Moonshot Goal 7 (AMED)

Mitochondrial Medicine

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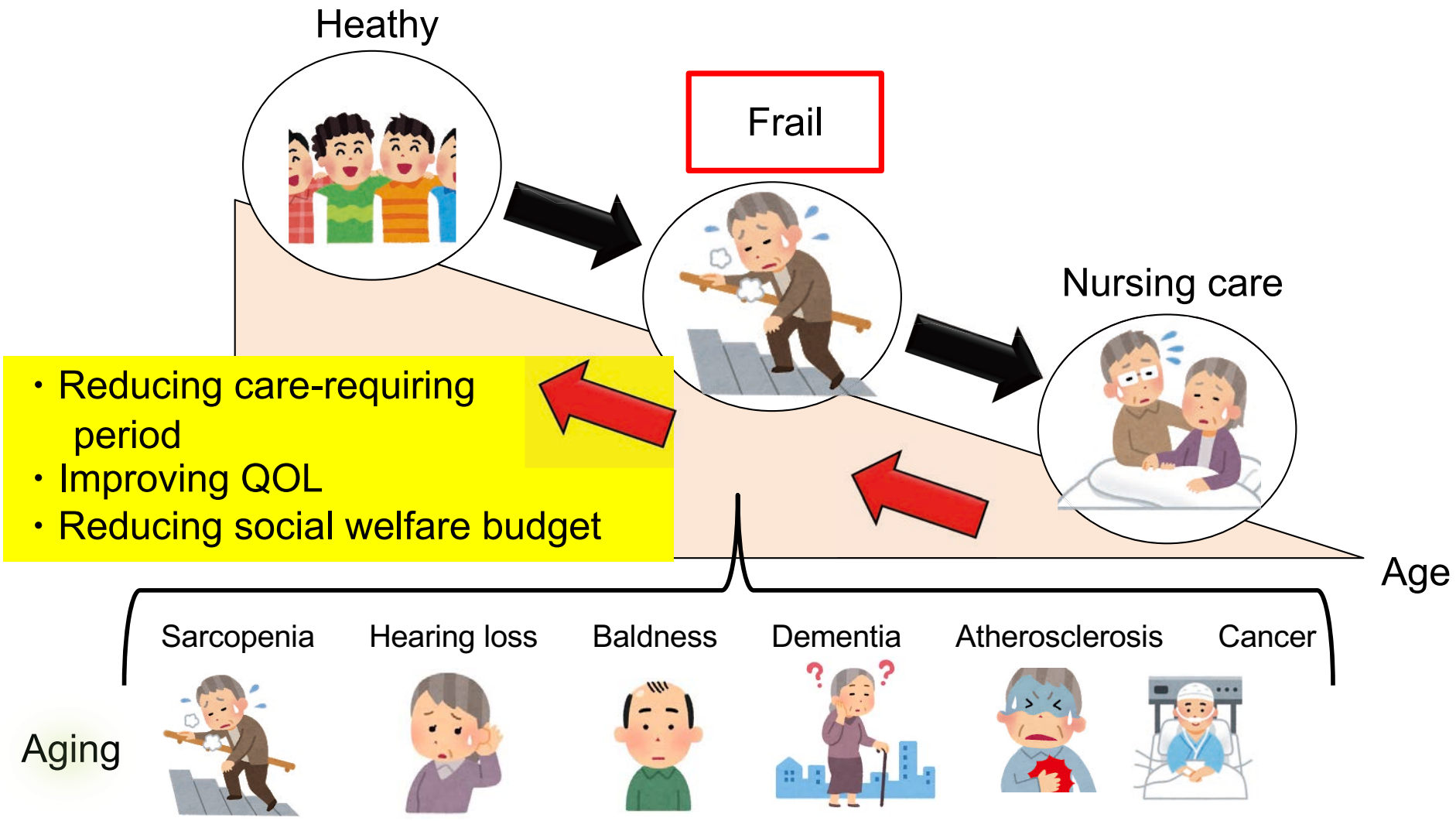
Sendai, JAPAN

Kick-off Symposium for Moonshot Goal 7: June 26, 2021

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



Drugs for immortality and longevity

Mitochondria

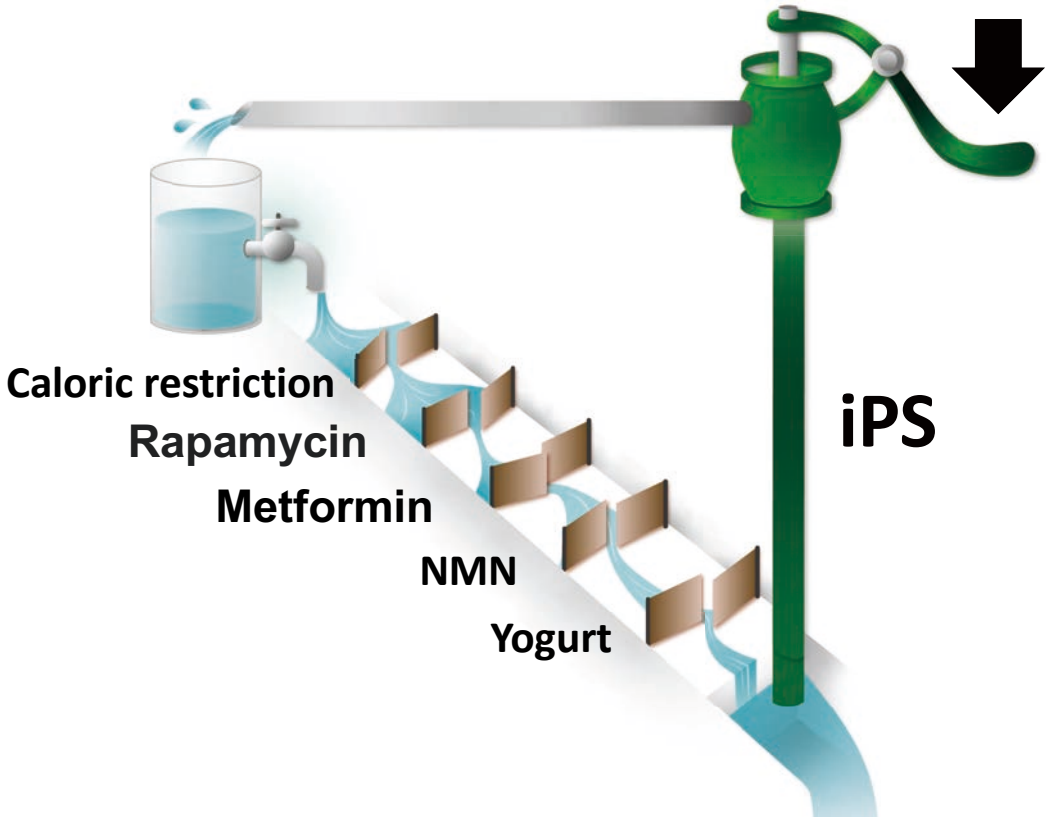
BC 2000 — BC200 — 720 — 1970 — 2009

Overcome death — Cinnabar (HgS) — Tachibana orange — Vit, C — Caloric Restriction — Rapamycin — Metformin — NMN

Microbiota

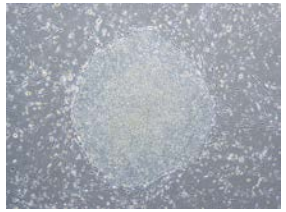
1907 — 1974

Bulgarian bacillus — Lactobacillus

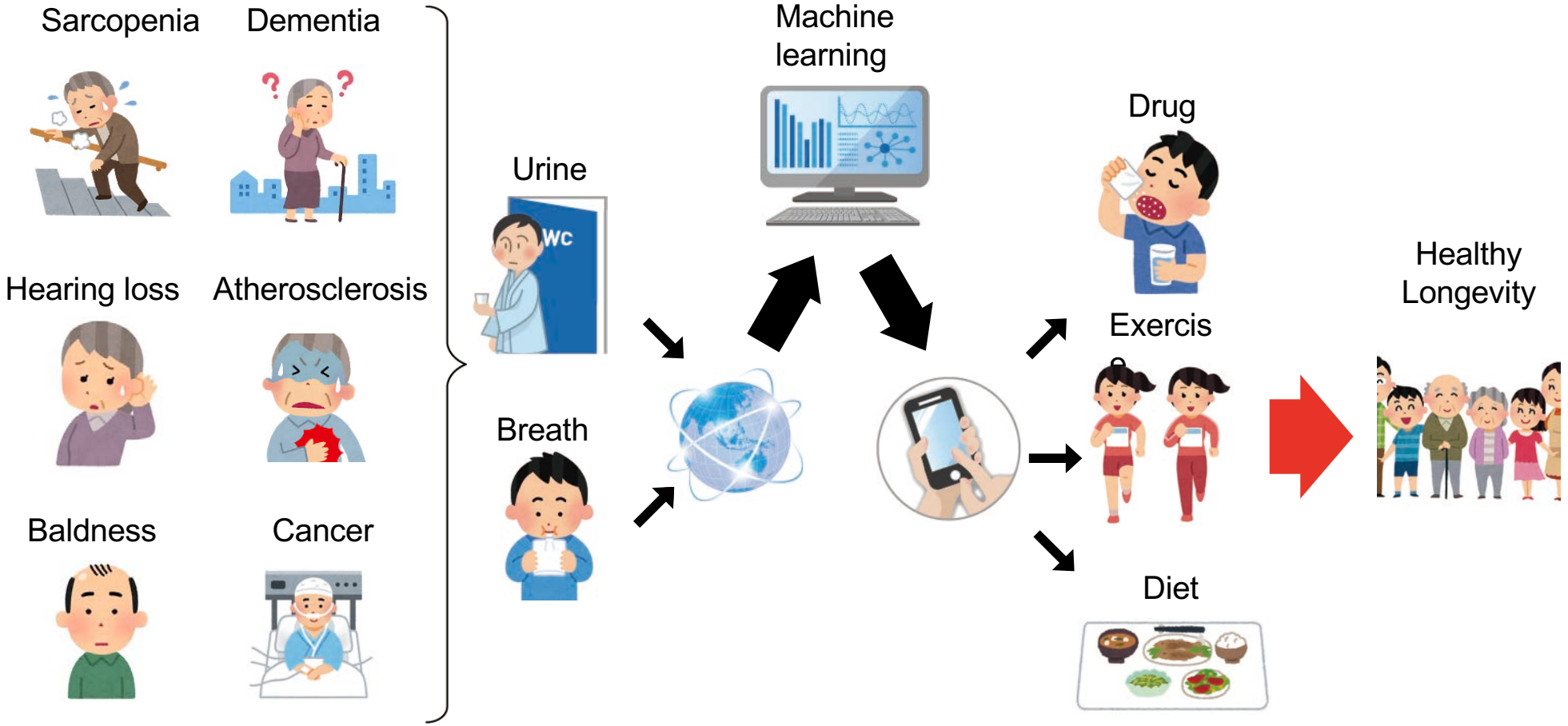


2023

iPS



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.



Mitochondrial diseases in a narrow and broad sense

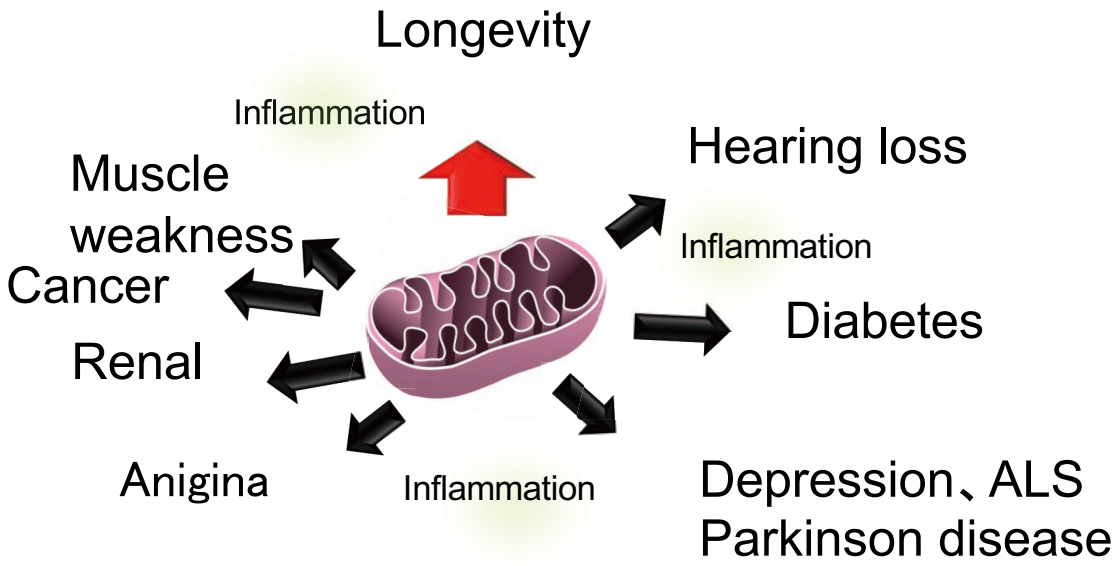
- ATP depletion
- Cell death by oxidative stress

Mitochondrial diseases (narrow sense)

Urgent needed

but no effective remedy

Mitochondrial diseases (broad sense)



Issues on Mitochondrial diseases

Complexity

ROS

Mitochondrial genome
Nuclear genome
Oxidative stress (ROS)
Glycolysis
Lipoid metabolism
Dynamics

Diagnosis

?

Doctor:
「Mito？」
「Dr. can‘t figure out the cause」
「wastebasket diagnosis”」
「Muscle biopsy is the only way」

Remedy

Mito cocktail

L-Carnitine CoQ10 Vit.B2 α-Lipoic acid

Family
「No cure」
「We mange」

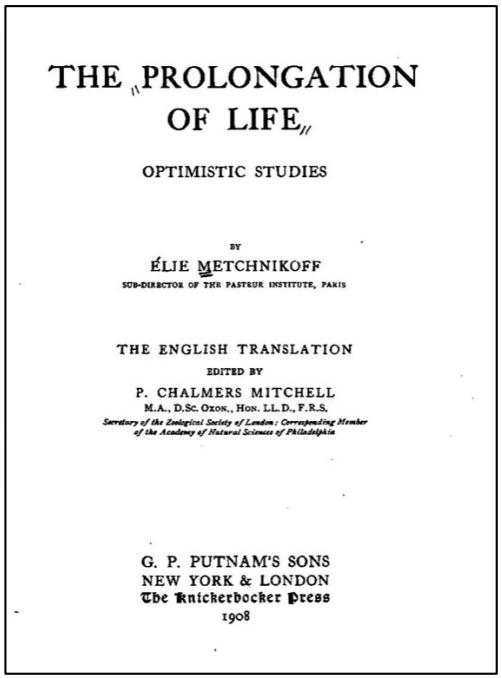
In Japan, AMED supports to develop drugs for Mitochondrial diseases

Gut microbiota and longevity

It is worth enquiring if there be any relation between longevity and locality. In Servia, Bulgaria and Roumania there were more than 5,000 centenarians (5,545) living in 1896.

THE PROLONGATION OF LIFE
From the general point of view of this book, the course recommended consists of the absorption either of soured milk prepared by a group of lactic bacteria, or of pure cultures of the Bulgarian bacillus, but in each case taking at the same time a certain quantity of milk sugar or saccharose.

PROF. ELIE METCHNIKOFF.



THE „PROLONGATION OF LIFE"

OPTIMISTIC STUDIES

BY

ÉLIE METCHNIKOFF

SUB-DIRECTOR OF THE PASTEUR INSTITUTE, PARIS

THE ENGLISH TRANSLATION

EDITED BY

P. CHALMERS MITCHELL

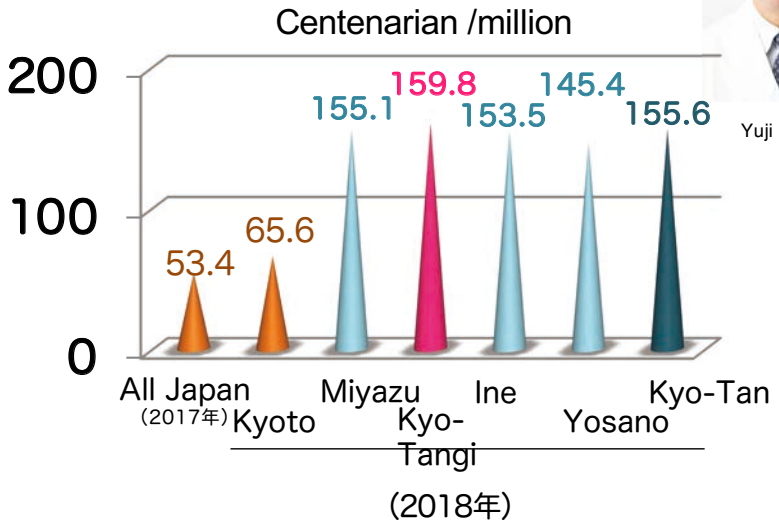
M.A., D.Sc. Oxon., Hon. LL.D., F.R.S.

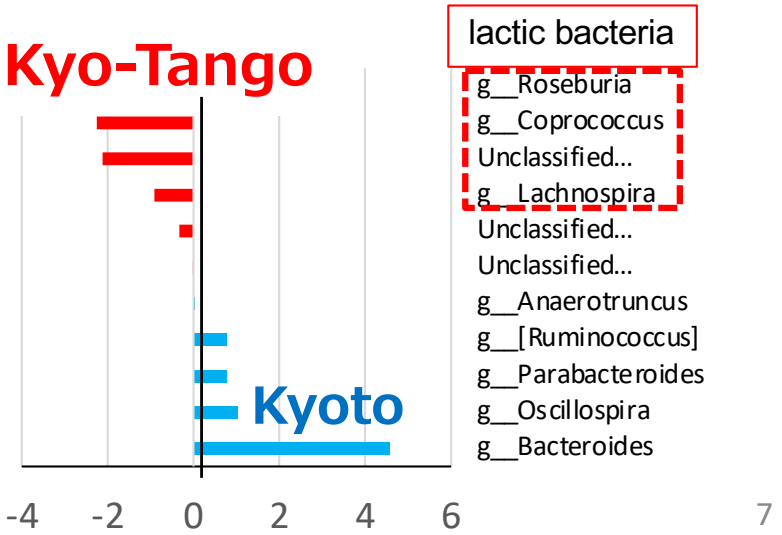
Secretary of the Zoological Society of London; Corresponding Member of the Academy of Natural Sciences of Philadelphia

G. P. PUTNAM'S SONS
NEW YORK & LONDON
The Knickerbocker Press
1908

https://archive.org/details/prolongationlif01metcgoog

Yuji Naito





Naito Y et al. J Clin Biochem Nutr 2019 65: 125-131.

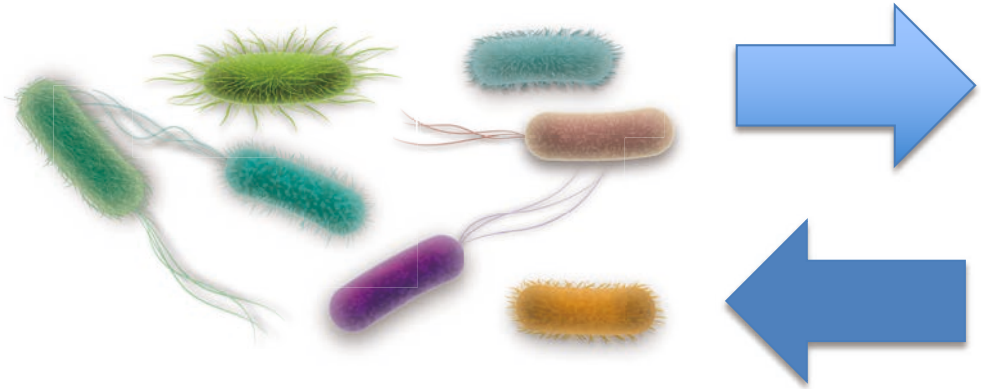
Coincidence of presence of mitochondrial abnormality and gut microbiota

Case or Effect?

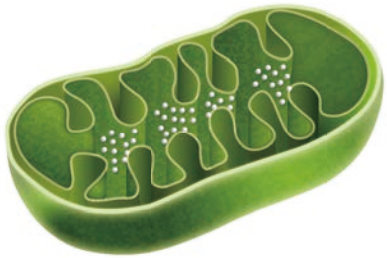
	mut. mtDNA	Circulating mtDNA	Mcirobiota	Tissue bacteria/metabolites
Depression	PLoS One0:e0127280, 2015	Neuropsychopharmacol 43: 1557, 2018	Trends Neurosci. 36: 305, 2013	
IBS	J Dig Dis 19 :295, 2018	Inflamm Bowel Dis. 24: 2113, 2018	Gastroenterology 157: 97, 2019	
ALS	Acta Neuropathol Commun 5: 13, 2017	Front. Immunol 10: 1064, 2019	Nature 572: 474, 2019	
Alzheimer's	Genes Brain Behav 5: 92, 2006	Mol Neurodegener15: 10, 2020	Lancet Neurol 19: 179, 2020	
Parkinson'	Neurol 41: 38, 1991	Brain 143: 3401, 2020	Cell 167: 1469, 2016	PNAS 114: E7892, 2017
Atherosclerosis		Exp Gerontol 69: 70, 2015	Trends Cardiovasc Med 29: 141, 2019	Emerg Infect Dis 20: 1942, 2014
Colon Ca.	Sci Rep 7: 15535, 2017	Br J Cancer 105: : 239, 2011.	Nat. Med 25: 968, 2019	Gut 68: 1335, 2019
Esophageal Ca.	Mol Med Rep16: 8537, 2017	Mitochondrion 47:238, 2019	Dig Dis Sci 61: 2217, 2016	Clin Cancer Res 22: 5574, 2016
Pancreatic Ca.	Gastroenterology 154: 1620, 2018	Cancer Prev Res 4: 1912, 2011	Nature 574: 264, 2019	Gut 2020 Aug 18, 2020
Parkinson's	Lancet Neurol 14: :274,2015	mut. Nuc DNA		

Interactive relation?

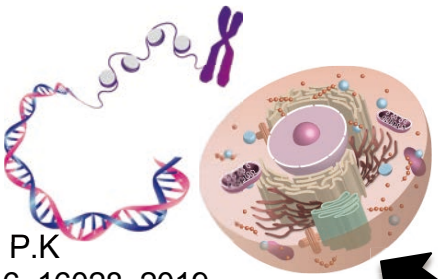
Gut microbiota



Mitochondria

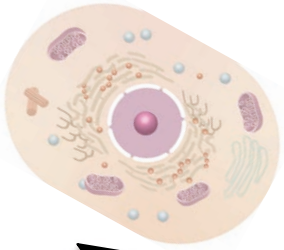


Mitochondria-gut microbiota relation (not in Human)



Kopinski, P.K
PNAS 116, 16028, 2019

Mitonuclear
Communication



Mottis A.
Science 366: 827, 2019

Mitocellular
communication

C. elegans

Han B.
Cell 169: 1249, 2017

Colanic acid

gut microbiota
-Mitochondria
Communication

Mitochondria-
gut microbiota
Communication

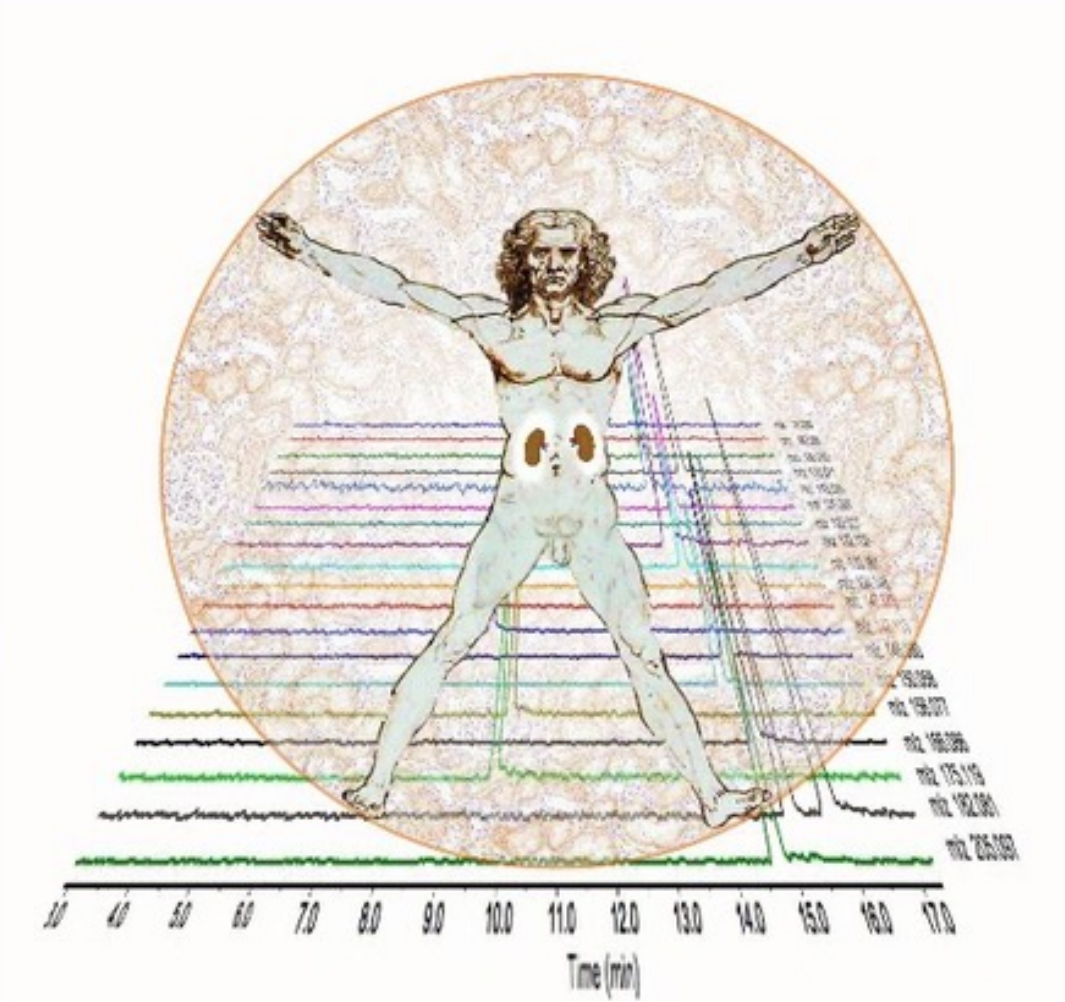
ROS

Microbiota A

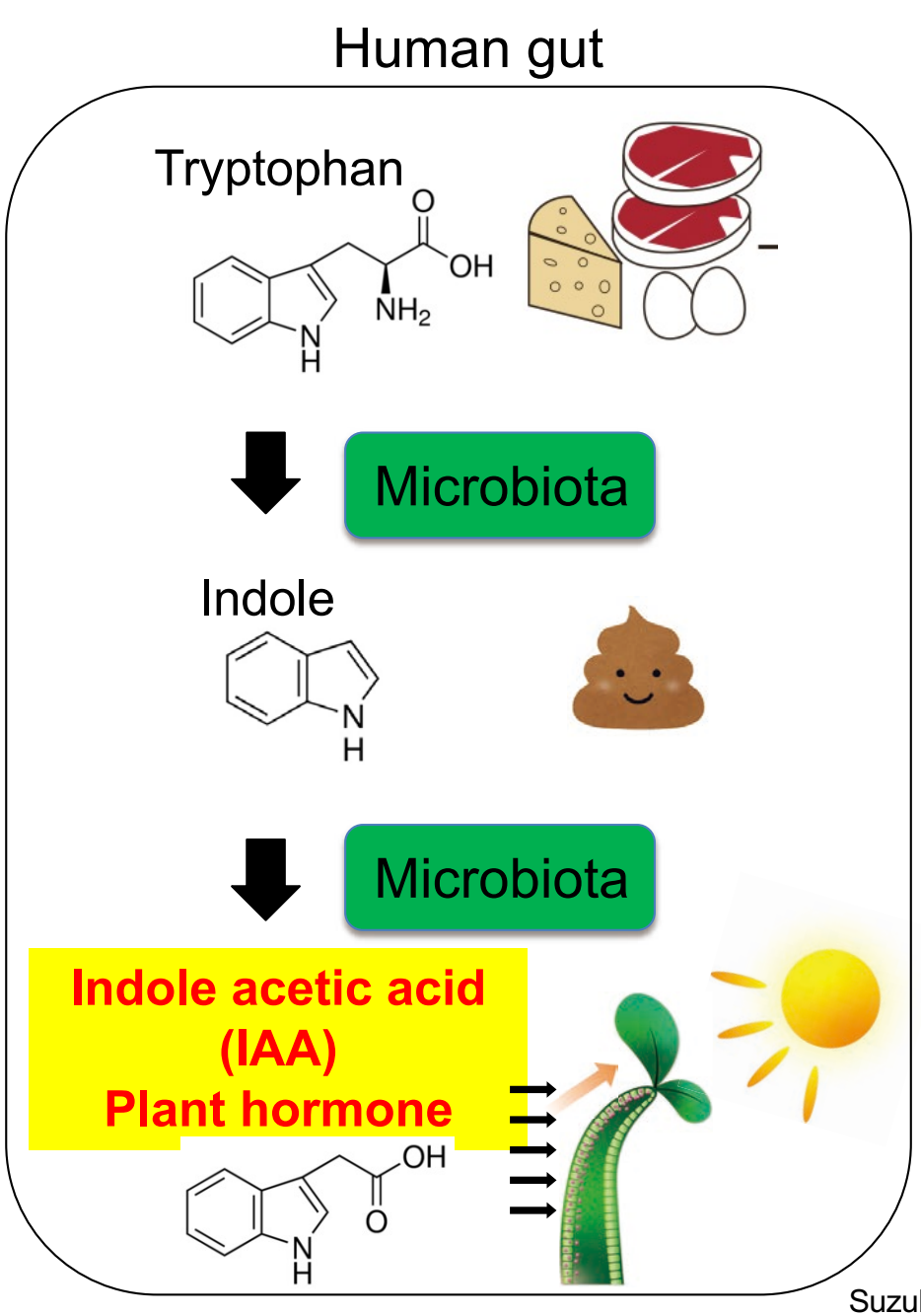
Microbiota B

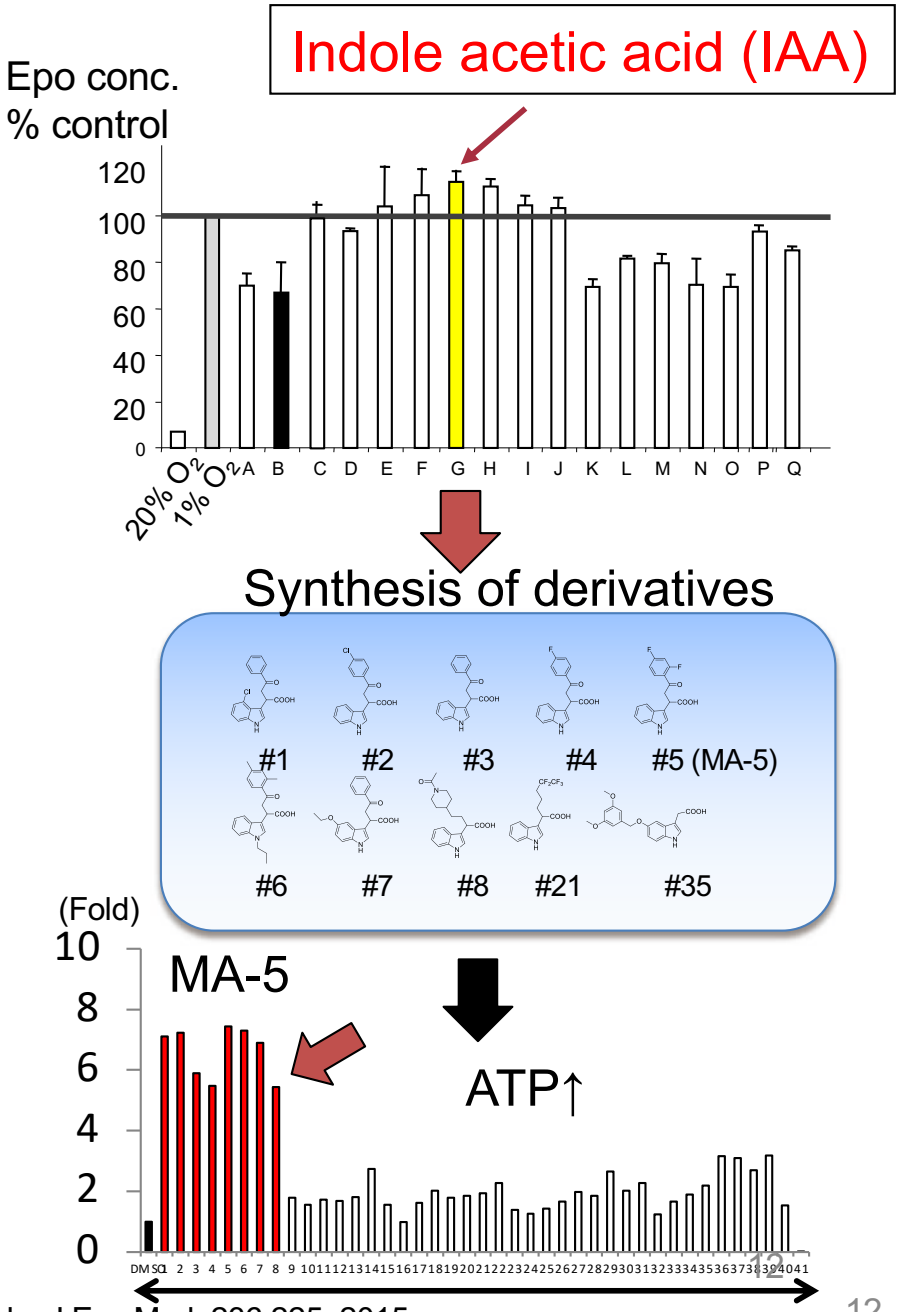
Yardeni T. Sci Signal 12 (588)
eaaw3159, 2019

In Human?



Microbiota-producing metabolites regulate mitochondrial function





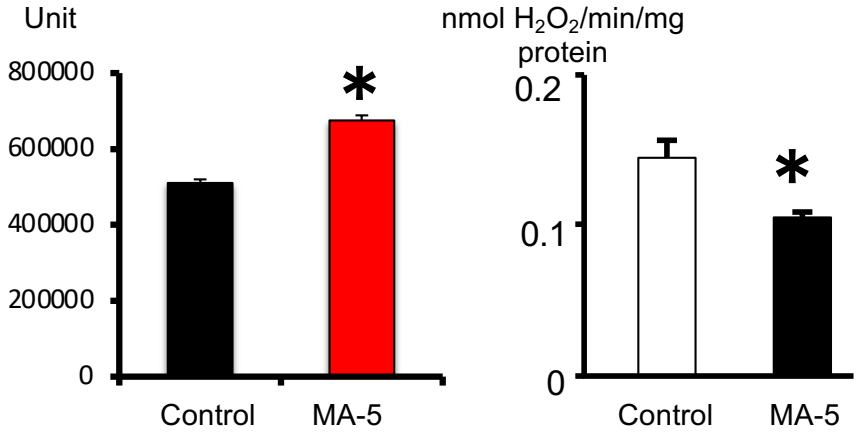
Suzuki T. Tohoku J Exp Med. 236:225, 2015

Diagnosis form patient's fibroblasts

Skin fibroblast

Fibroblast culture

＜ATP＞ ＜Mitochondrial ROS＞



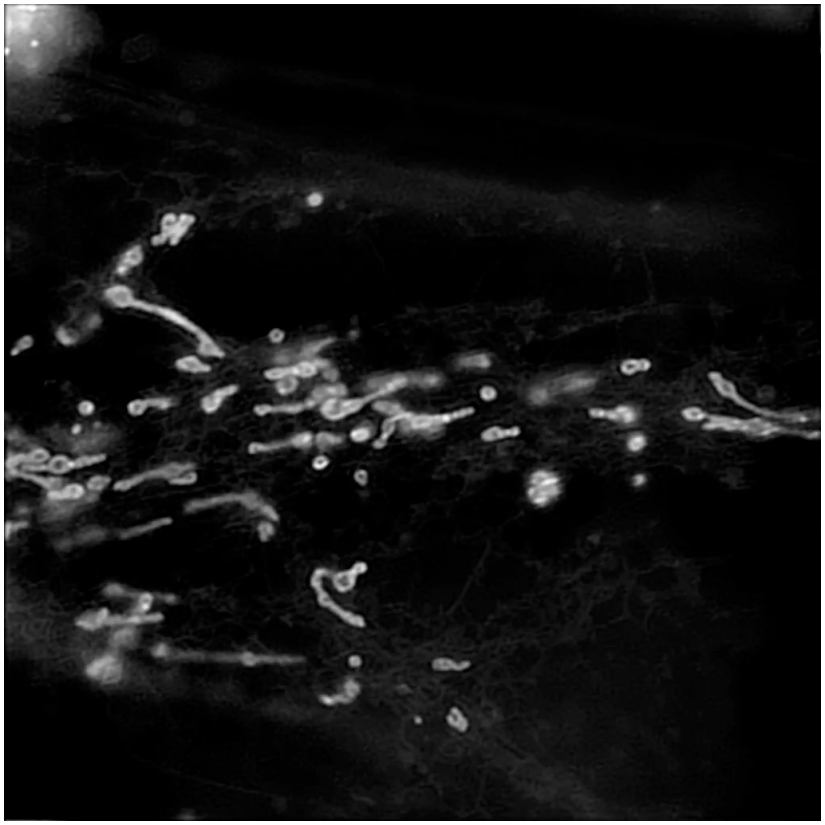
＜Effective in 100 mito-patients＞

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用(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.4450G>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

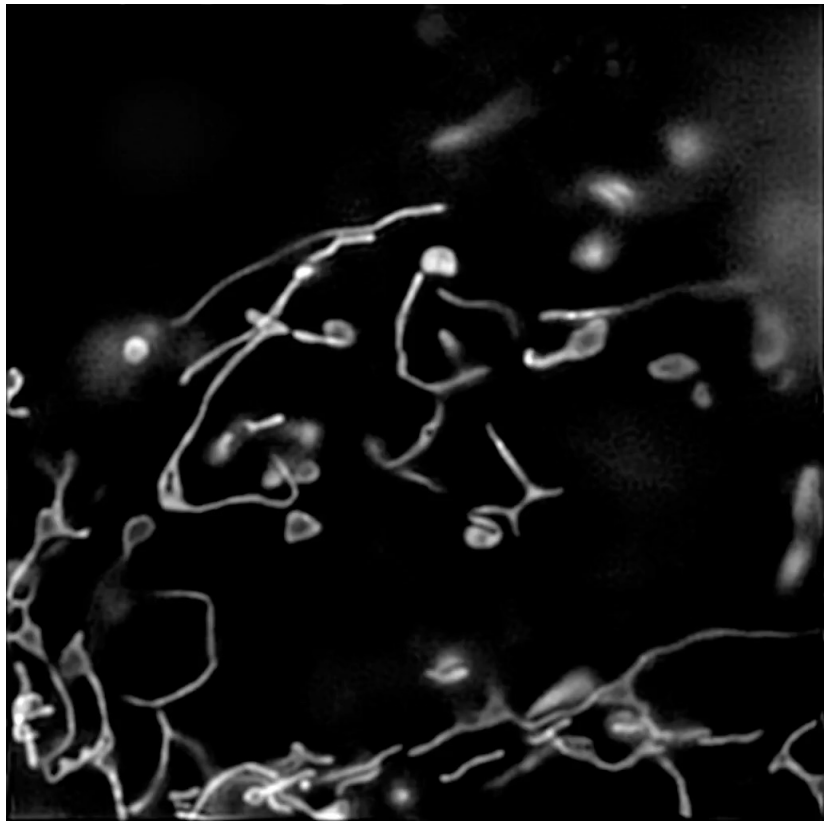
Matsuhashi T. EBioMedicine 20: 27, 2017

Improving mitochondrial dynamics

Pt. mitochondria



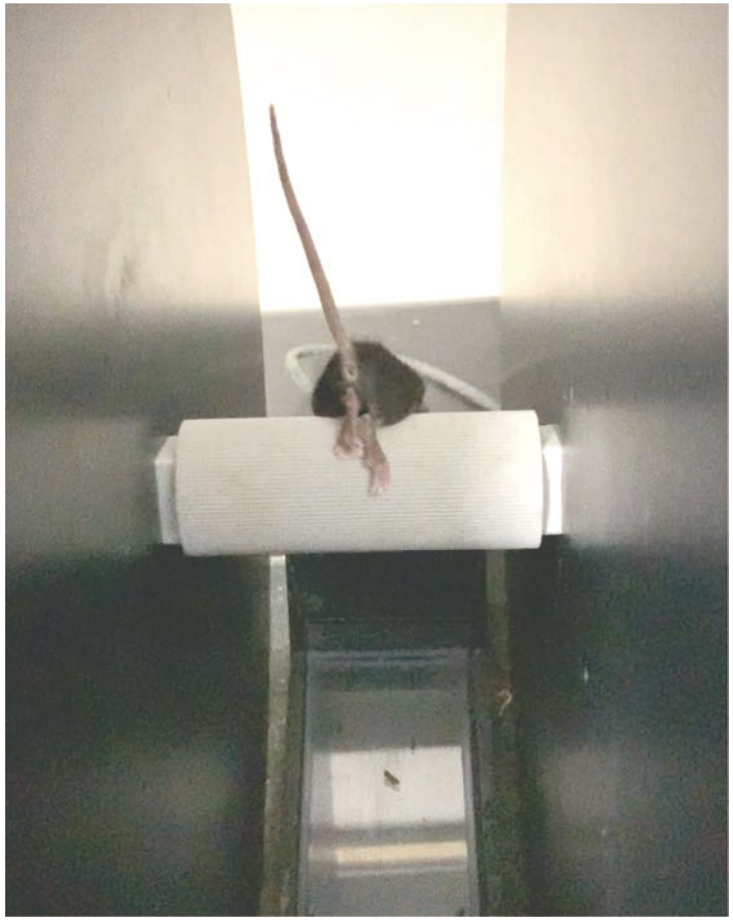
With MA-5



Matsuhashi T. et al. *EBioMedicine*, 2017

Improving exercise capacity

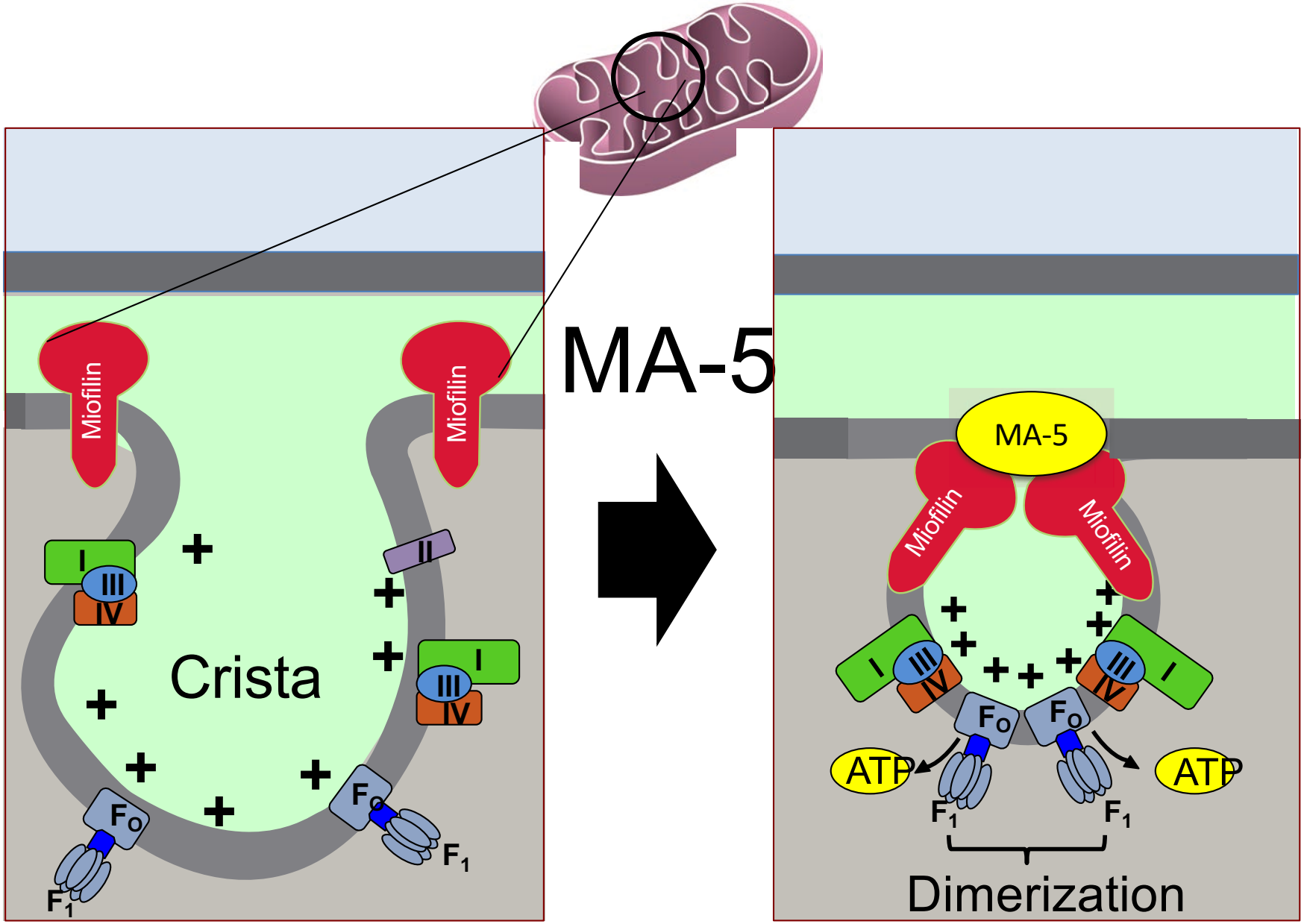
Disease mouse



Disease+ MA-5

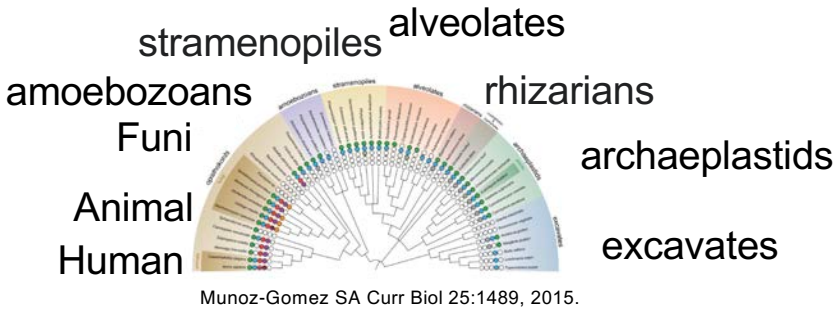
Unpublished

Binding with mitofilin facilitates dimerization of ATPase and increase ATP production

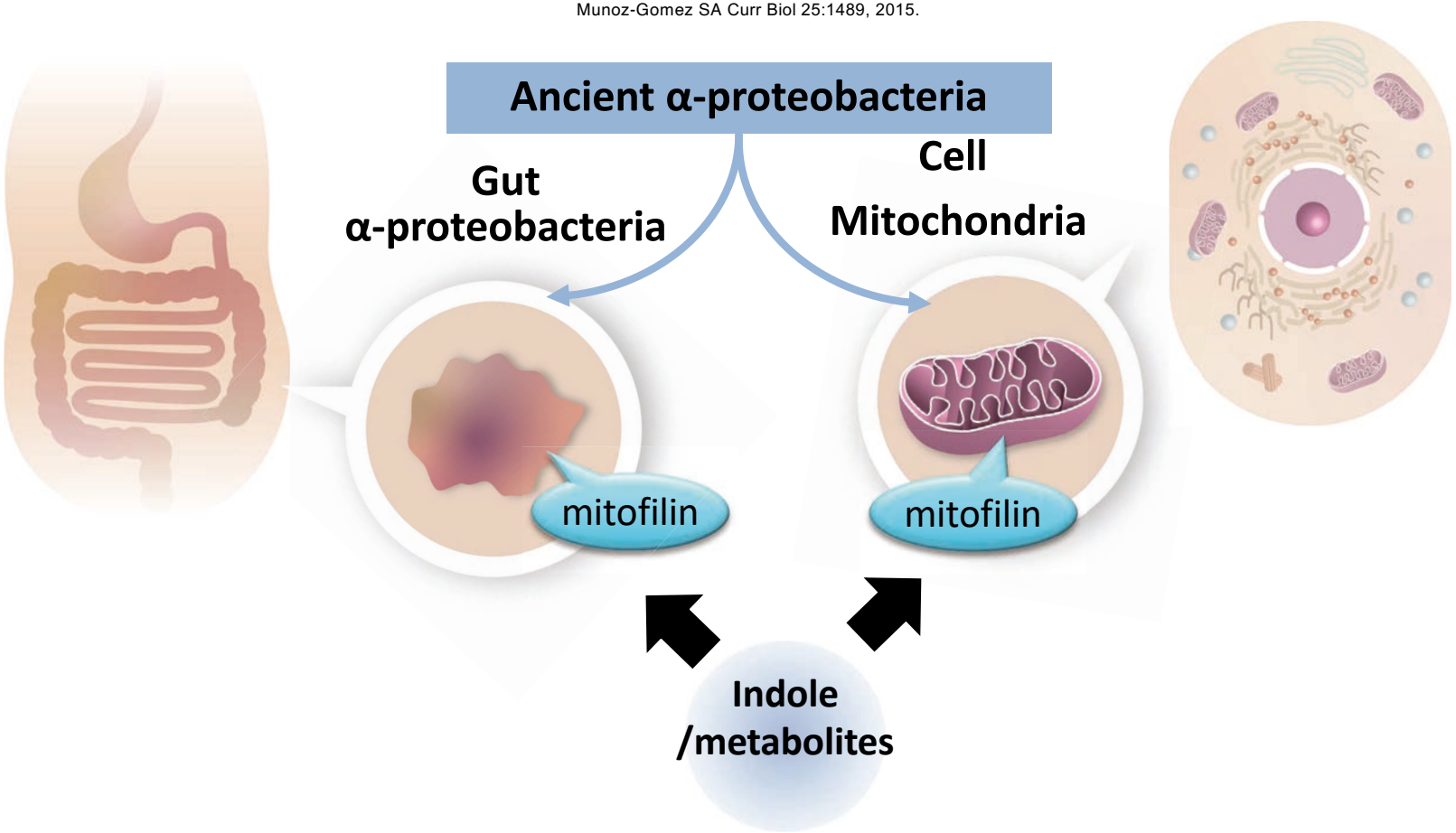


Matsuhashi T. et al. *EBioMedicine*, 2017

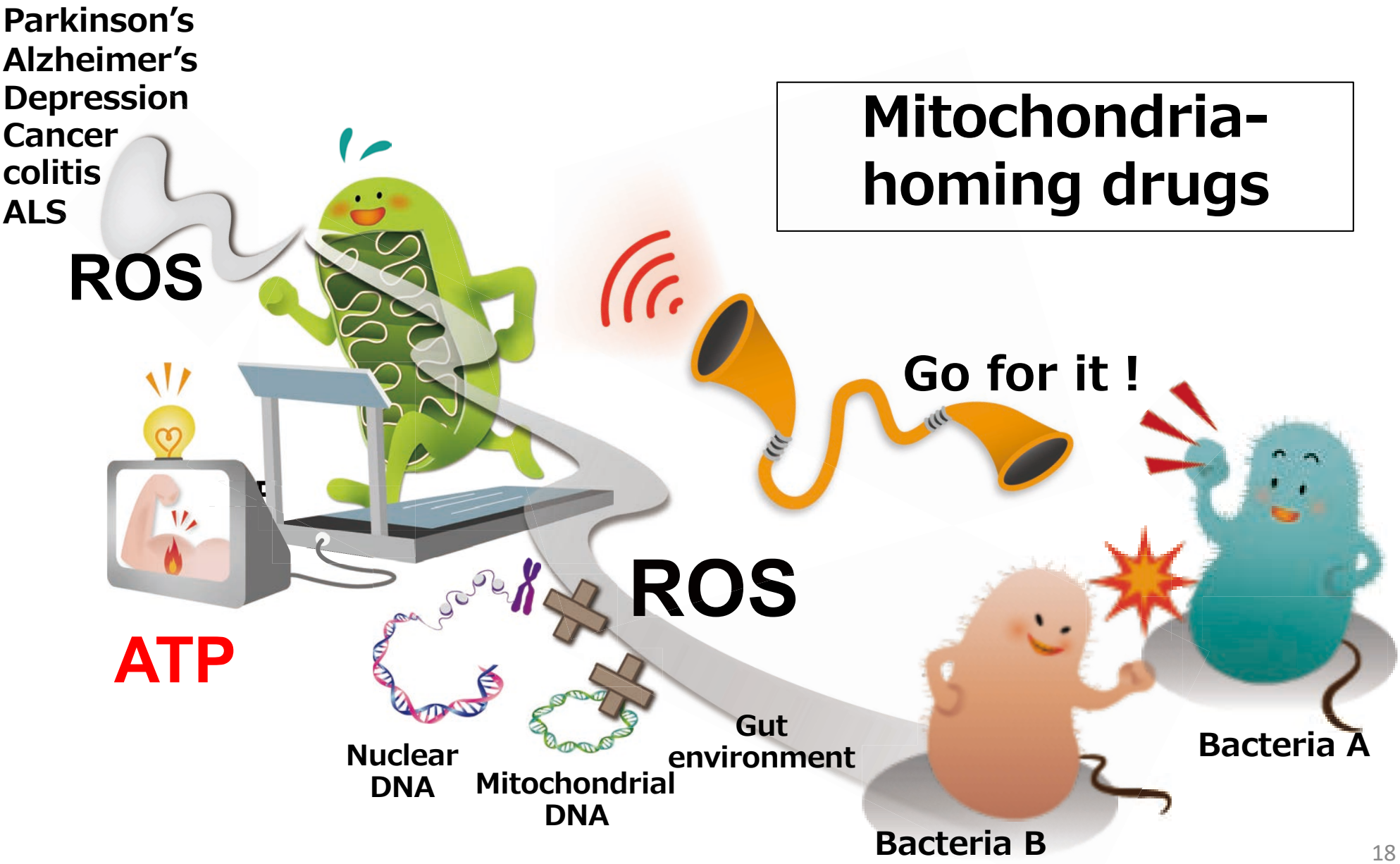
Mitofilin is preserved from bacteria to human mitochondria



Munoz-Gomez SA Curr Biol 25:1489, 2015.



Mitochondria-gut microbiota relation (Human)



Clarifying Mitochondria-gut microbiota relation

CRIETO
Clinical Innovation And Education center

TU-OI
Open-Innovation Organization

INGEM
Innovations in Next-Generation Medicine

Yale University

Harvard University

Personalized Mitochondrial Medicine

Mito-Omics

Tohoku University Hospital

- cancer
- depression
- IBS
- ALS、Mitochondrial disease

Cancer

genome

metabolites

Metabolome/metagenoe

Keio Univ.

Mitochondria

Juntendo Univ.

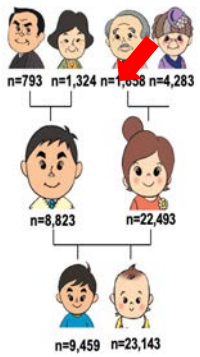
Chiba Cancer Ctr.

Chiba Child Hosp.

Tohoku Medical-Megabank

Genome

Three generation cohort



feces

血液　尿

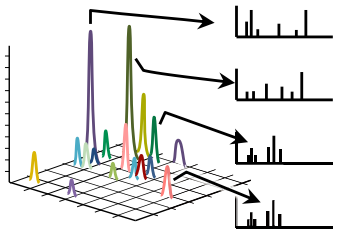
Non-invasive mitochondrial sensors

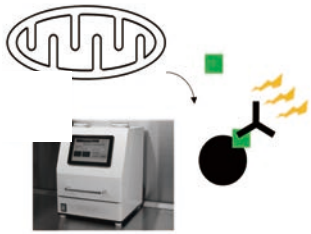
Breath omics

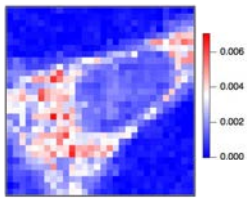
Mito-sensor

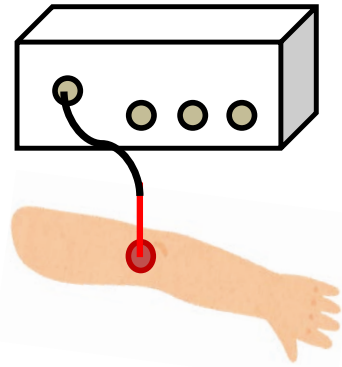
Light mito-sensor

Bacteria sensor



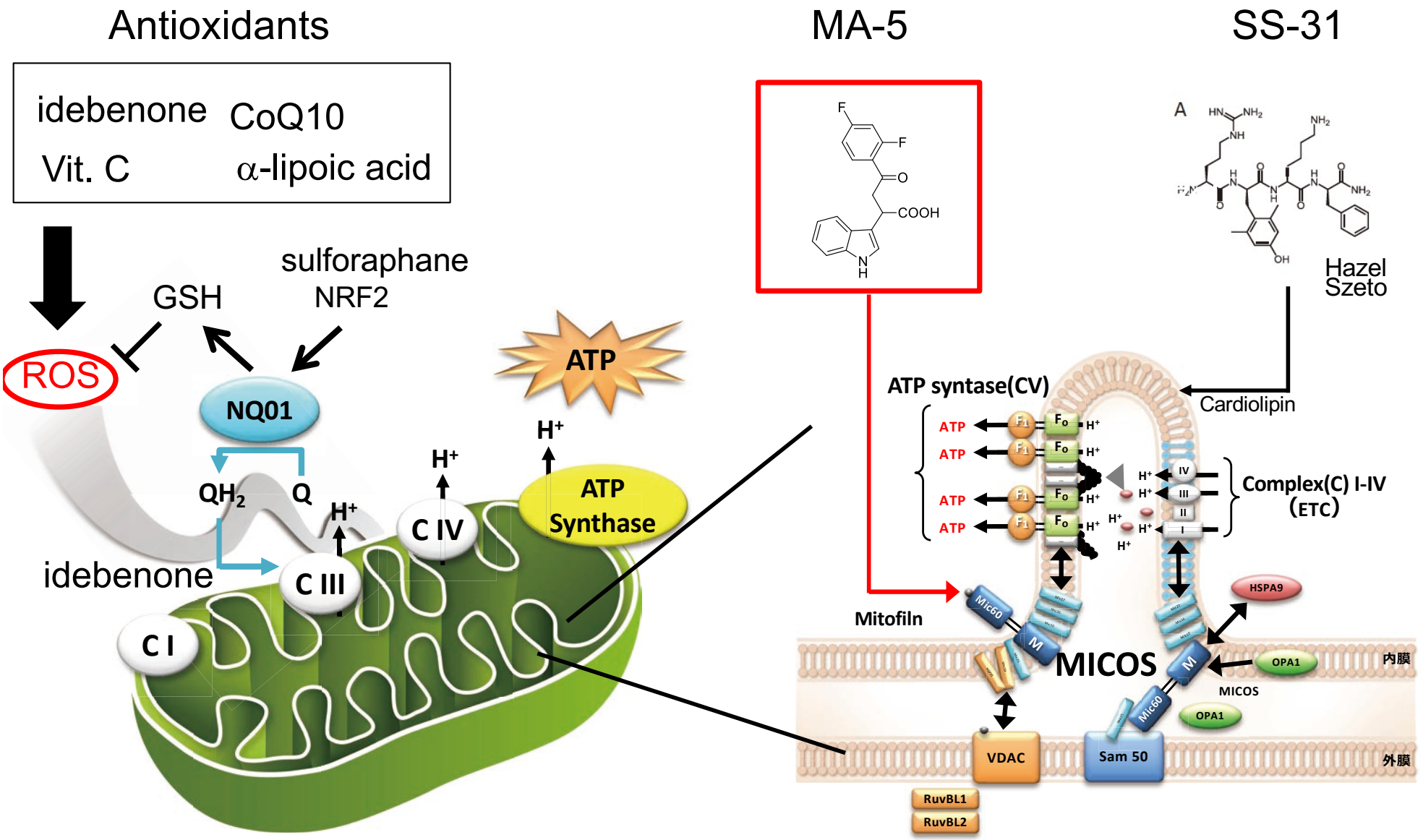






Mitochondrial damage

Target for drug discovery



International collaborations

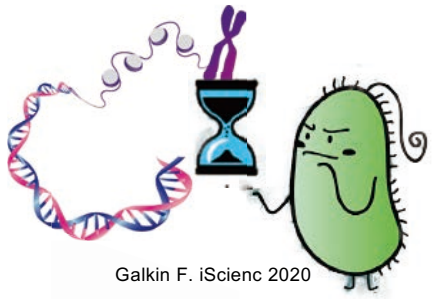
Paul Anderson
Harvard University

Stress response

Laurie Comstock
Harvard University

ROS

Microbiome aging clock



Galkin F. iScienc 2020

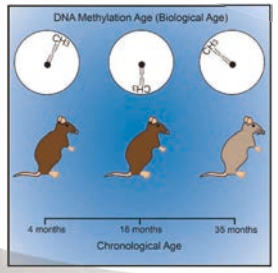
Vadim Gladyshev,
Harvard University

Elizabeth Jonas
Yale University

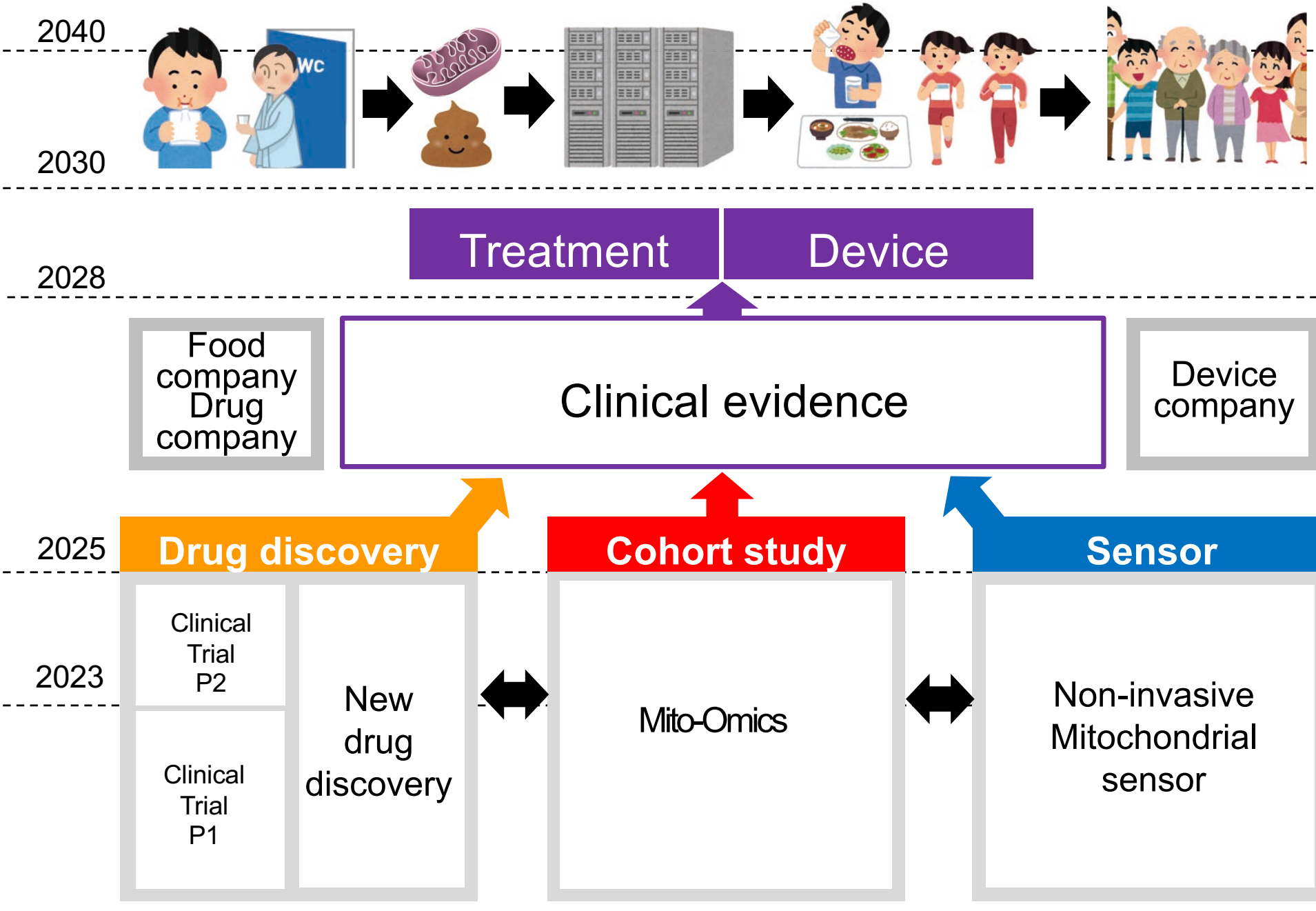
ATP

ROS

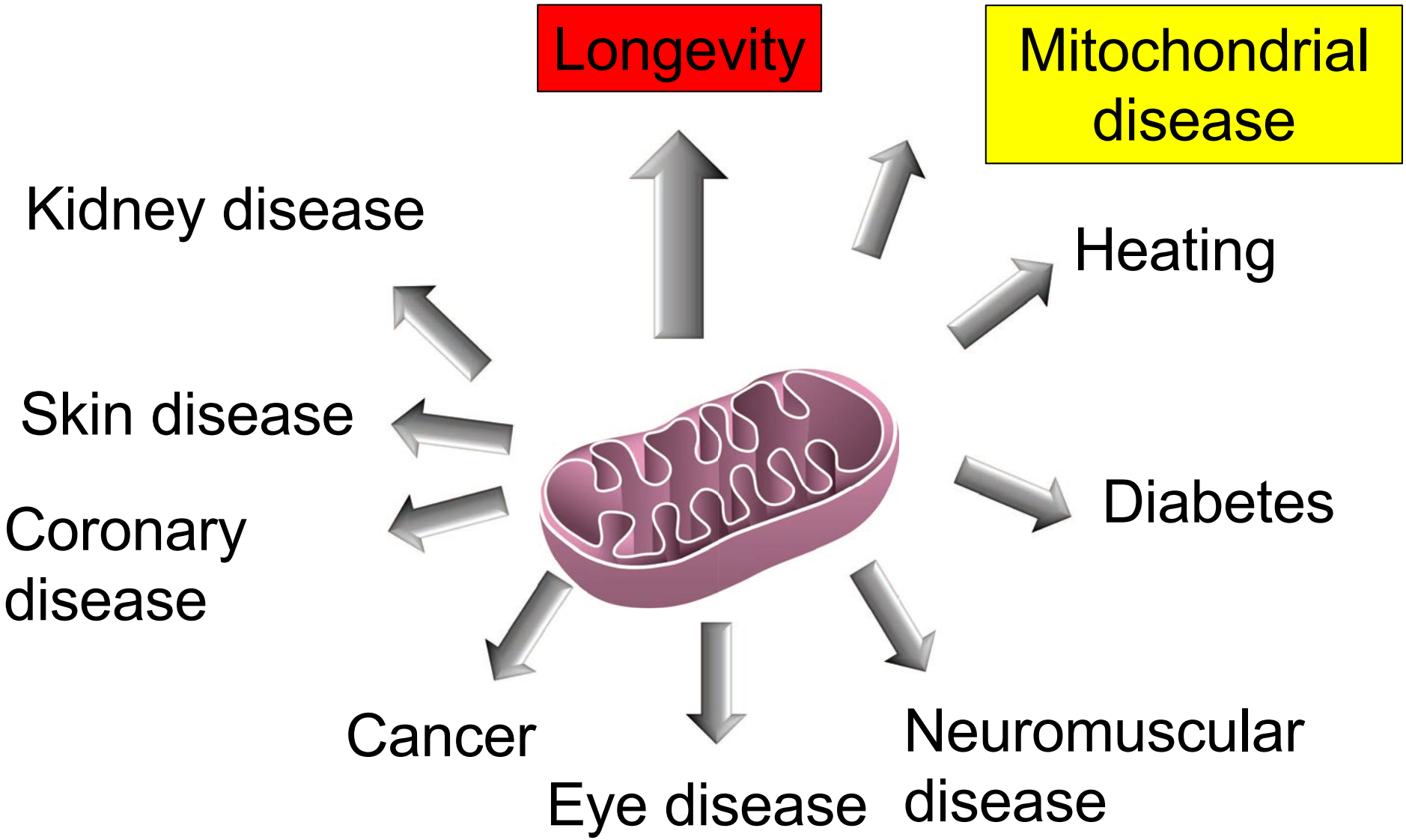
Epigenomic aging clock



Way to the Mitochondrial Medicine



Intervening aging symptoms by modulating mitochondria



Mito? Go to Japan!

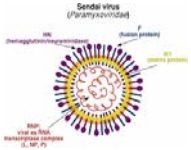
Tohoku University Hospital

Narrow sense Mito

From abroad

Japan

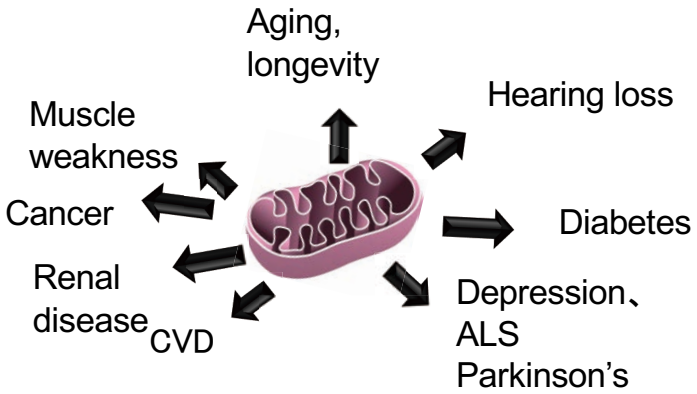
Broad sense Mito



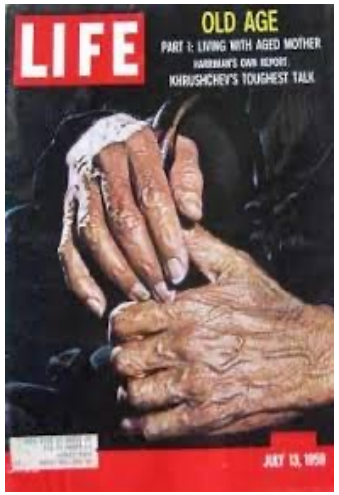
Sendai virus

Hideaki Sena

Photo by Ryuji Sasaki



To live too long is nuisance ! ?



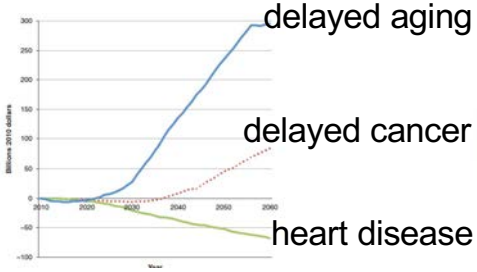
LIFE Magazine
Old Age

July 13, 1959

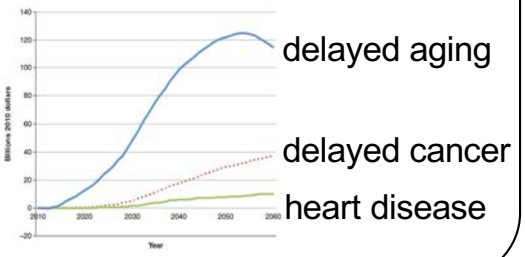
Public domain as Title 17 of the United States Code

- Increasing population with consumption and environmental deterioration
- lose job of young worker
- Social security system collapses

Change in Medicare And Medicaid spending



Change in income support



Goldman D. Cold Spring Harb Perspect Med 6:a025072, 2015

The Economic Promise of Delayed Aging

The potential economic benefits of delayed aging are enormous.

END