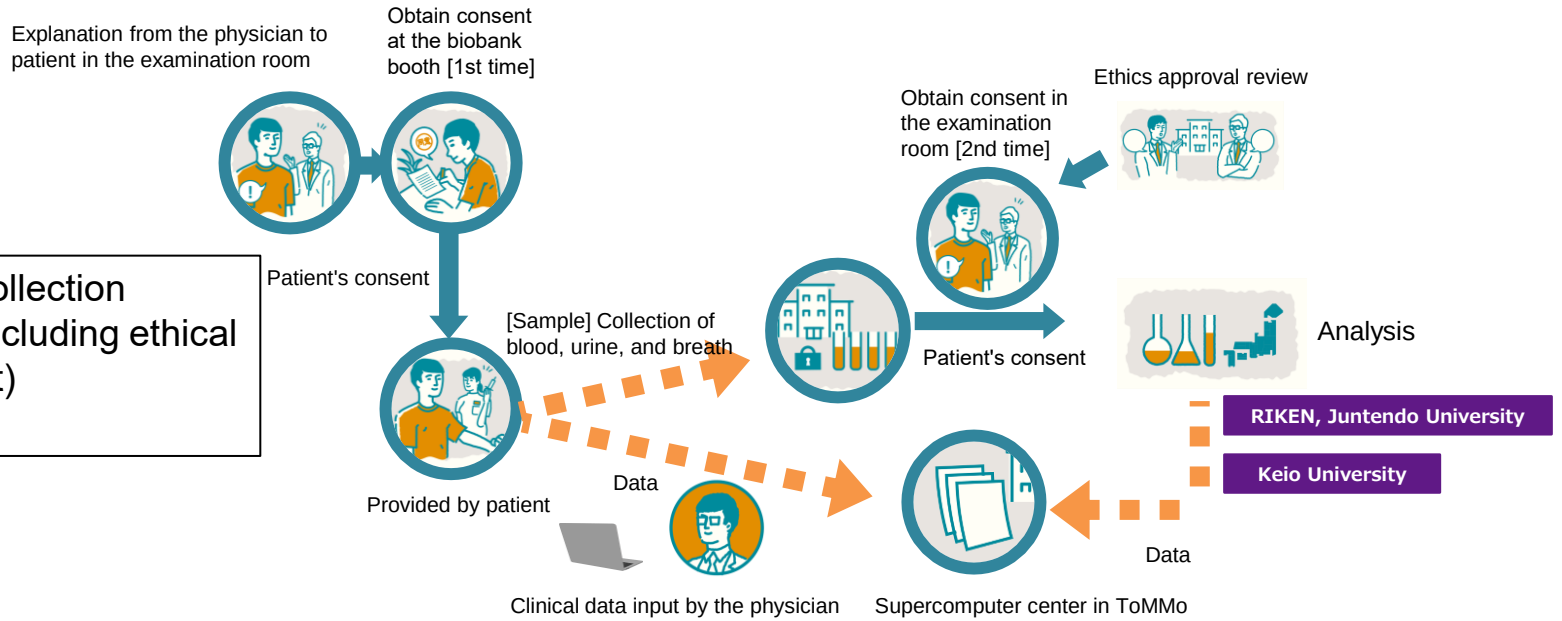


Mitochondrial data of ToMMo represented Japanese average population

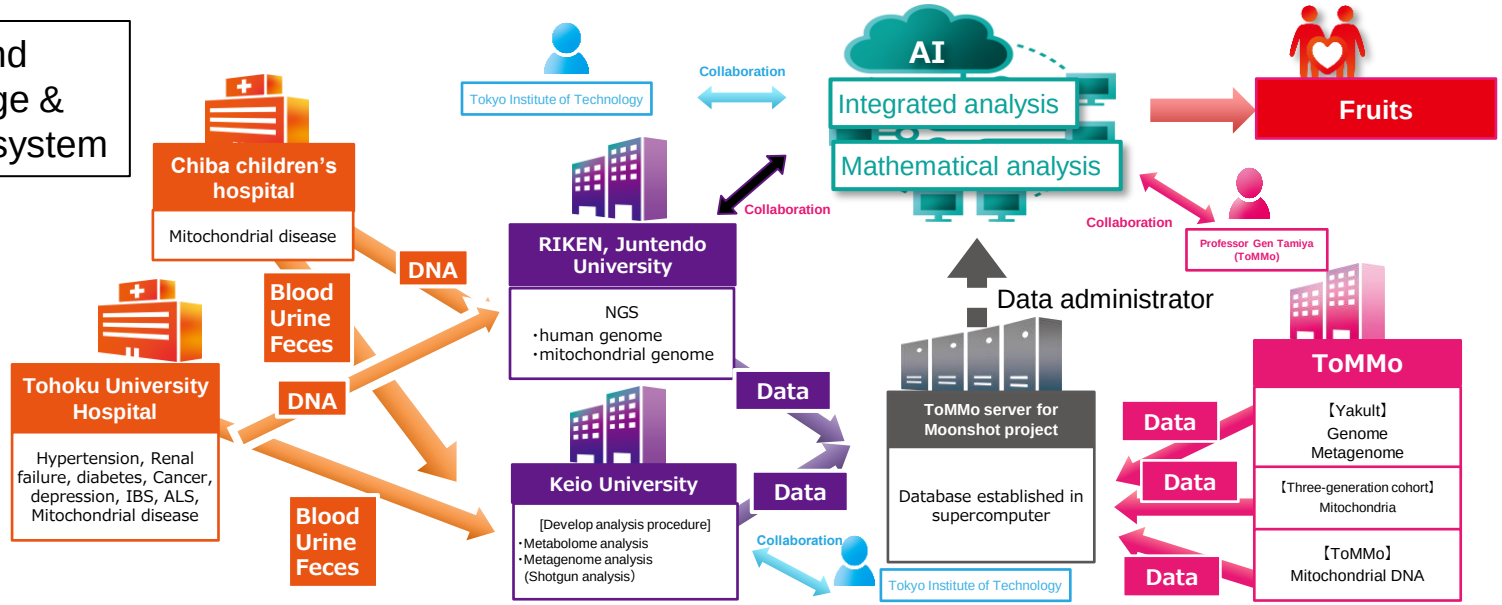


System architecture for the collection of clinical specimens and data management in the hospital

Sample Collection System (including ethical agreement)



Analysis and Data storage & Managing system



Mitochondria-targeted drug development

＜Existing drug＞

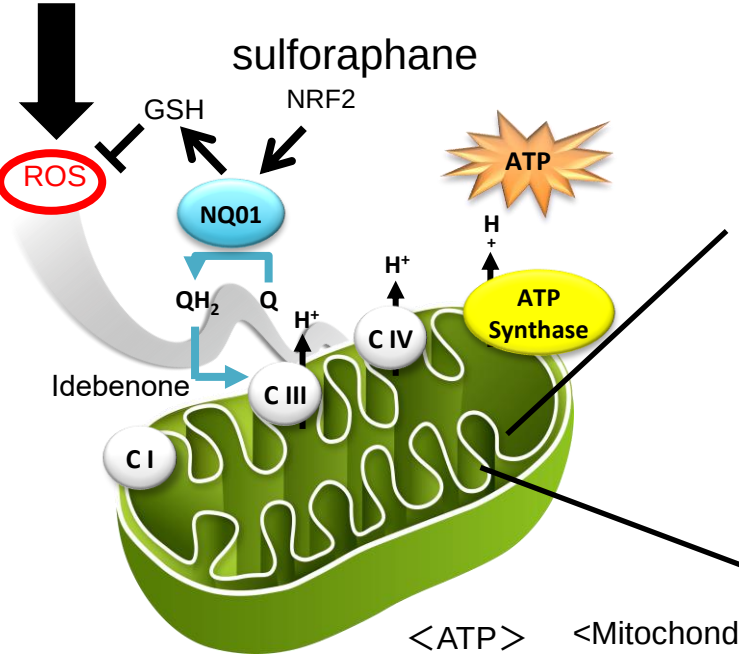
Antioxidants

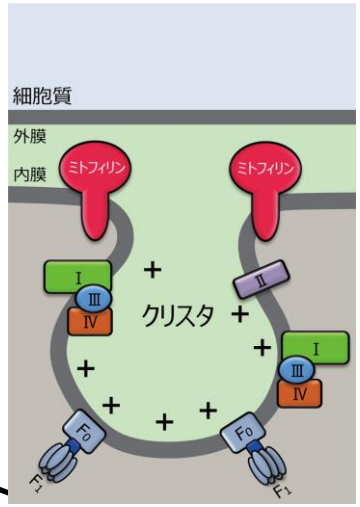
Idebenone	CoQ10
Vit. C	α-lipoic acid

＜MA-5＞

Novel structure-activity correlation mechanism mediated by mitofilin, a binding protein for MA-5.

MA-5 exhibits the therapeutic intervention effect on any-types of mitochondrial disease cells that has an impairment of mitochondrial complex protein





Leigh encephalopathy

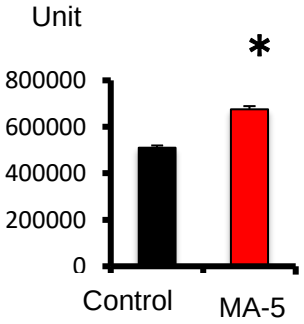
MELAS

Leber disease

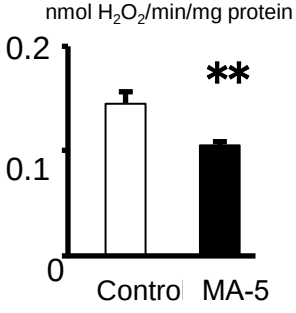
KSS

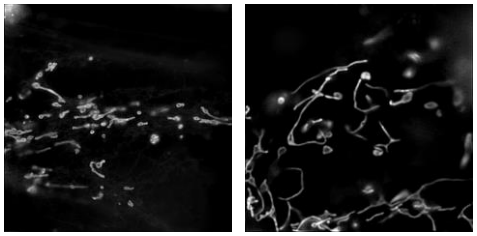
番号	疾患名	名称	Age	Mito.遺伝子変異	変異タンパク	BSO	MA-5効果	GDF-15(血液)	FGF-21測定
1	Normal fib.	Nor.	0	(−)	(−)	(−)	(−)		
2	Leigh (complex I異常)	THK2	8	m.10191 T>C	ND3	(+)	(+)	4555.7	3230.0
3	Leigh	THK5	12	未検	未検	(+)	(+)		
4	Leigh (complex I異常)	THK6	8	m.10191 T>C	ND3	(+)	(+)	2051.5	3241.8
5	Leigh	THK7	16	既知の変異無し	無し	(+)	(+)		
6	Leigh	KCMC10	0	m.10158 T>C	ND3	(+)	(+)		
7	Leigh (complex I異常)	ME54-1		(c.55 C>T)	(NDUFA1)	(+)	(+)	671.2	
8	Leigh (complex IV異常)	KCMC17		(c.367_368delAG)	(SURF1)	(+)	(+)		
9	Leigh(Homoplasmy)	KCMC14		m.8993 T>G	ATPase6	(+)	(+)		
10	Leigh	KCMC15		(p.Ala 248 Asp)	(SURF1)	(+)	(+)		
11	LHON (高齢)	THK9	66	m.11778 G>A	ND4	(−)	(−)	2647	434.9
12	LHON(若年)	THK8	18	m.11778 G>A	ND4	(+)	(+)	520.1	80.9
13	LHON(中年)	THK10	41	m.11778 G>A	ND4	(+)	(+)	1322.4	912.1
14	MALAS (腎障害なし)	KCMC9		m.3243 A>G	tRNA-Leu	(+)	(+)		
15	MELAS(腎障害あり)	KCMC5		m.3243 A>G	tRNA-Leu	未検	未検		
16	MELAS	KCMC11		m.3243 A>T	tRNA-Leu	(+)	(+)		
17	MELAS	KCMC12		m.586 G>A	tRNA-Phe	(+)	(+)		
18	MELAS(腎障害あり)	THK12	56	m.3243 A>G	tRNA-Leu	(+)	(+)	5505.7	1708.1
19	MELAS	ME54-1		m.4458G>A	tRNA-Met	(+)	(+)	784.5	
20	KSS(complex normal)	THK4	13	既知の変異無し	無し	(+)	(+)	2900.2	2088.5
21	先天性大脳白質形成不全症	F488		c.227 G>A (c.574 C>T	(PNPT1)	(+)	(+)		
22	SMA(脊髄筋萎縮症)	KCMC6		未検	未検	(+)	(+)		
23	OPA1 欠損症	THK14	73	c.1377_1381delTGTAA	p.Asn459 Metfs	(+)	(+)	1310.2	215.8
24	未分類(Rui CKD)	THK1	13	既知の変異無し	無し	(+)	(+)	4910	789.9
25	未分類(complex IV異常)	THK3	3	検討中	不明	(+)	(+)	1071.4	66.5
26	未分類(Mine)	THK11	64	既知の変異無し	無し	(+)	(+)	4428	396.4

＜ATP＞



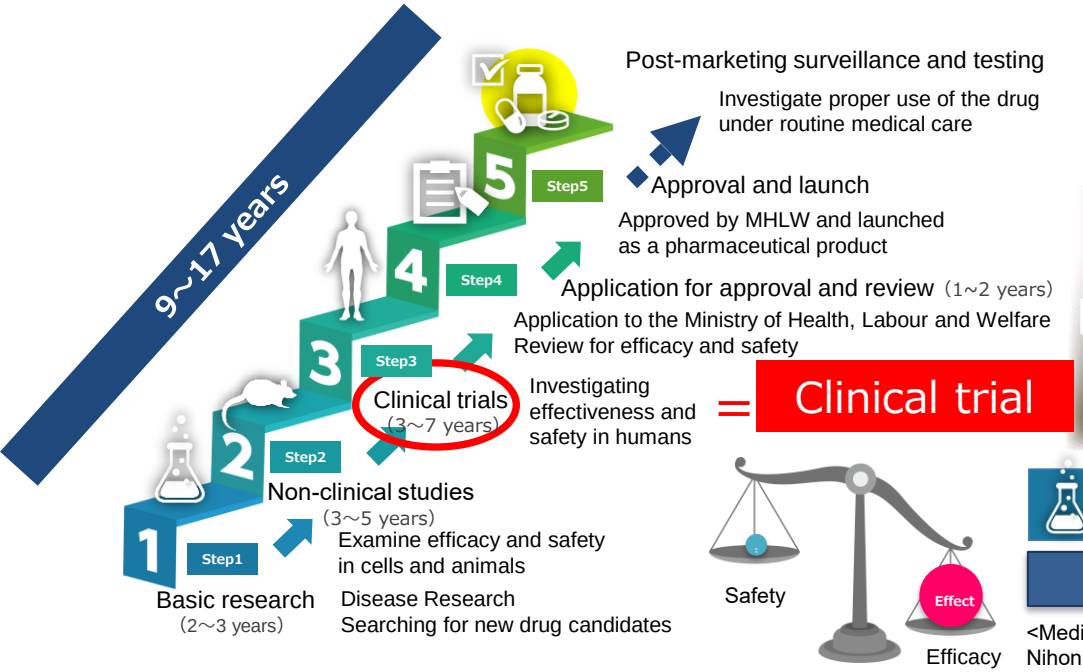
<Mitochondrial ROS production>





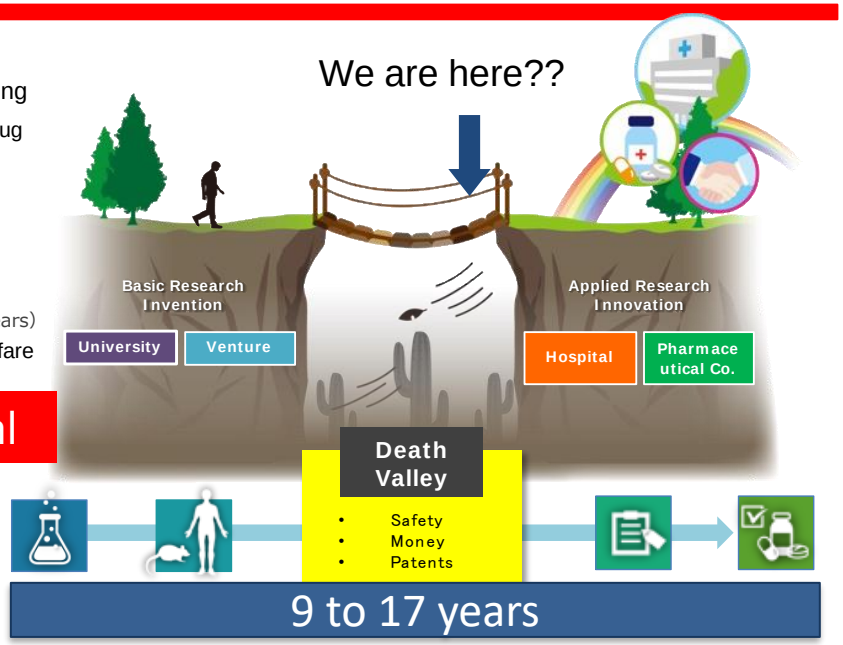
Matsuhashi T. et al. EBioMedicine, 2017

A clinical trial for MA-5, a candidate drug for the mitochondrial disease, is now underway with healthy adult subjects. Phase 1 trial.



= Clinical trial

The balance between risk and benefit



<Media > Listed in
Nihon Keizai Shimbun, Nikkei Biotech, Nikkei Medical
Nikkei Medical, FNN Prime Online, 0Tele News 24, Jiji Press, Kahoku Shimpo, Nikkei Biotech, Sendai Broadcasting System, Miyagi Television, Tohoku Broadcasting System, NHK, etc.

Photo offered by clinical trial hospital

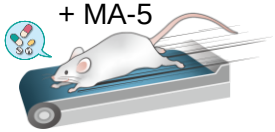
- World's first, from Japan. The first step toward overcoming the mitochondrial disease.
- MA-5, which has been developed, is an epoch-making candidate compound for the treatment of mitochondrial disease whose efficacy has been confirmed in cells of patients with mitochondrial disease and animal models of the disease.
- A clinical trial was initiated in which MA-5 was administered orally to 56 healthy adult subjects.
- The objective is to confirm the safety and pharmacokinetics of MA-5 in healthy adult subjects.
- Collaboration with patient associations is promoted.

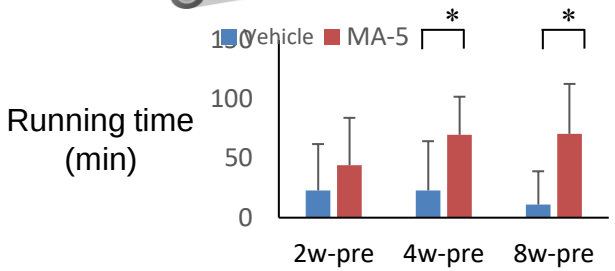
Indication of MA-5 treatment and conceivable application for cure

Muscle weakness

Disease mouse

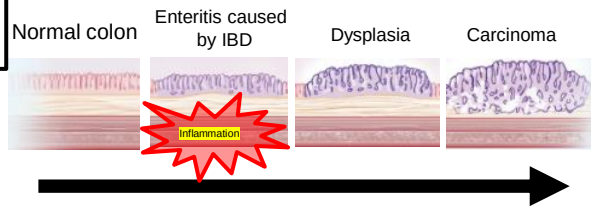
Disease mouse + MA-5

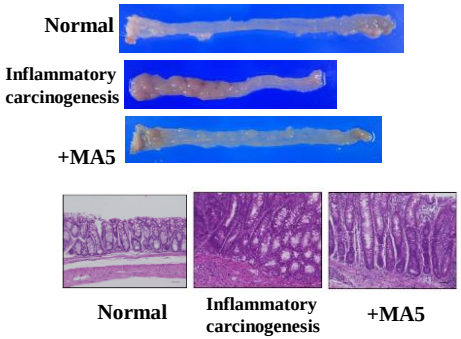


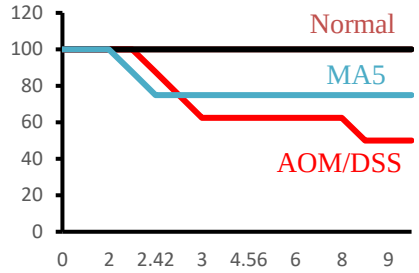


unpublished

Inflammatory carcinogenesis



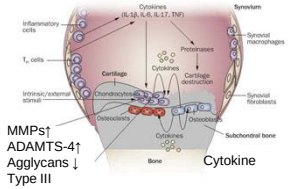




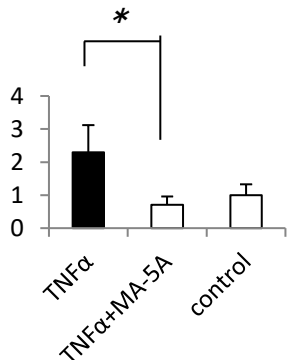
Pat application # 2019- 63638
Title：Anti-cancer drug
Submission：03/28/2019

Osteoarthritis

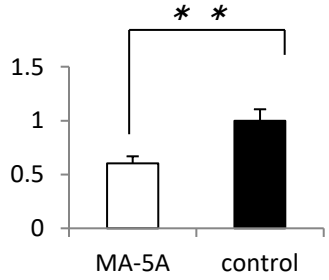
Chondrocytes in osteoarthritis produce inflammatory cytokines such as IL-1β and TNF-α. Inflammatory cytokines promote the expression of the cartilage matrix-degrading enzymes MMP-13 and ADAMTS.



ADAMTS-5



MMP13

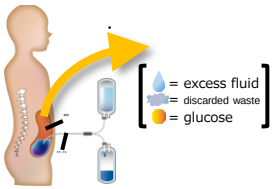


Drug for osteoarthritis
Patent #: 6977990
Date Dec.3. 2021

Peritoneal dialysis

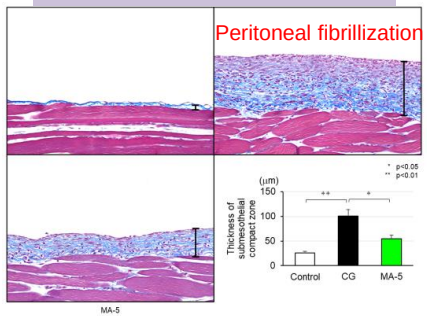
Collaboration research with Professor Tomoya Nishino at Nagasaki University

Hemodialysis ⟷ Peritoneal dialysis



Internationally, it has an affinity for developing countries due to the simplicity of the treatment, the fact that it can be done while working, the low electricity requirements, and the scarce human resources requirements.

Suppression of peritoneal fibrogenesis by MA-5

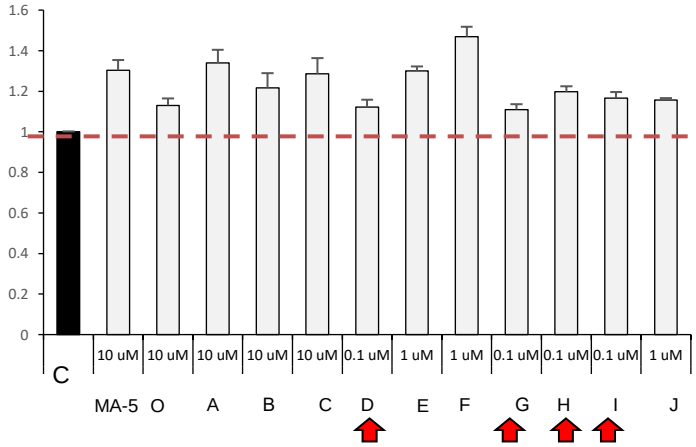


+MA-5

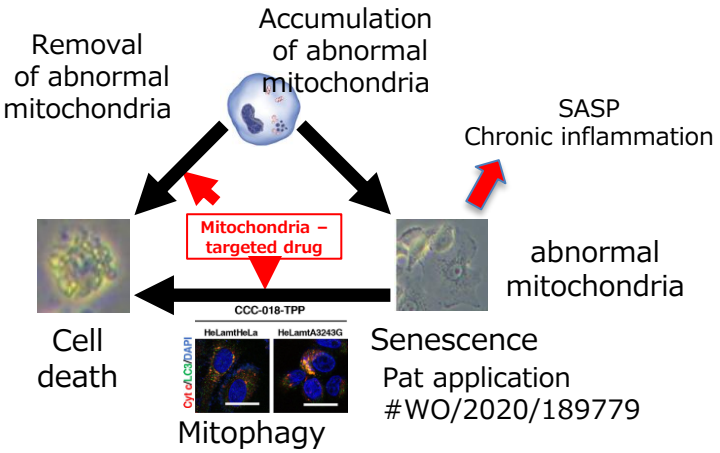
Inoue D. Med Mol Morphol 55: 27, 2022.

Developing drugs for mitochondria

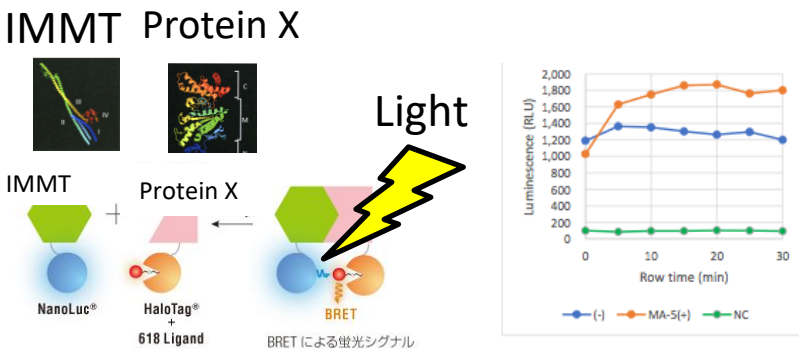
Other indole compounds for ATP production



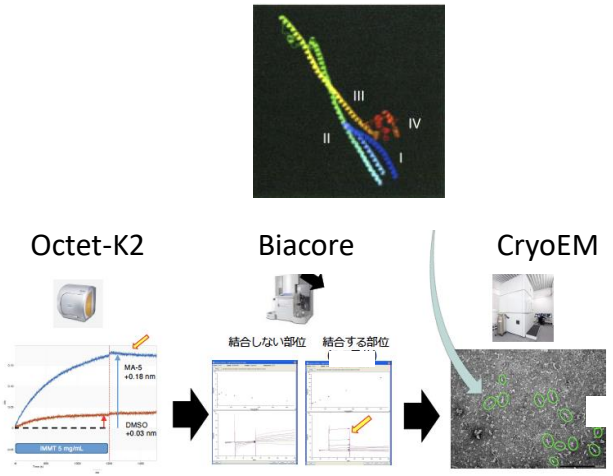
Drugs for eliminating abnormal mitochondria



High throughput assay system

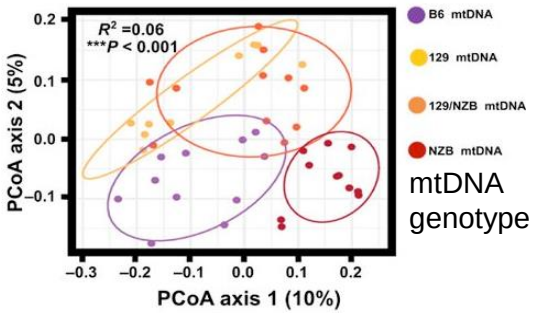


Structure-based drug discovery



Relation between gut, mitochondria and aging

Composition of gut flora



mtDNA genotype

Yardeni et al,
Science Signal,12,
eaaw3159 2019

Human

Diversity of gut microbiome is altered by mitochondrial DNA mutation.

Sequence analysis of host mtDNA in fecal samples

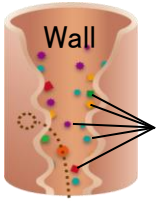
Capture mtDNA → Sequence analysis

Medicine

Metagenomic analysis

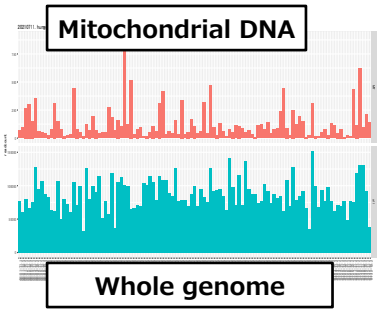
Mouse

Fecal sample
Metagenome DNA
Global analyses

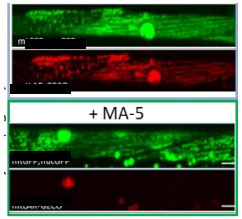


bacteria
Epithelial cells

Human cells
Mitochondrial DNA



Muscle disorder is mitigated by MA-5



Early deterioration of mitochondria suppressed by MA-5

Life Science

Biomedical Engineering

Intestine model

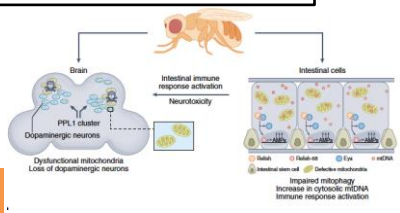
Agriculture

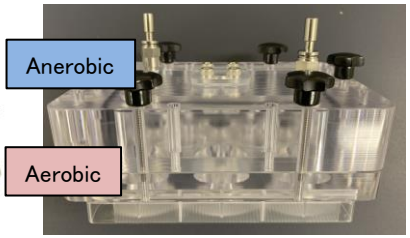
Colon model

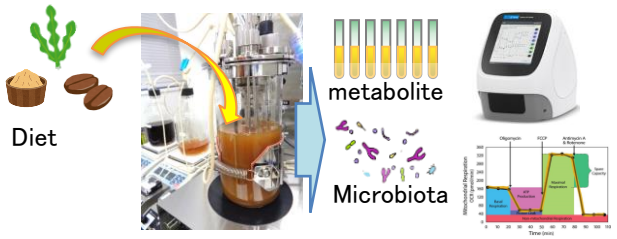
Life Science

mitochondrial toxicity in the gut contributes to adverse effects in the brain

Anerobic culture



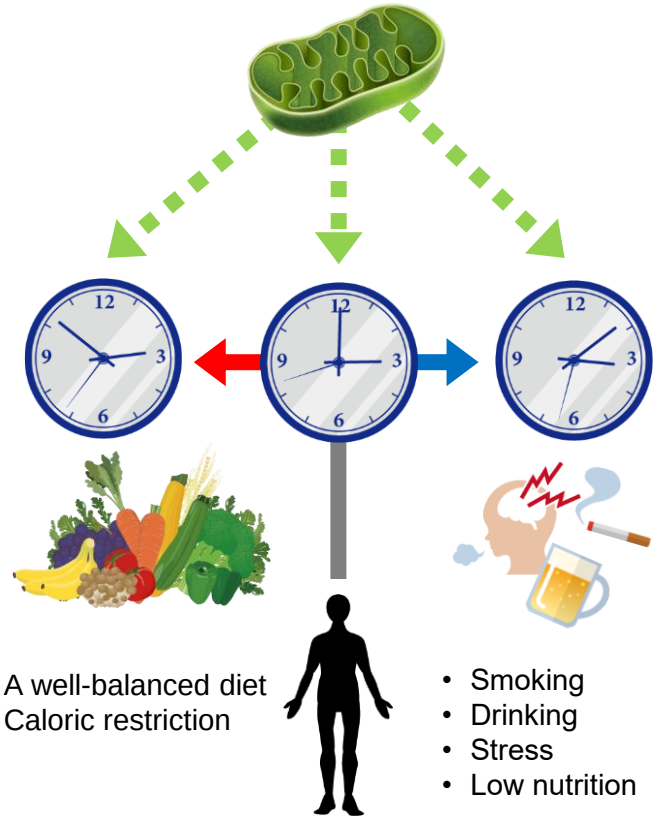




Drosophila

Fedele G. Nature Aging **2**: 317–331, 2022

Interventions on aging

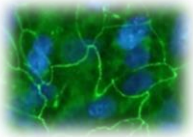


- A well-balanced diet
- Caloric restriction

- Smoking
- Drinking
- Stress
- Low nutrition

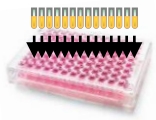
Quach A. Aging 9: 419, 2017

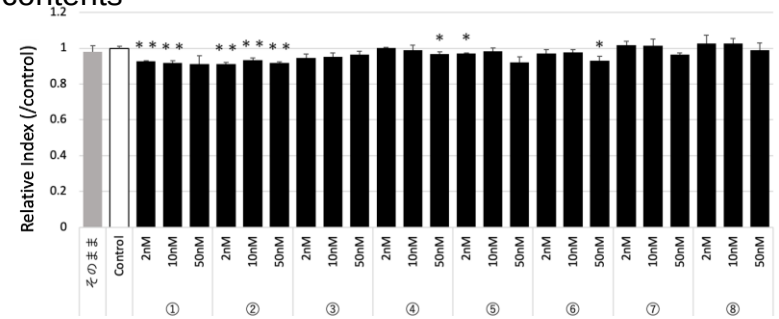
Gut epithelium



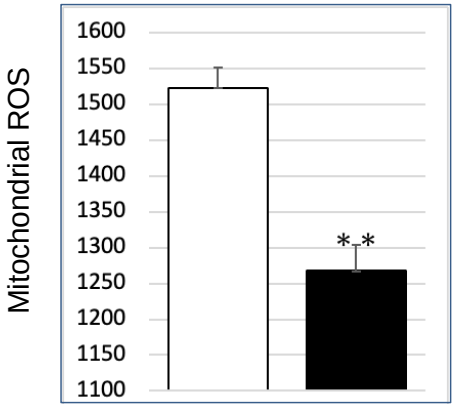
Evaluate the effect of food contents on the cell viability

Food contents

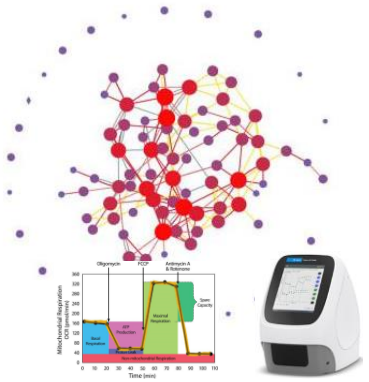




24h food element → 3h 1%DSS



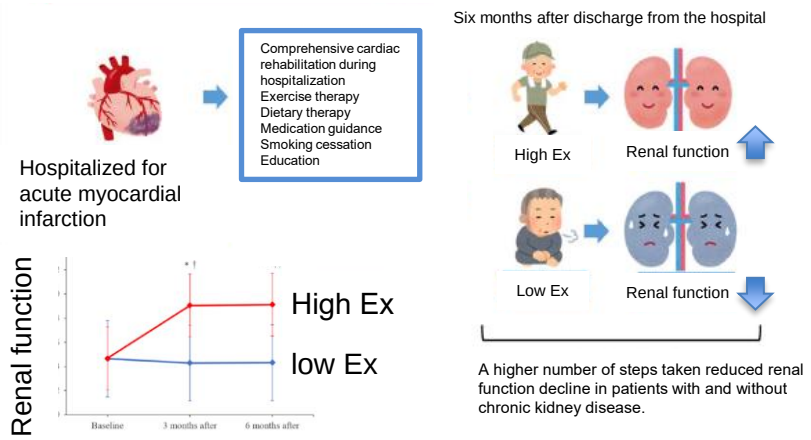
Multi-analysis



MoReDiet

Mobilization and Resilience Diet

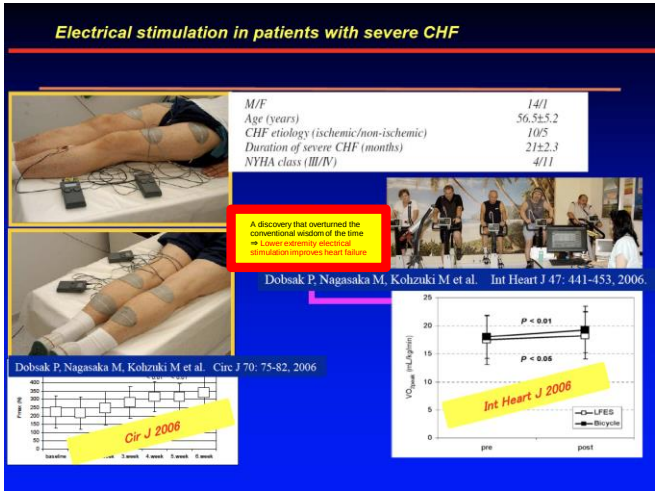
CKD is a model for sarcopenia



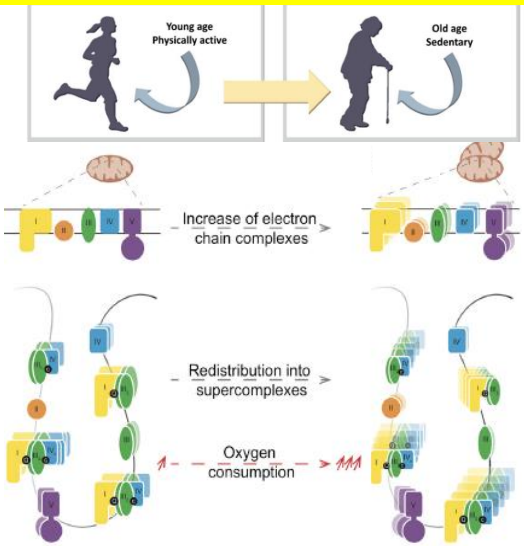
Sato T. J Cardiol . 2021 Aug;78(2):120-128.

Ergometer

Electrostimulation



Exercise modified mitochondrial structure and enhances ATP production



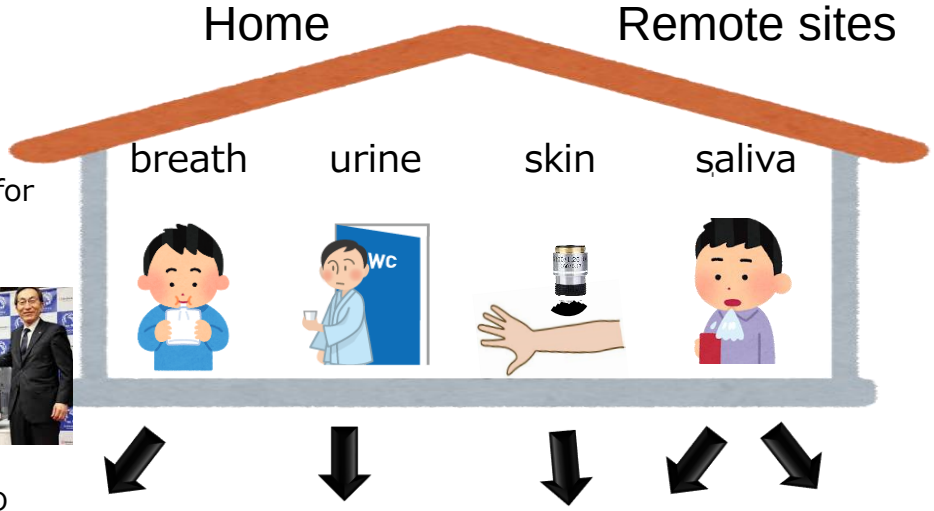
Rezus E. Int J Mol Sci 21:592, 2020
Greggio C. Cell Metab 25: 301, 2017

Non-invasive mitochondrial sensors

Press release for Breath-omics 2020.10.16

Shimadzu Corp. President and CEO Teruhisa Ueda

Tohoku University's President Hideo Ohno

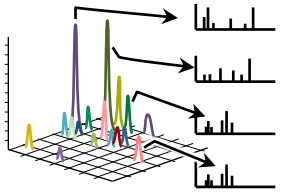


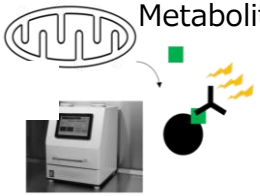
Breath omics

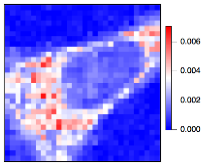
Mito-sensor

Light mito-sensor

Bacteria sensor







Metabolites by energy production
Inflammatory metabolites
Sulfur metabolites

Develop the devices to measure the profiles derived from the mitochondrial function using breath, saliva, and urine at home or remote sites.

Examine a new approach with novel devices to measure the profiles on the mitochondrial disease patients.

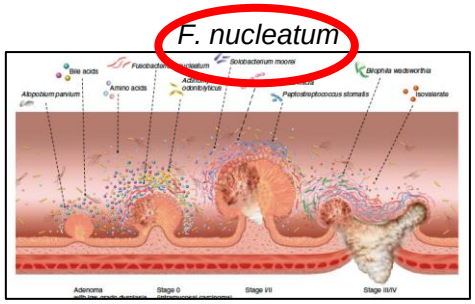
Verify the practicability of the devices on mito-omics cohorts.

Practical realization

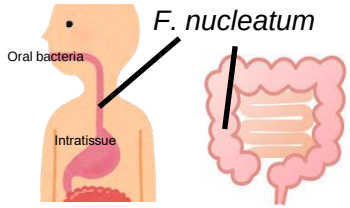
Current status of sensor-development (1)

Cooperation research of Surgery and Biomedical Engineering

Development of the portable-type sensor to detect cancer-related microbiota.



Yachida S. Nat. Med 25: 968, 2019

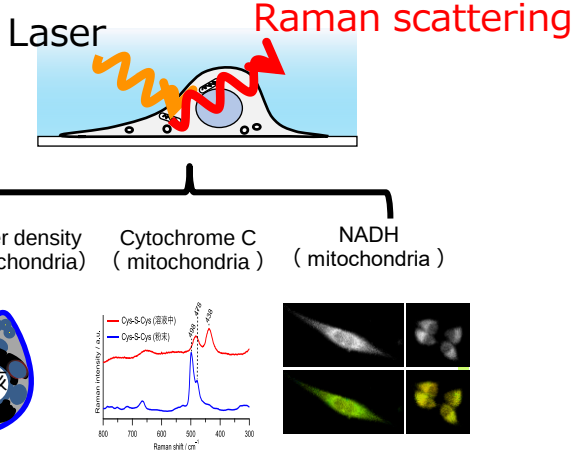


Prognosis of esophageal cancer　Inflammation of large bowel

Yamamura K. Clin Cancer Res 22: 5574, 2016

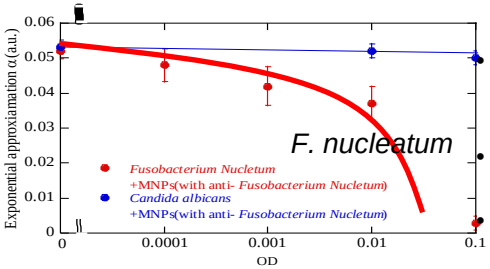
Gut 68: 1335-1337, 2019

Non-invasive skin mitochondrial sensor



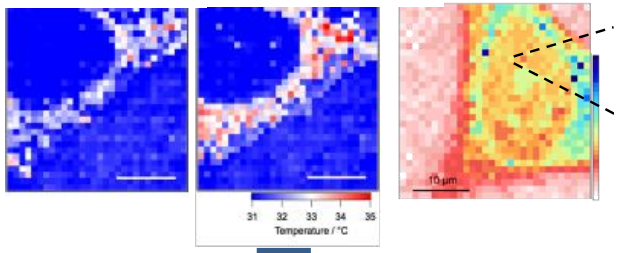
Portable IoT for bacteria sensor capable of measuring real-time

Multi-sensor (capable of simultaneously measuring 6 bacterial strains)

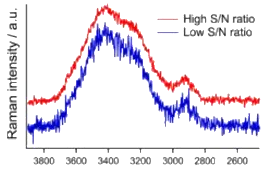


Detect the oral bacteria from saliva samples (40 individuals including healthy volunteer and tumor patients) using the portable-type multi-sensor.
Compare the data of the sensor with that of real-time PCR and DNA sequence
Detect the intratumor tissue resident bacteria

Pre-addition of FCCP　Post-addition of FCCP



Improvement of accuracy on temperature measurement using machine learning

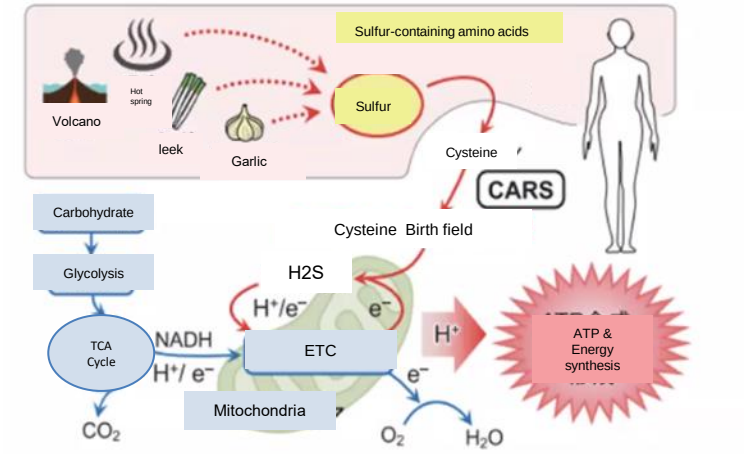


DOI: 10.1109/TMAG.2022.3161508

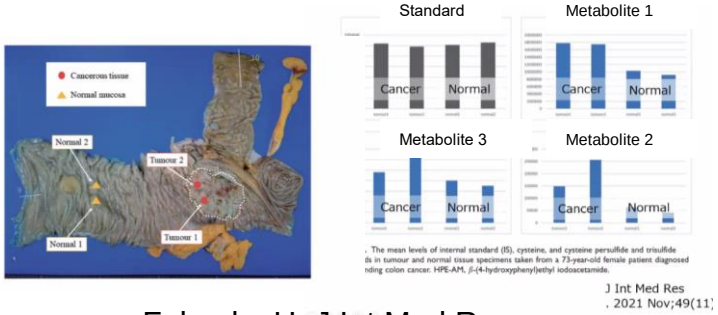
Current status of sensor-development (2)

Sulfur change in Mitochondria cancer patient breath

Breath and Mitochondria

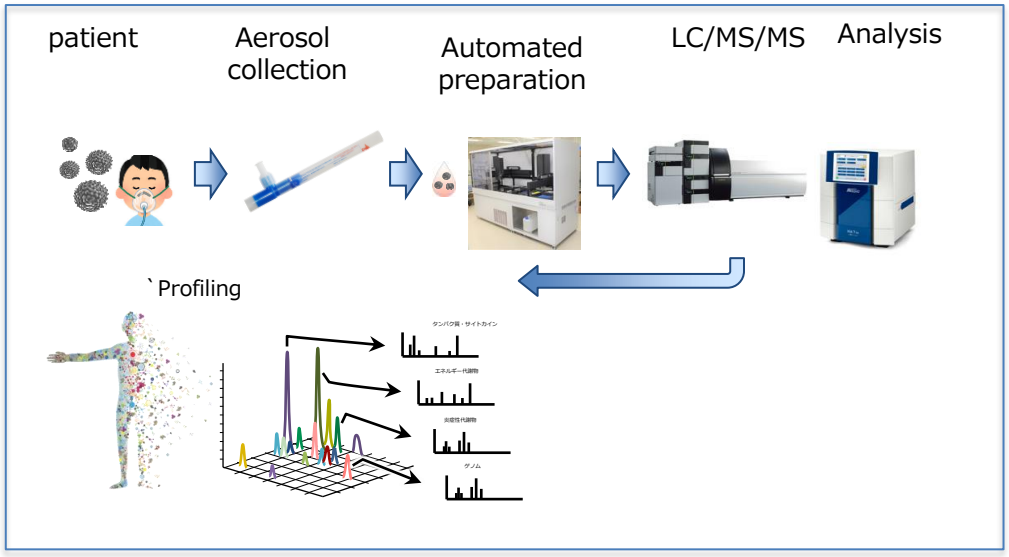


Sulfur change in cancer tissue

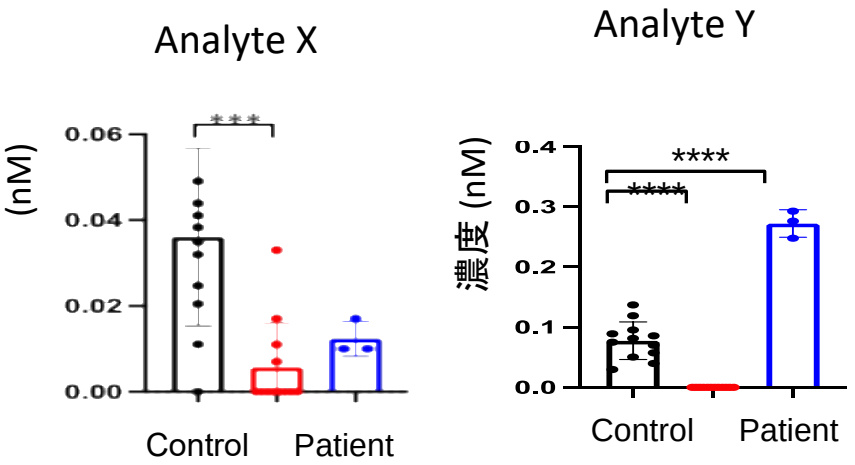


Fukuoka H. J Int Med Res
. 2021 Nov;49(11):3000605211059936

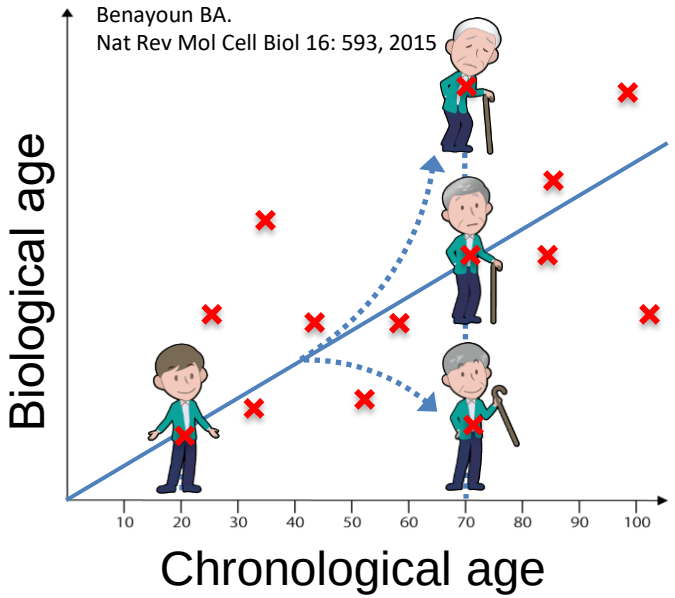
Breath omics



Sulfur change in cancer patient breath



Individual difference in aging

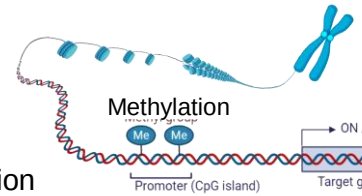


Steve Hovarth

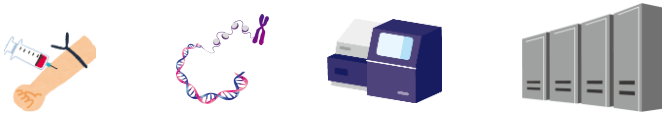
Epigenetic Age

Aging by DNA-modification

DNA methylation
"Epigenetic age"



Horvath S. Genome Biology , 14:R115 2013

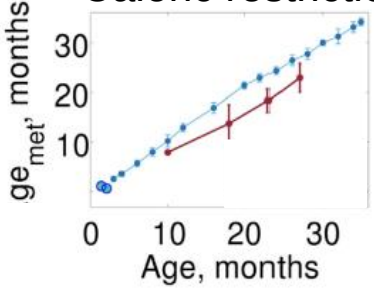


Blood Tissues → DNA → NGS → Analysis using super computer

Vadim Gradyshev

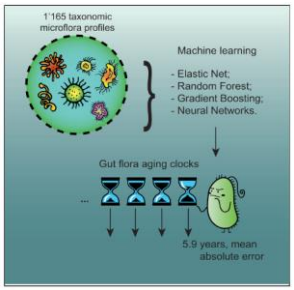
Collaborator Academy member of American Academy of Sciences

Caloric restriction



Petkovich DA. Cell Metab. 25: 954, 2017

Gut microbiome Clock

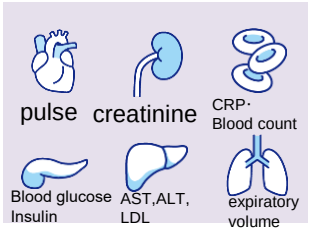


Galkin F.
iScience 23, 101199, 2020

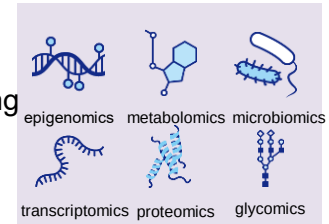
ATP
ROS
SIRT

Mitochondria

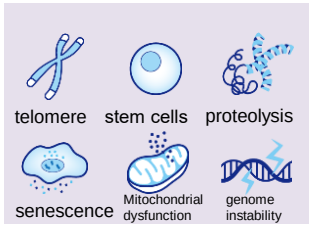
Health and Disease Biomarkers



Omics-based Composite Ageing Biomarkers



Molecular and Cellular Hallmarks of Aging



Rutledge J Nat Rev Genet. 2022 Jun 17. doi: 10.1038/s41576-022-00511-7.

International collaborations

Paul Anderson
Harvard University

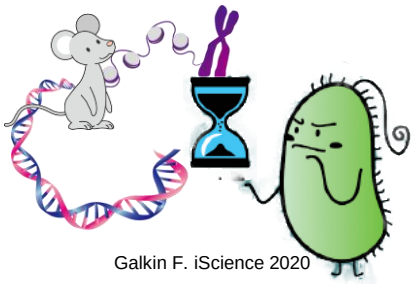
Laurie Comstock
University of Chicago

Stress response

ROS

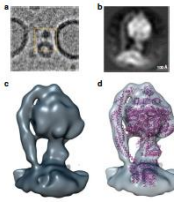
Microbiome aging clock

Vadim Gladyshev,
Harvard University



Galkin F. iScience 2020

CryoEM

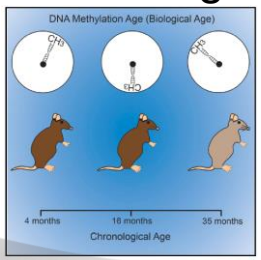


Elizabeth Jonas
Yale University

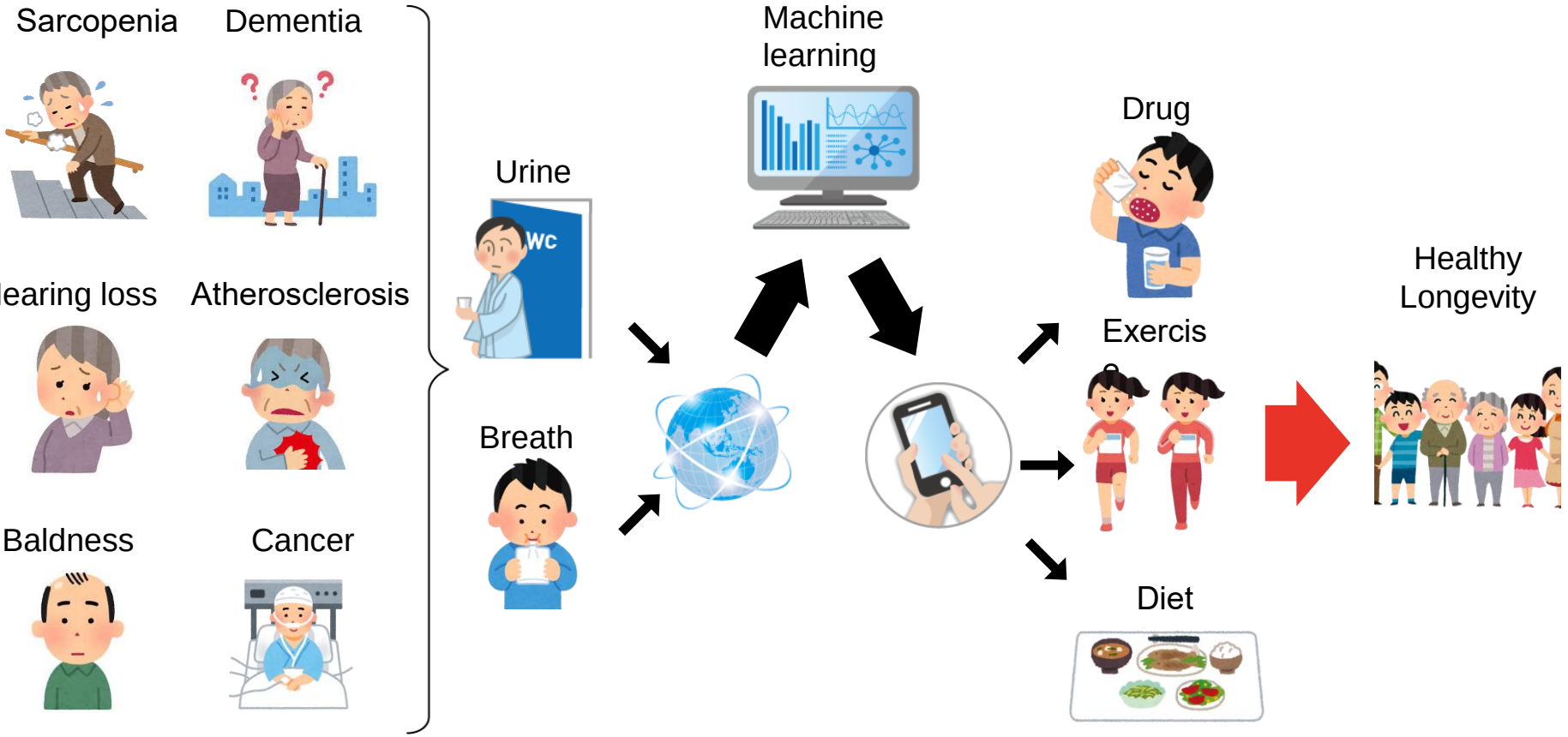
ATP

ROS

Epigenomic aging clock



The goal of this study is establishing the sensing system, drug, functional foods, exercise, and sleep for ageing that can restore the mitochondrial dysfunction, preventing aging, hearing loss, muscle weakness, organ failure, carcinogenic to achieve healthy society until 100 years old.



Summary of project progress over this year

1, Mito-Omics (whole genome, mitochondria, metabolome analysis of blood, urine, feces, microbiome analysis of feces)

- Collection of specimens from cancer, depression, IBS, mitochondrial disease, and ALS patients (Average:25%, 2~40 % achieved)
- Mito-omics analysis of control patients (100 patients) (100% except for genome (30%))
- Tohoku Medical Megabank Collection of mitochondrial genome information of 50 thousand people
- Tohoku Medical Megabank + collection of 276 number of faces samples
- Hospital specimen collection system and storage database development

2 , Mitochondria therapeutic drug, food, and rehabilitation development

- Phase I investigator-initiated clinical trial of MA-5, a novel mitochondrial therapeutic agent
- Establishment of a new drug screening system and identification of more effective patented compounds
- Identification of antioxidant and mitochondrial supplement foods
- Rehabilitation development without the burden

3, Sensor development

- Development of bacterial sensor to identify bacteria related to cancer
- Skin sensor to measure intracellular temperature combined with AI learning
- Mitochondrial metabolites specifically identified by breath sensor

4 , Exploration of basic principles

- Prolonged running time in a mouse model
- Development of human iPS cell artificial gut model

5 , Collaborative research with overseas institutions

- Harvard University >> >> Signing completed, research initiated
- Yale University, University of Chicago >> Awaiting final review results.

END