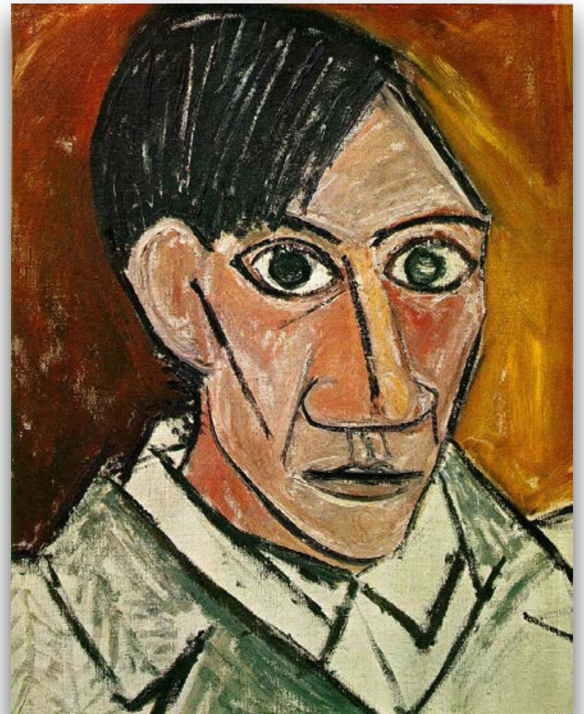
Building Multidisciplinary Research in Understanding Aging Biology

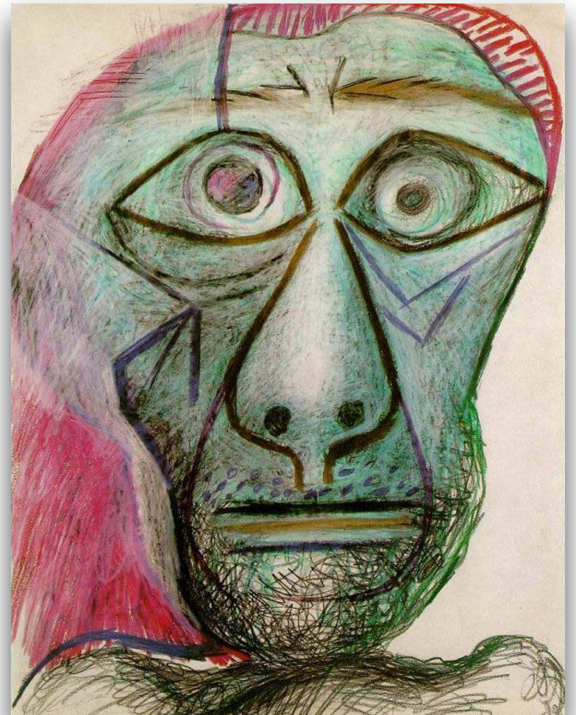
Meng Wang

Department of Molecular and Human Genetics
Huffington Center on Aging

San Diego Nathan Shock Center Workshop
March 25, 2022

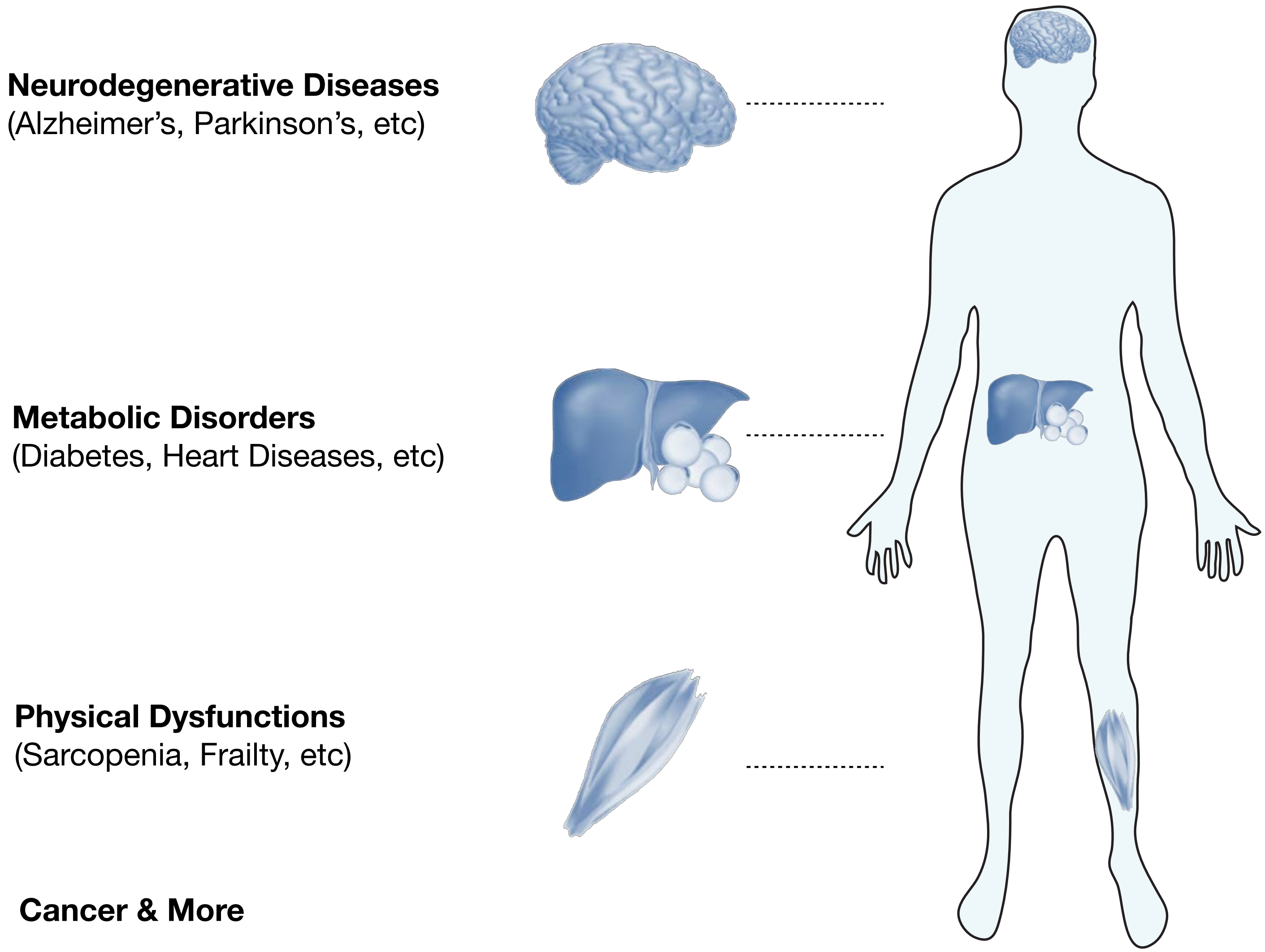


1907, 25 years old



1972, 90 years old

Pablo Picasso


Neurodegenerative Diseases
(Alzheimer's, Parkinson's, etc)
Metabolic Disorders
(Diabetes, Heart Diseases, etc)
Physical Dysfunctions
(Sarcopenia, Frailty, etc)
Cancer & More

Risk for COVID-19 Infection, Hospitalization, and Death By Age Group

Updated Nov. 22, 2021 Print

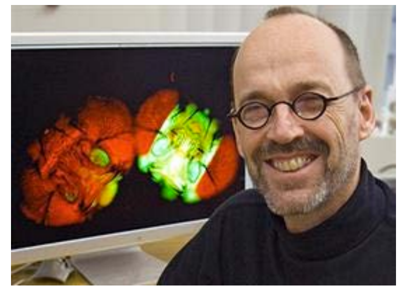
Rate compared to 18-29 years old[1]	0-4 years old	5-17 years old	18-29 years old	30-39 years old	40-49 years old	50-64 years old	65-74 years old	75-84 years old	85+ years old
Cases[2]	<1x	1x	Reference group	1x	1x	1x	1x	1x	1x
Hospitalization[3]	<1x	<1x	Reference group	2x	2x	4x	5x	8x	10x
Death[4]	<1x	<1x	Reference group	4x	10x	25x	65x	150x	370x

Meet the 101-year-old who was born on a ship during the 1918 flu pandemic and just beat coronavirus

102-year-old born during 1918 pandemic beats COVID-19 for second time

'He just got better and better': 104-year-old veteran beats coronavirus in time to celebrate his birthday

PhD, University of Rochester

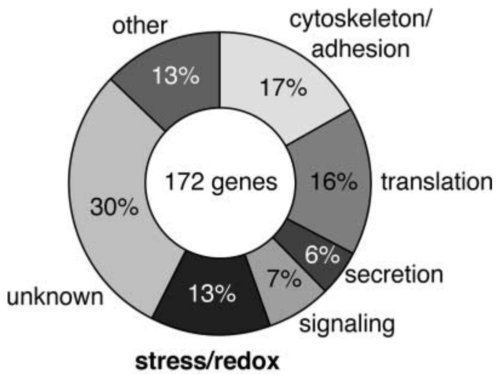


Dirk Bohmann

Henri Japser

JNK signaling in longevity regulation

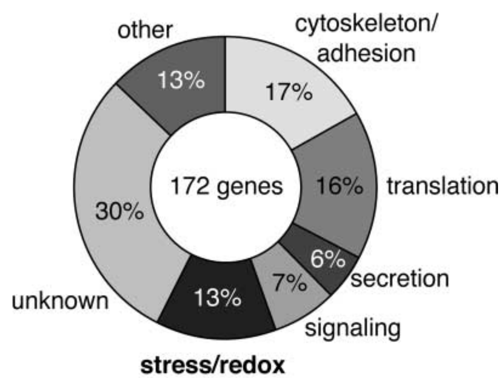
SAGE reveals redox/stress genes induced by JNK activation



✓ Activation of JNK signaling increases oxidative stress tolerance

Wang et al. Dev Cell 2003

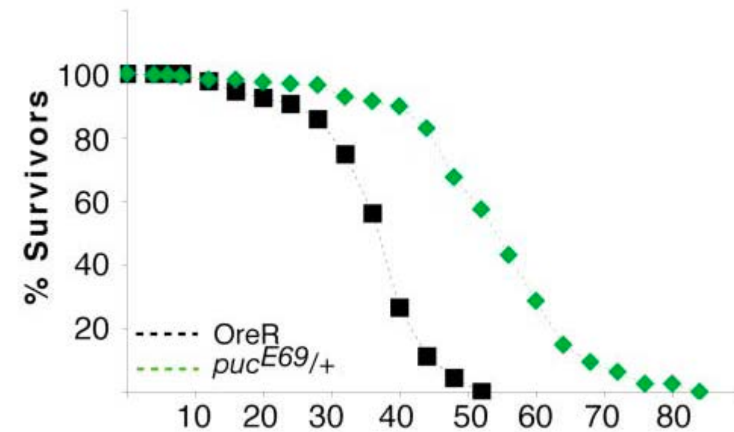
SAGE reveals redox/stress genes induced by JNK activation



- **Power of systemic approach**
  Reveal new regulatory mechanisms in a systematic manner

✓ Activation of JNK signaling increases oxidative stress tolerance

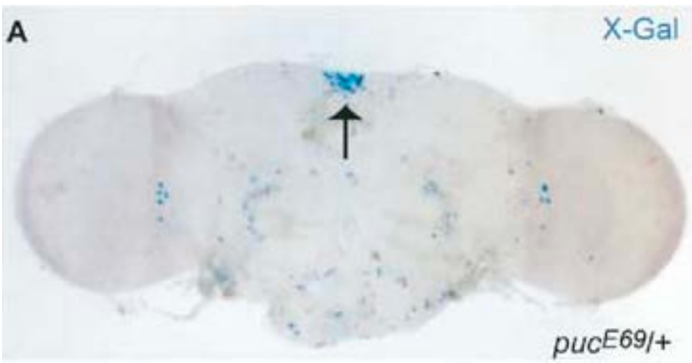
✓ Activation of JNK signaling prolongs lifespan in *Drosophila*



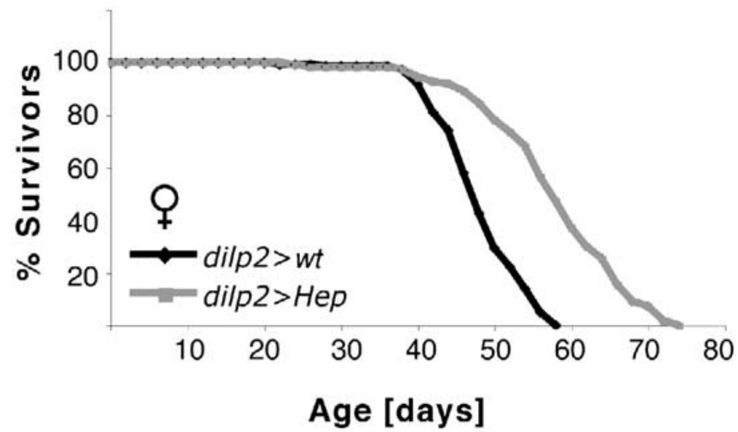
Wang et al. Science 2008

Wang et al. Dev Cell 2003

Cellular analysis reveals JNK activation in Insulin-Producing Cells



✓ Activation of JNK signaling in IPC prolongs lifespan in *Drosophila*



- **Power of cellular imaging**

  Visualize *in vivo* cellular changes in time and space

JNK ⊣ IIS

Wang et al. Cell 2005

✓ **Whole-body Transparency:**

Visualize cellular phenotypes in live organisms

✓ **Genetic Tractability:**

Search for new regulatory genes via high-throughput screening

❑ **Power of systemic approach**

Reveal new regulatory mechanisms in a systematic manner

❑ **Power of cellular imaging**

Visualize *in vivo* cellular changes in time and space

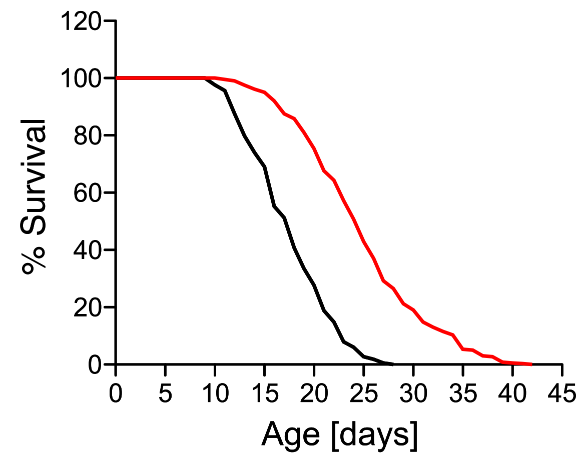
✓ **Whole-body Transparency:**

Visualize cellular phenotypes in live organisms

✓ **Genetic Tractability:**

Search for new regulatory genes via high-throughput screening

✓ **Short Lifespan:**



❑ **Power of systemic approach**

Reveal new regulatory mechanisms in a systematic manner

❑ **Power of cellular analysis**

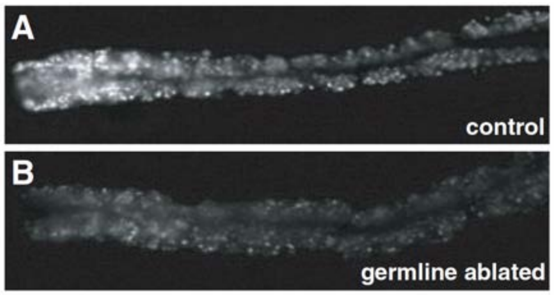
Visualize *in vivo* cellular changes in time and space

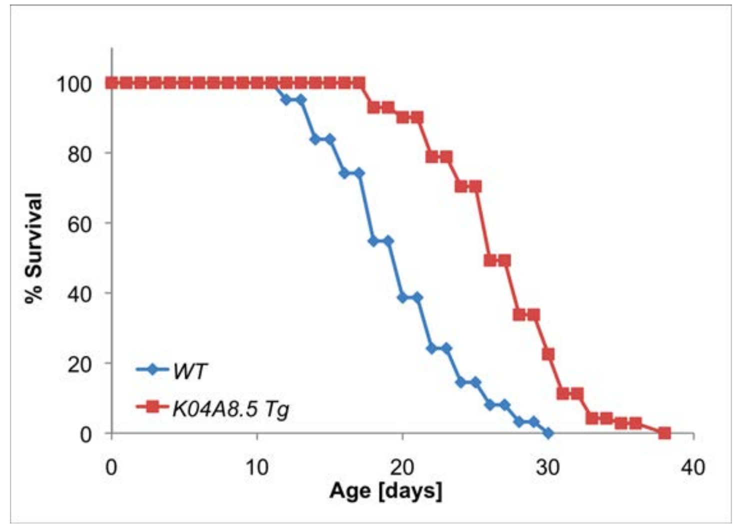
Postdoc, MGH/Harvard

Gary Ruvkun

Lipid Metabolism and Longevity

Identification of a pro-longevity lipase

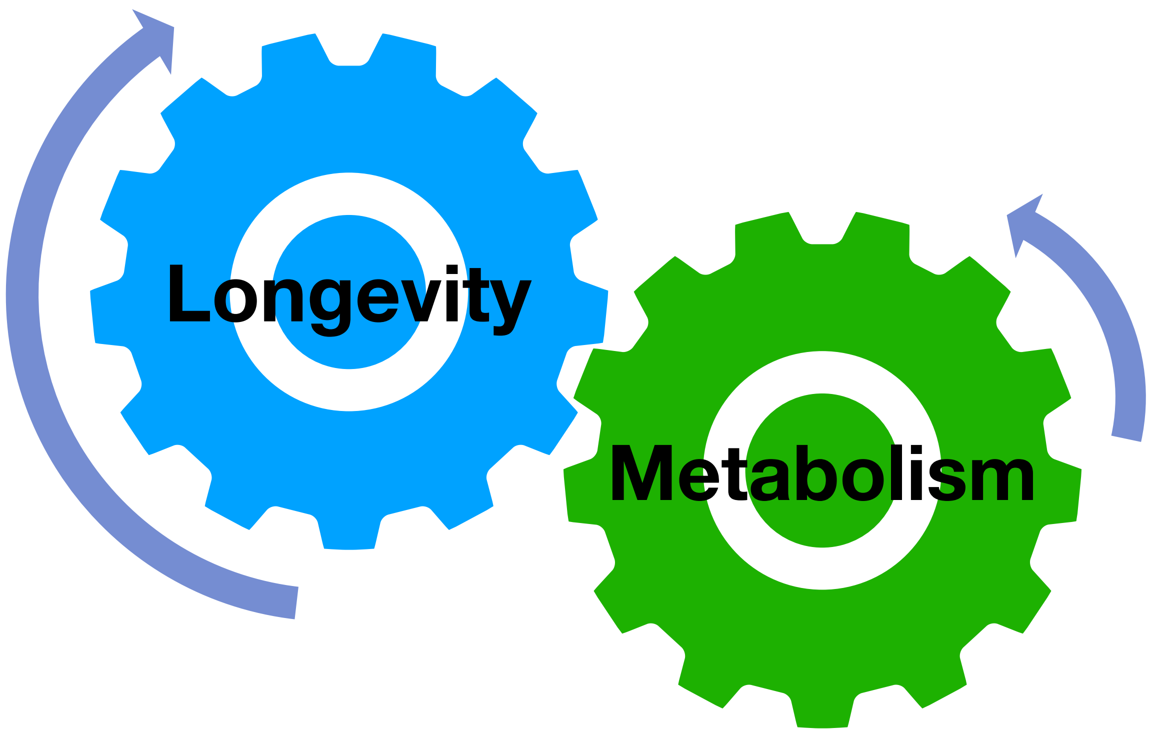


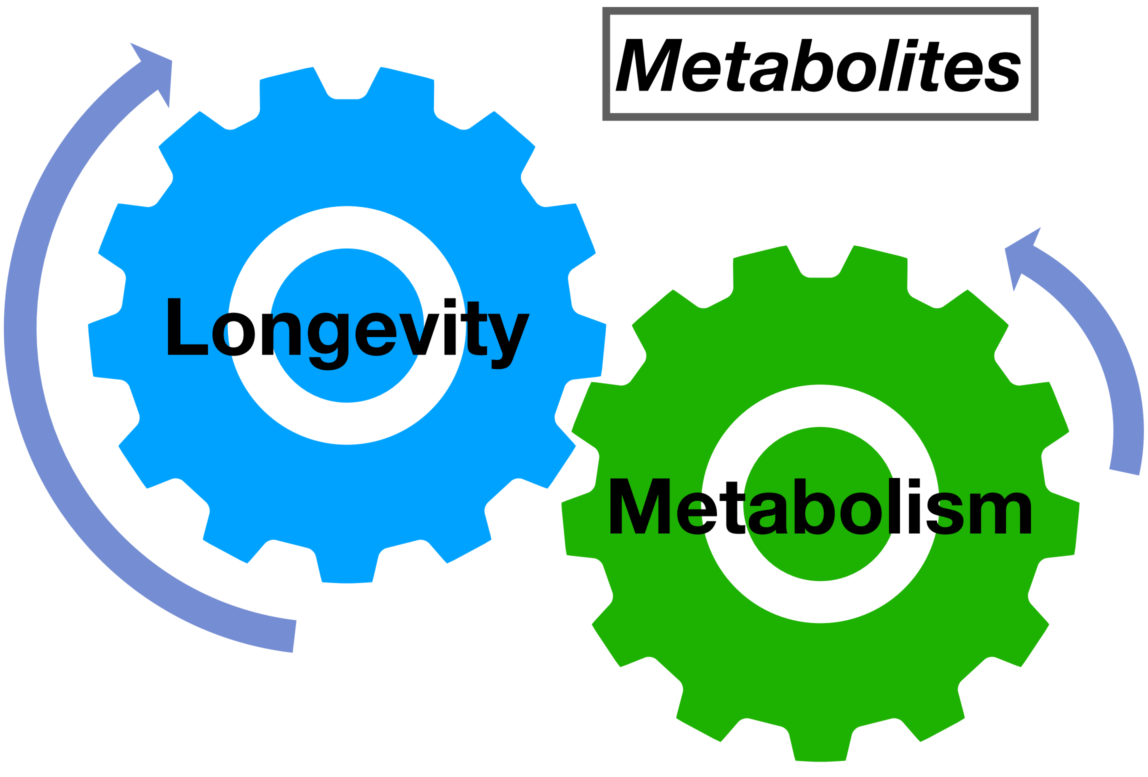


Wang et al. Science 2008

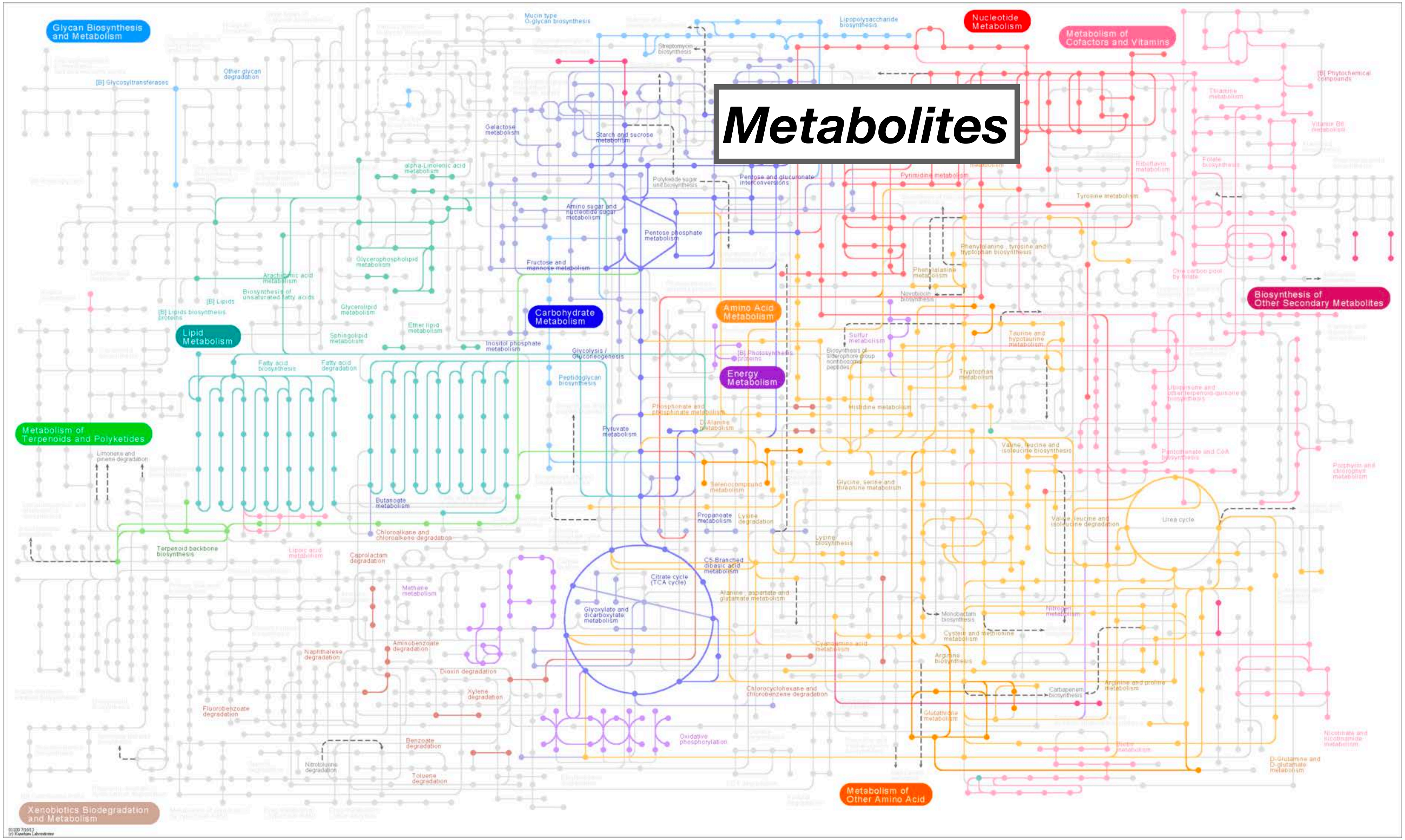
K04A8.5 Lipase

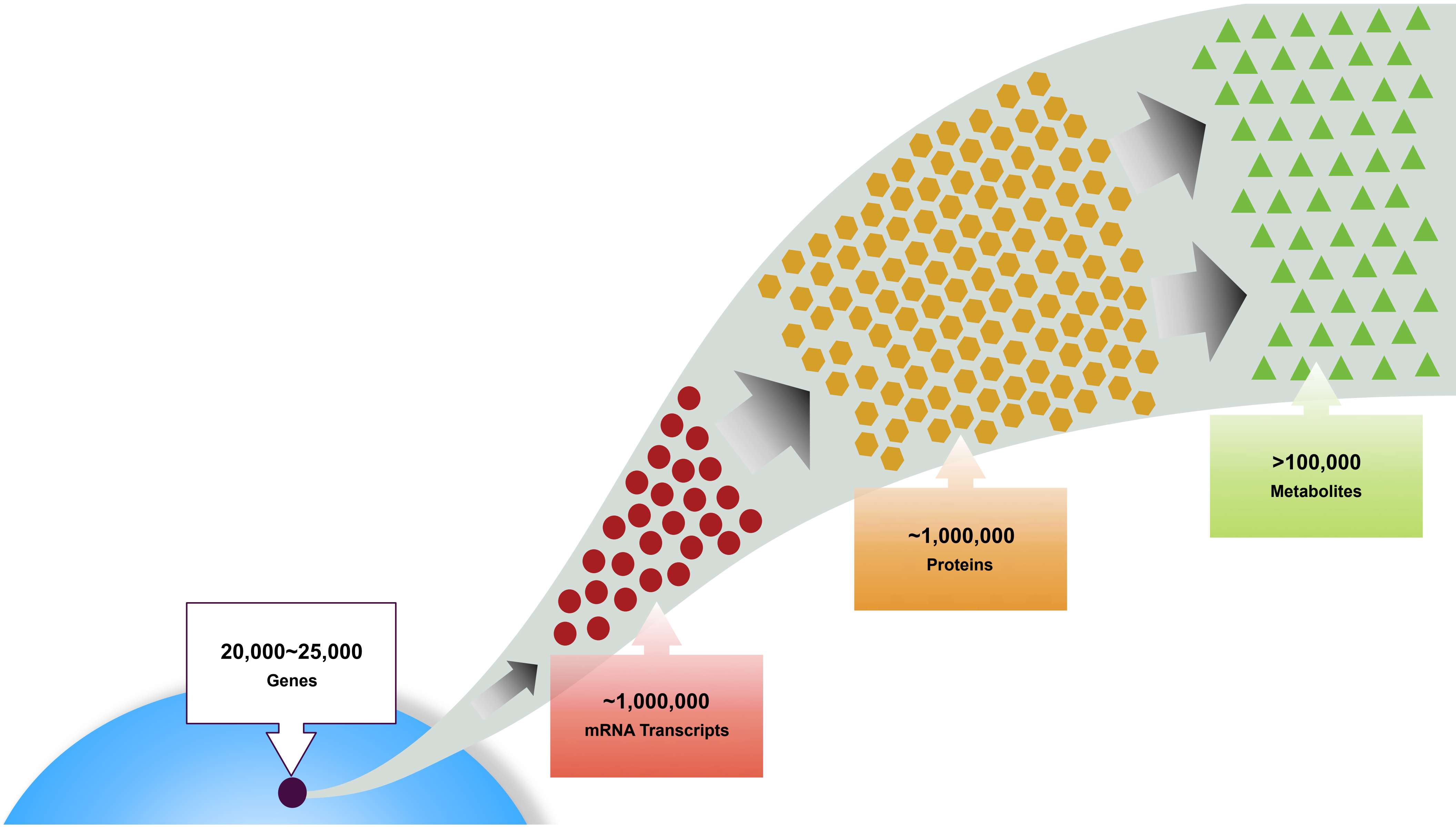
- RNA interference screening
- Nile Red cellular imaging

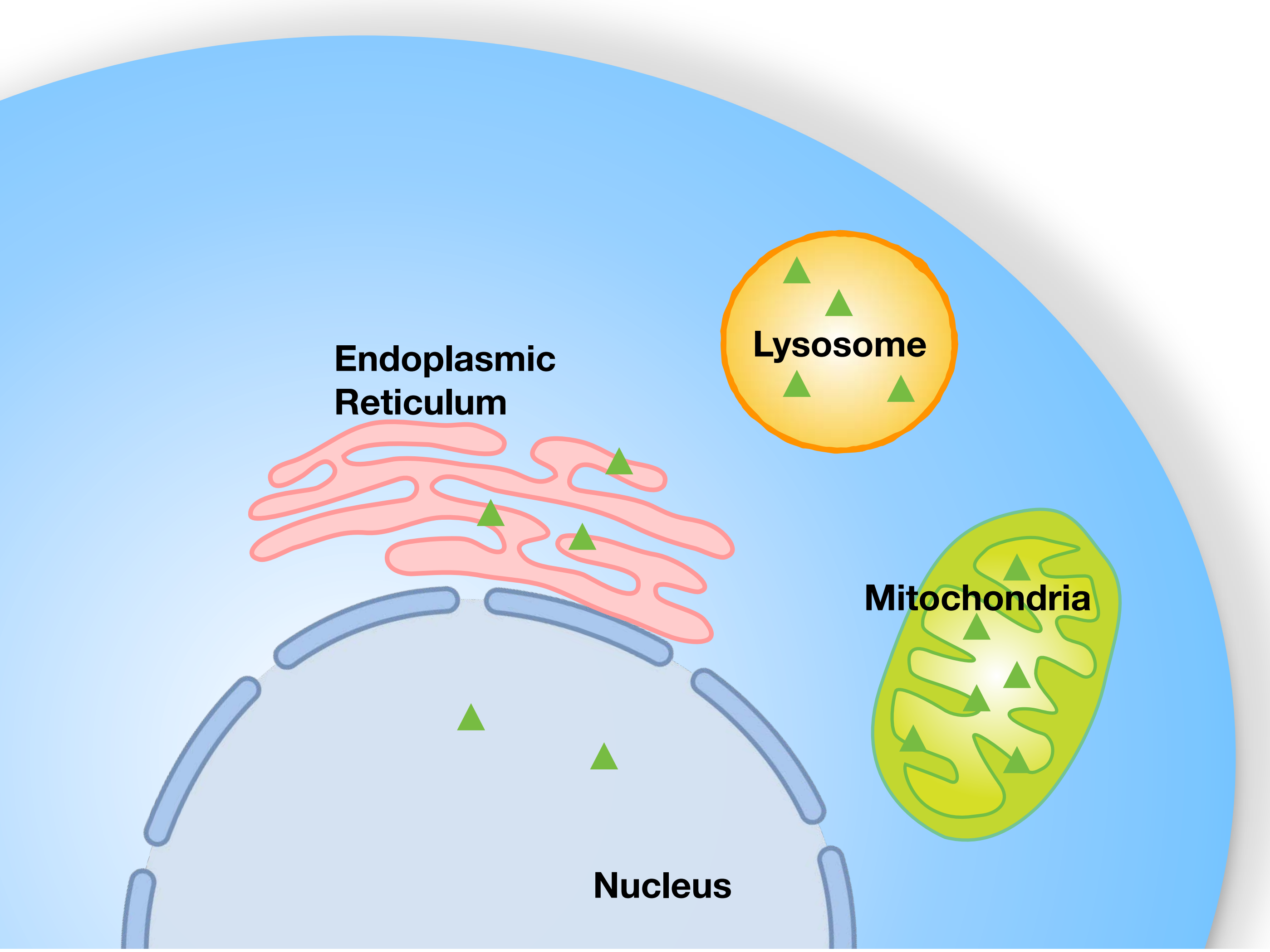

Longevity
Metabolism

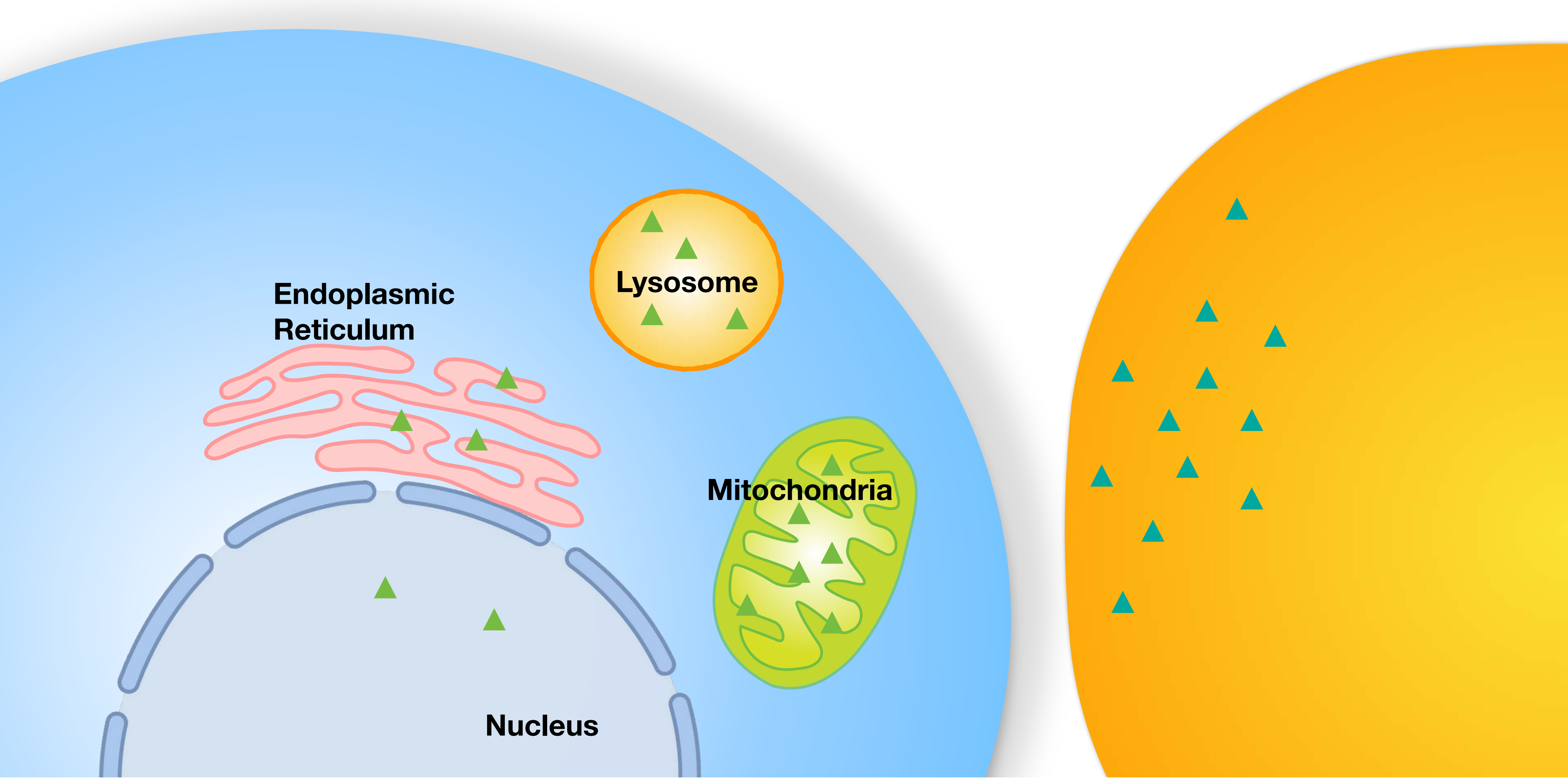

Metabolites
Longevity
Metabolism

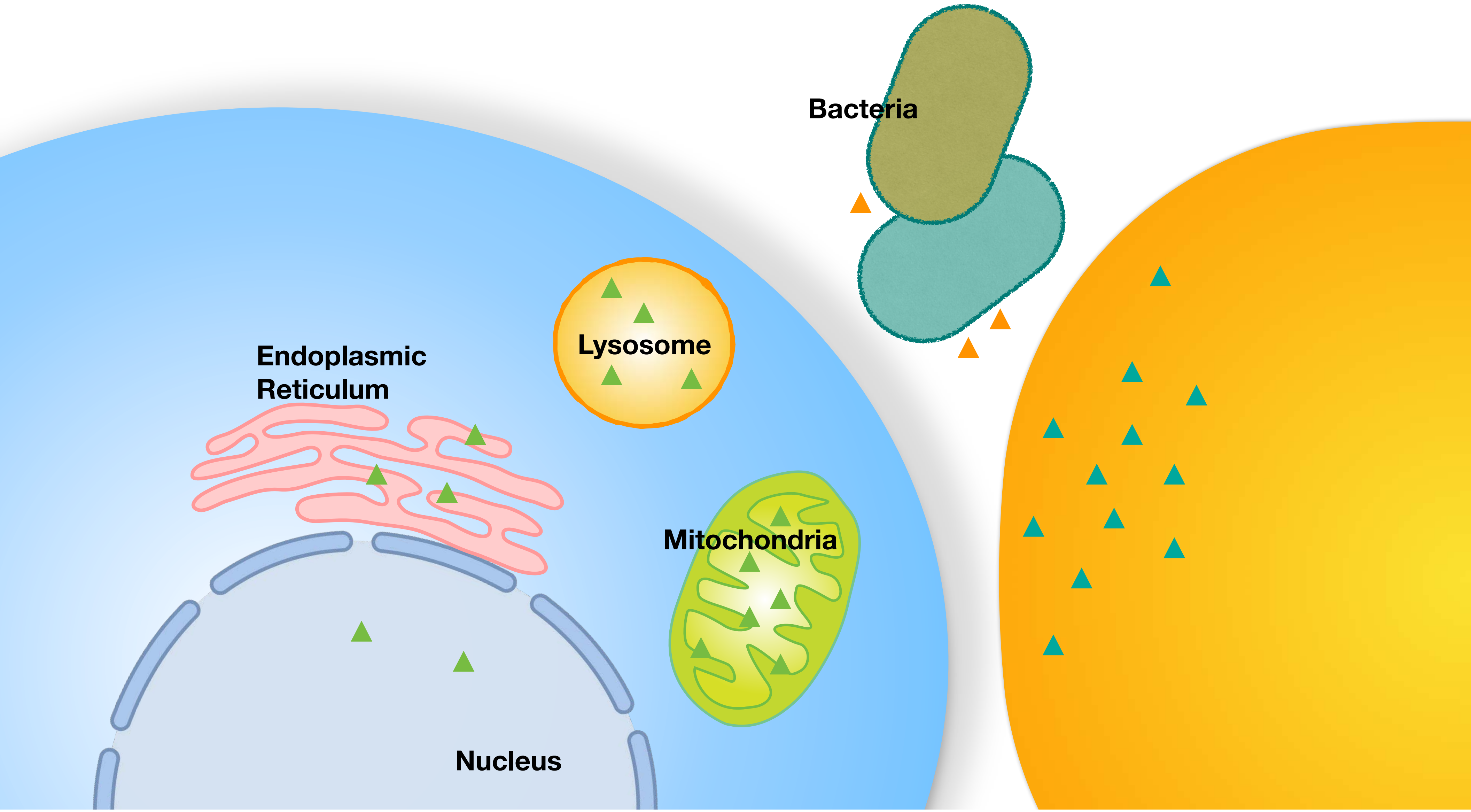
Metabolites

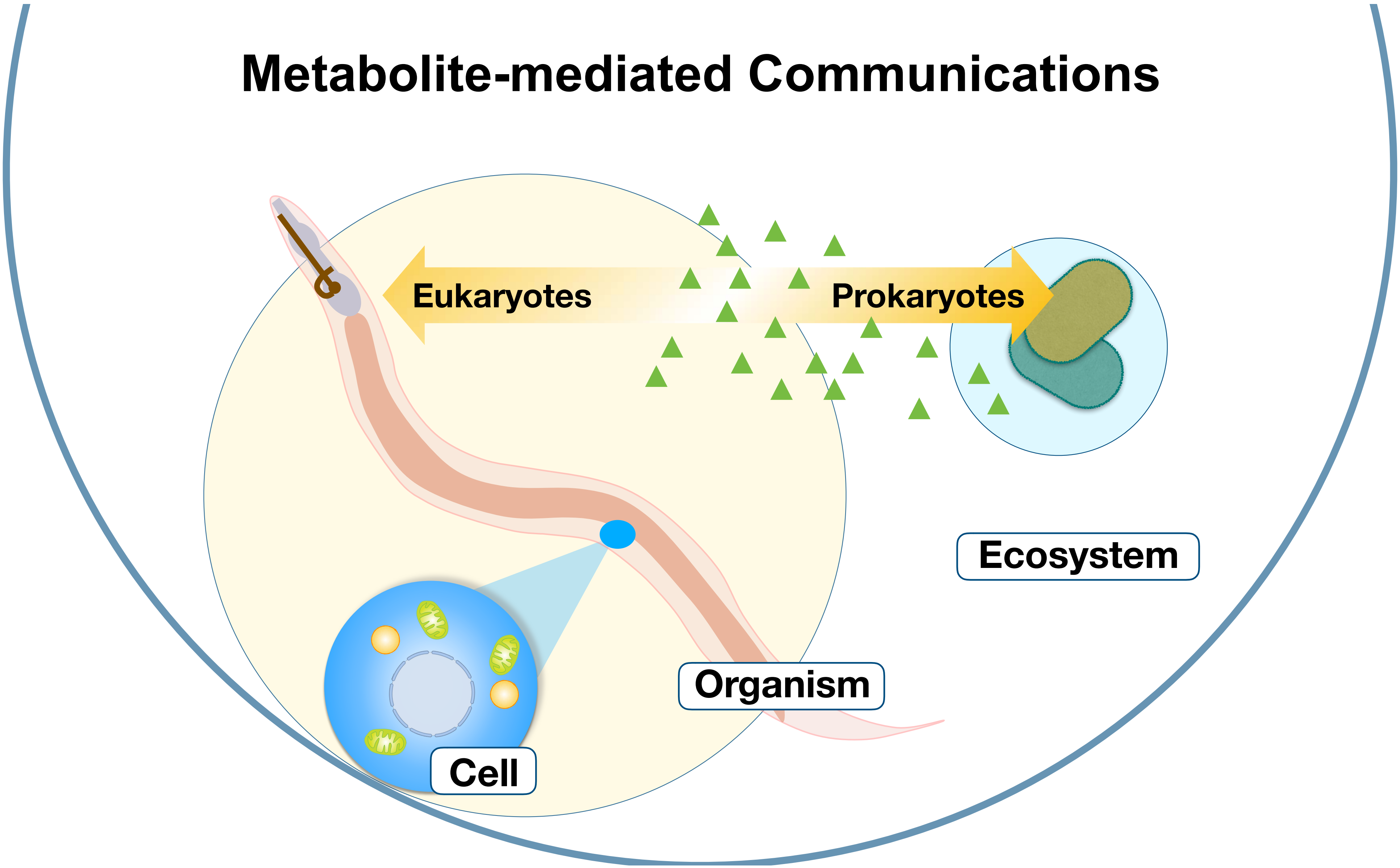



20,000~25,000
Genes
~1,000,000
mRNA Transcripts
~1,000,000
Proteins
>100,000
Metabolites

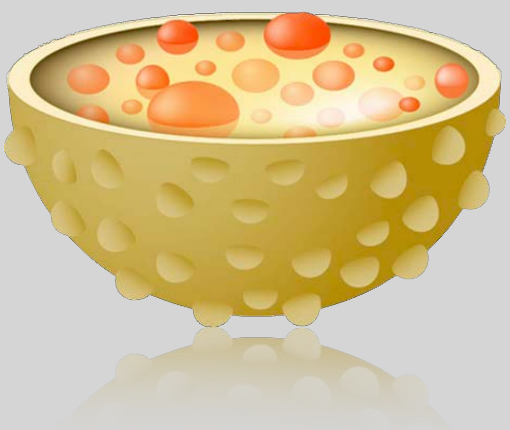

Endoplasmic
Reticulum
Lysosome
Mitochondria
Nucleus


Lysosome
Endoplasmic
Reticulum
Mitochondria
Nucleus

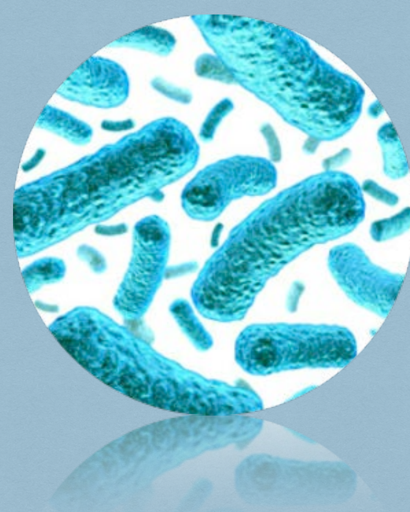

Bacteria
Lysosome
Endoplasmic
Reticulum
Mitochondria
Nucleus


Metabolite-mediated Communications
Eukaryotes
Prokaryotes
Ecosystem
Organism
Cell

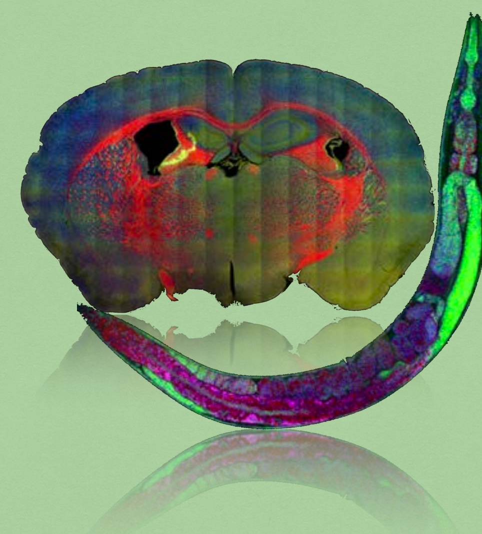
Lysosomal Metabolism
&
Longevity



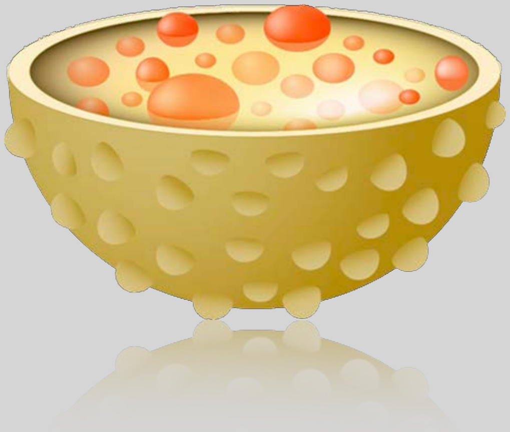
Microbial Metabolism
&
Longevity

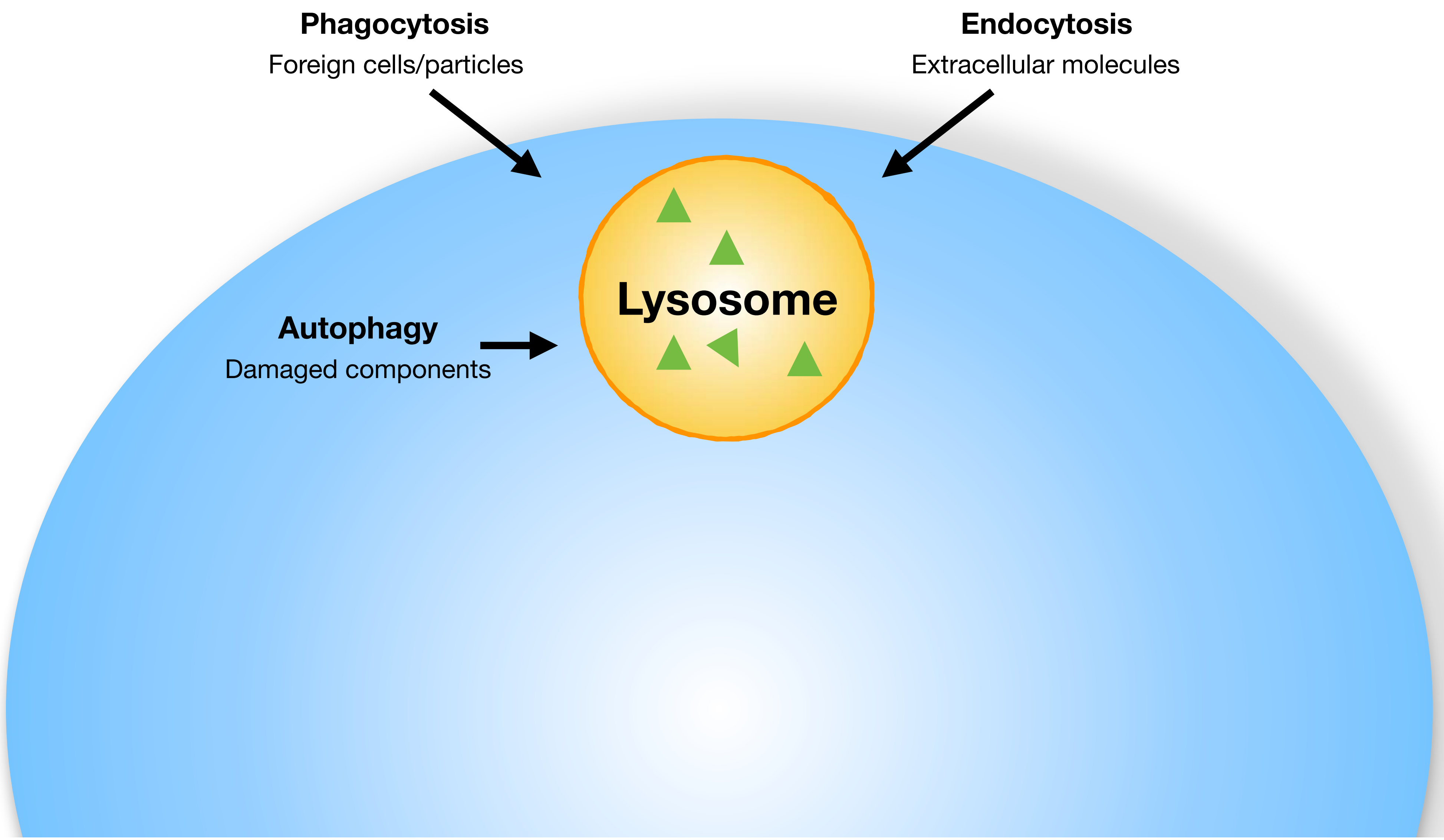


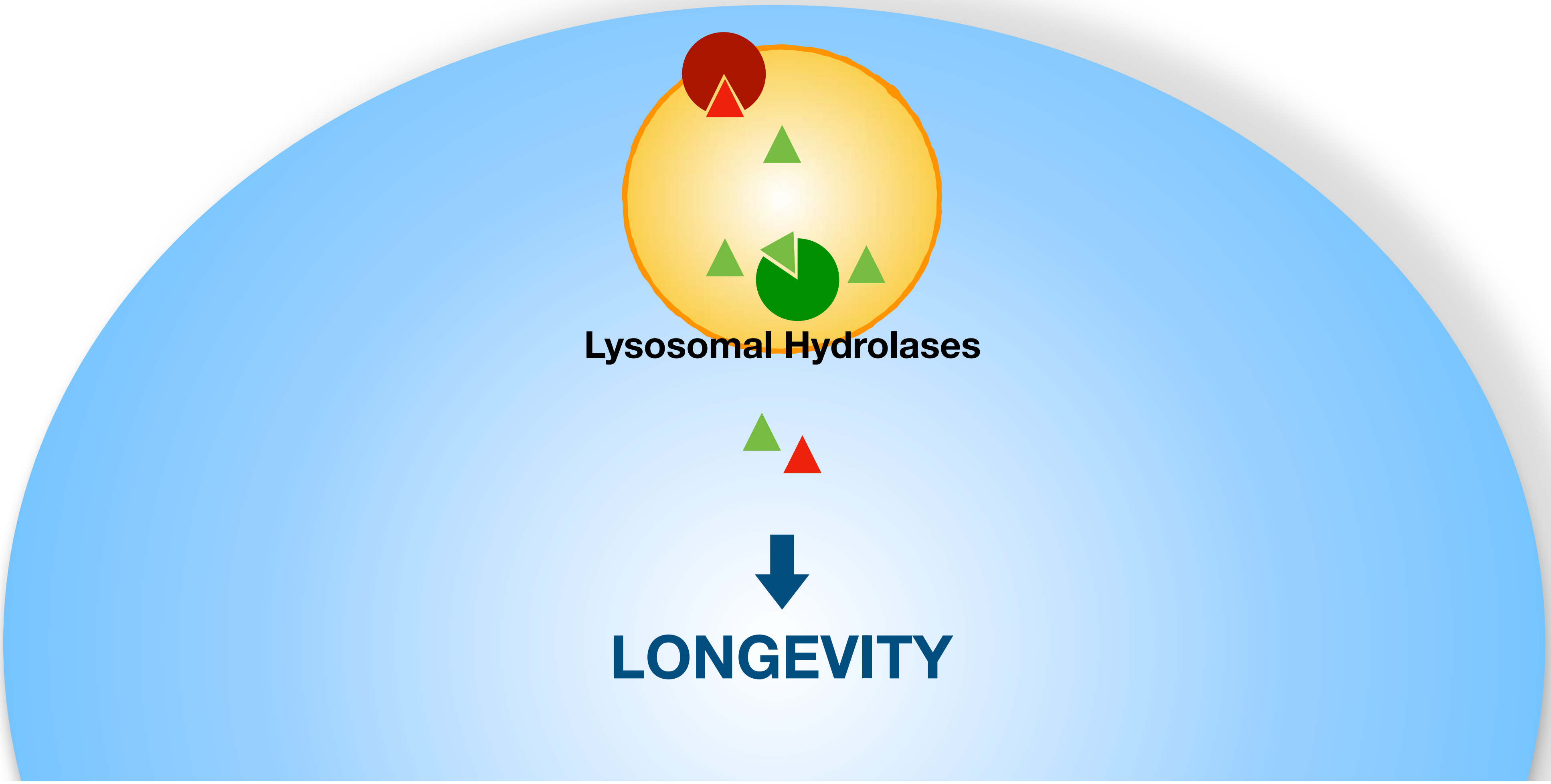
Metabolic Imaging
&
Longevity



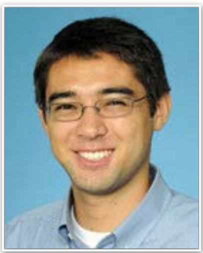
Lysosomal Metabolism
&
Longevity




Phagocytosis
Foreign cells/particles
Endocytosis
Extracellular molecules
Lysosome
Autophagy
Damaged components

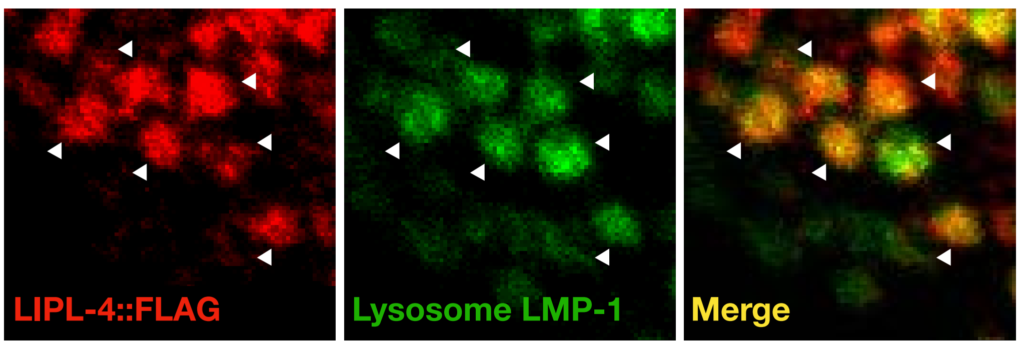

Lysosomal Hydrolases
LONGEVITY

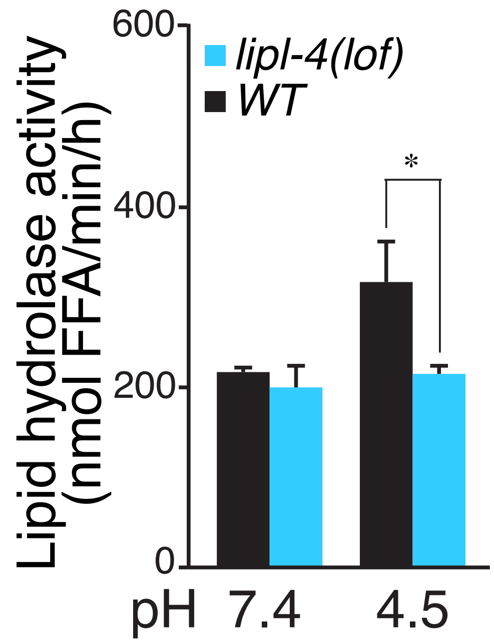
Lysosomal LIPL-4/K04A8.5 lipase promotes longevity



Andy Folick

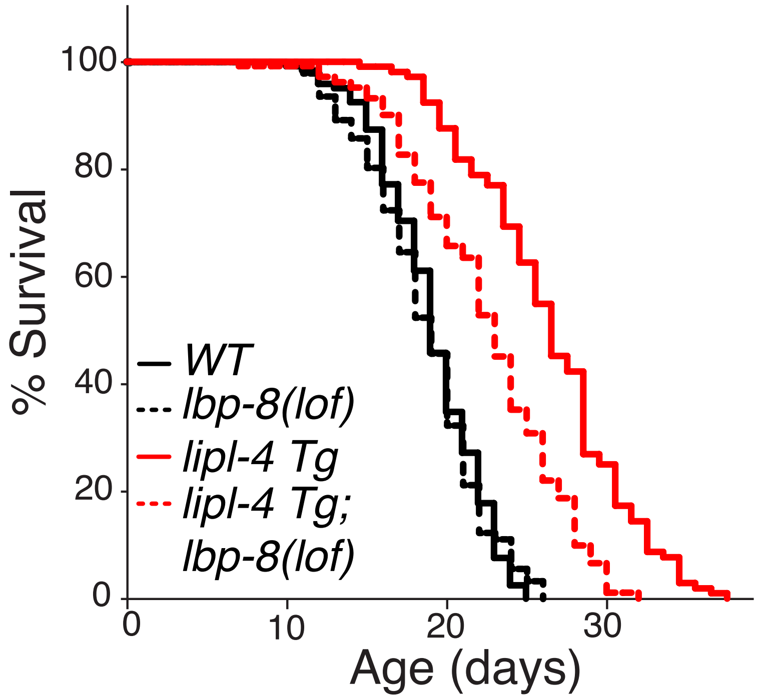
Rudy Zechner Group



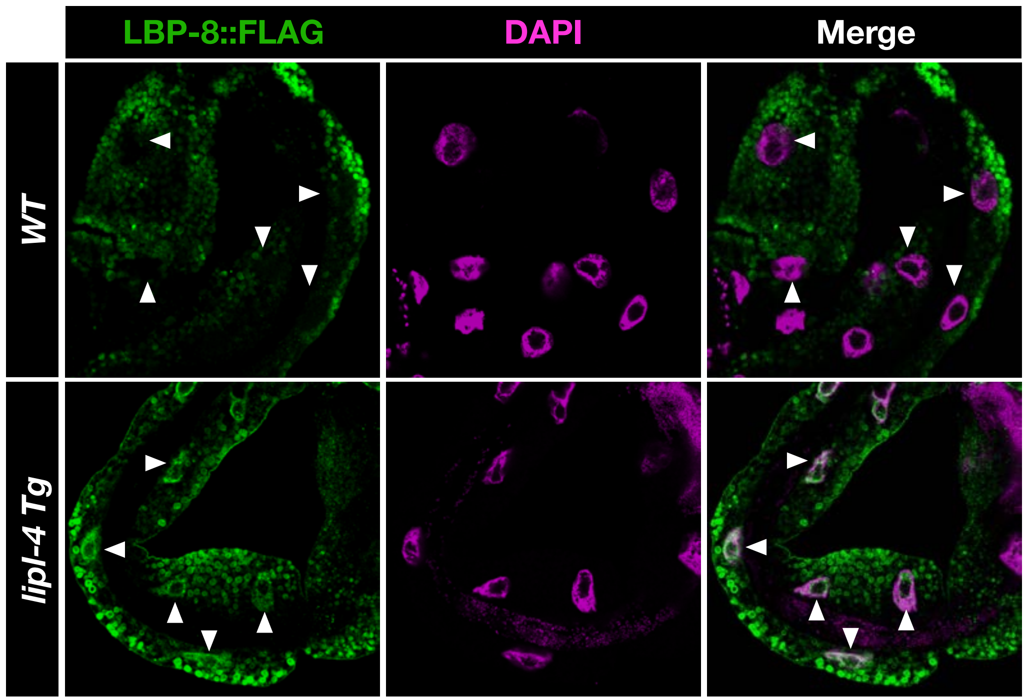


Folick et al. Science 2015

LIPL-4-induced lipolysis enhances nuclear translocation of LBP-8

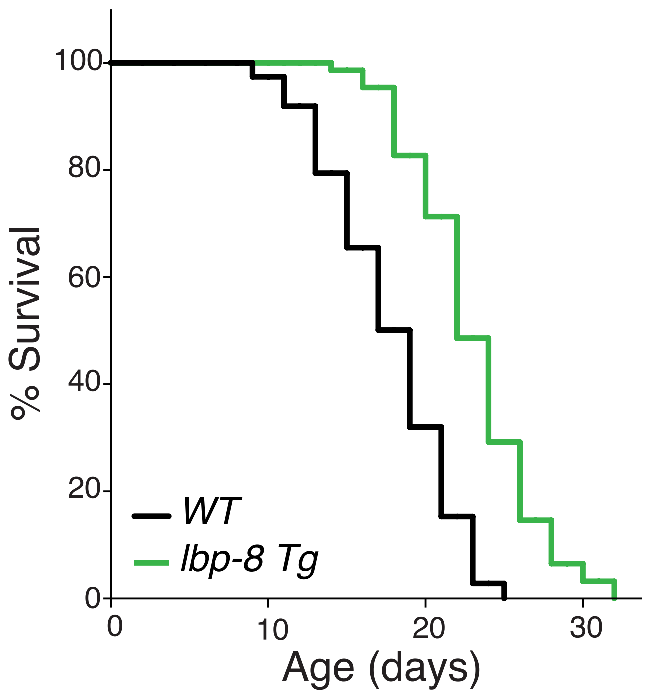


LBP-8: fatty acid binding protein

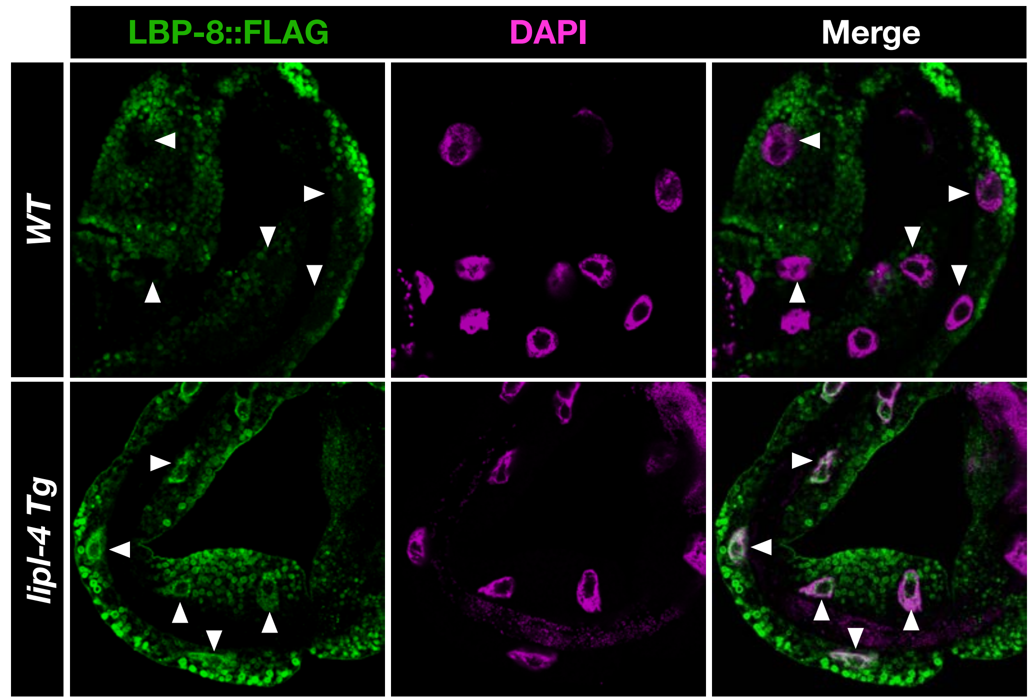


Folick et al. Science 2015

LBP-8 is sufficient to promote longevity

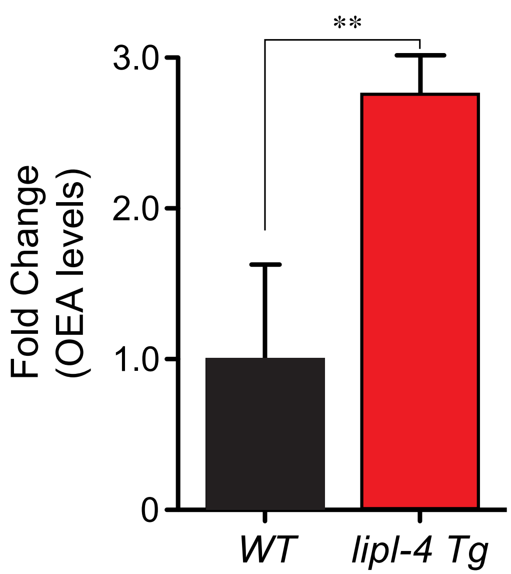


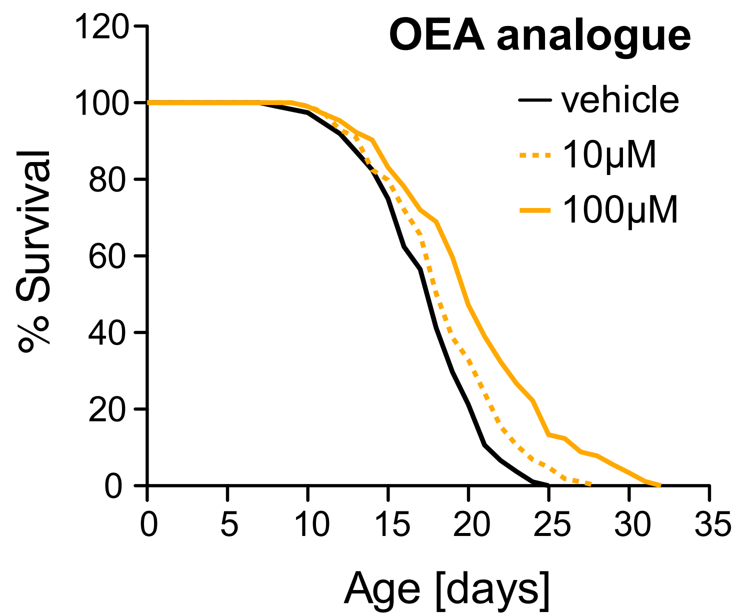
LBP-8: fatty acid binding protein



Folick et al. Science 2015

LIPL-4-induced lipolysis induces lysosomal levels of OEA

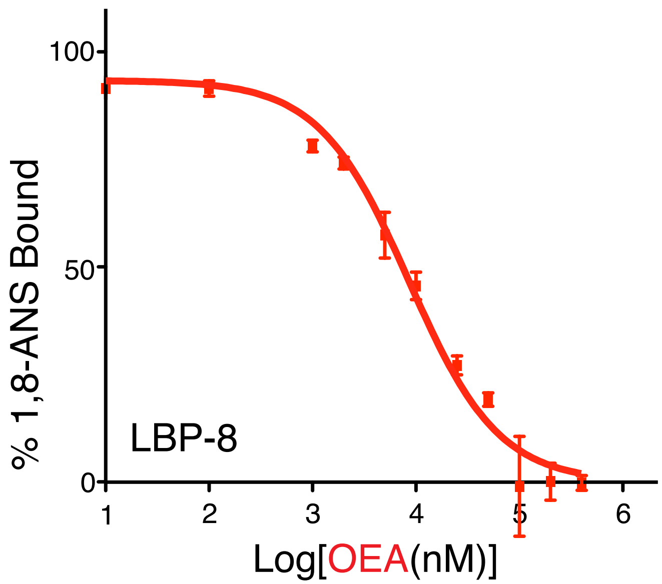


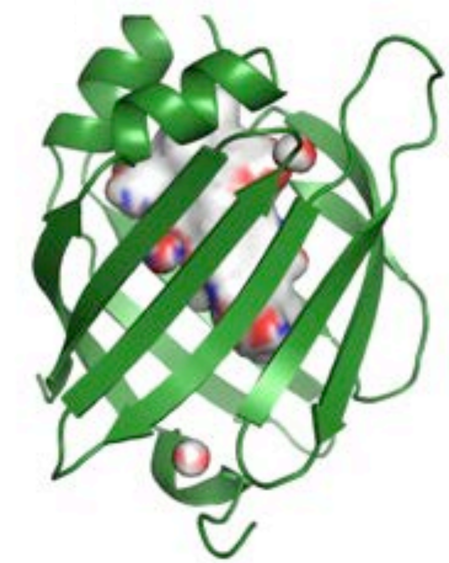


OEA: Oleoylethanolamide

Folick et al. Science 2015

OEA directly binds with LBP-8 and promotes longevity



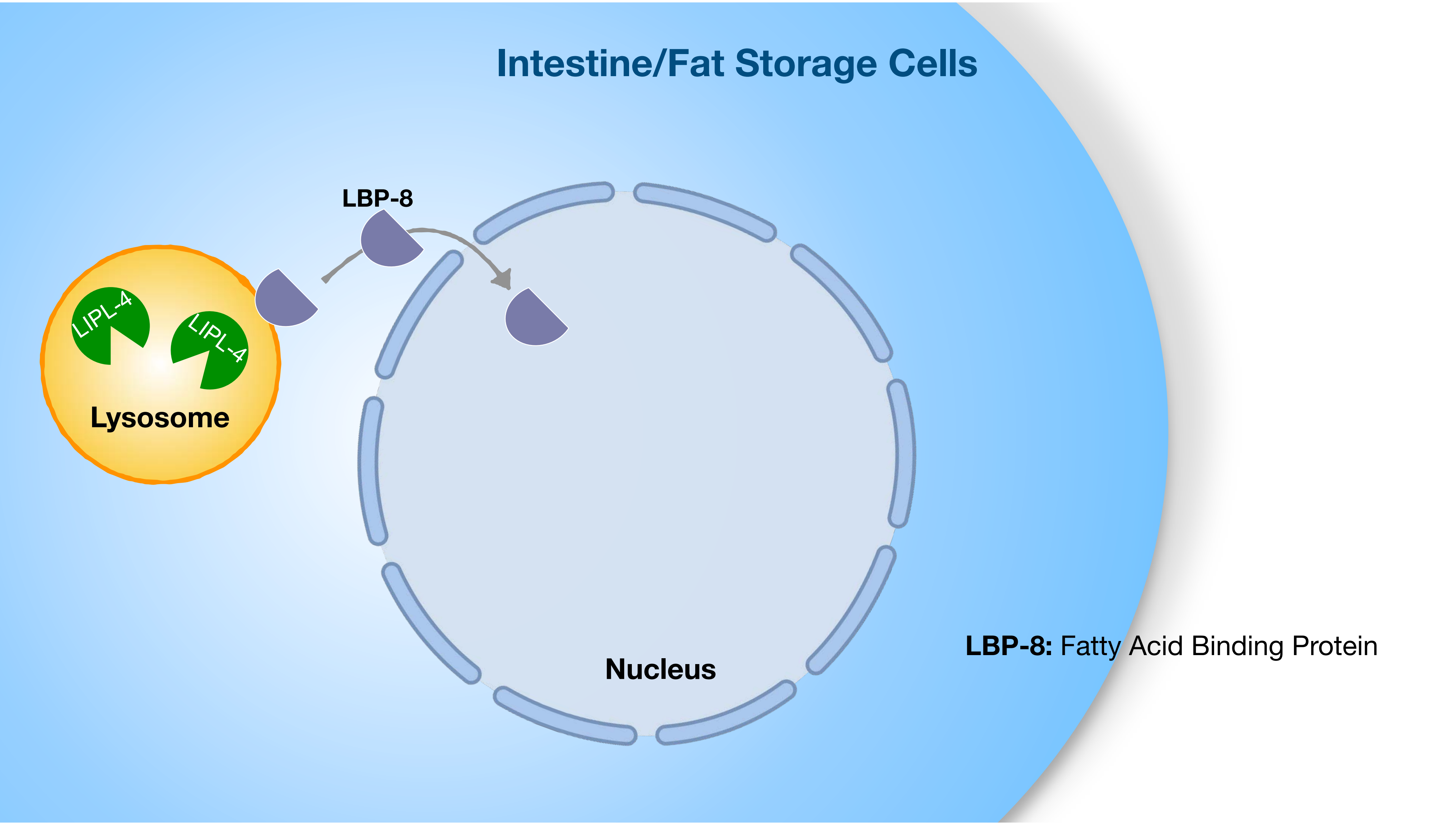


Eric Ortlund Group

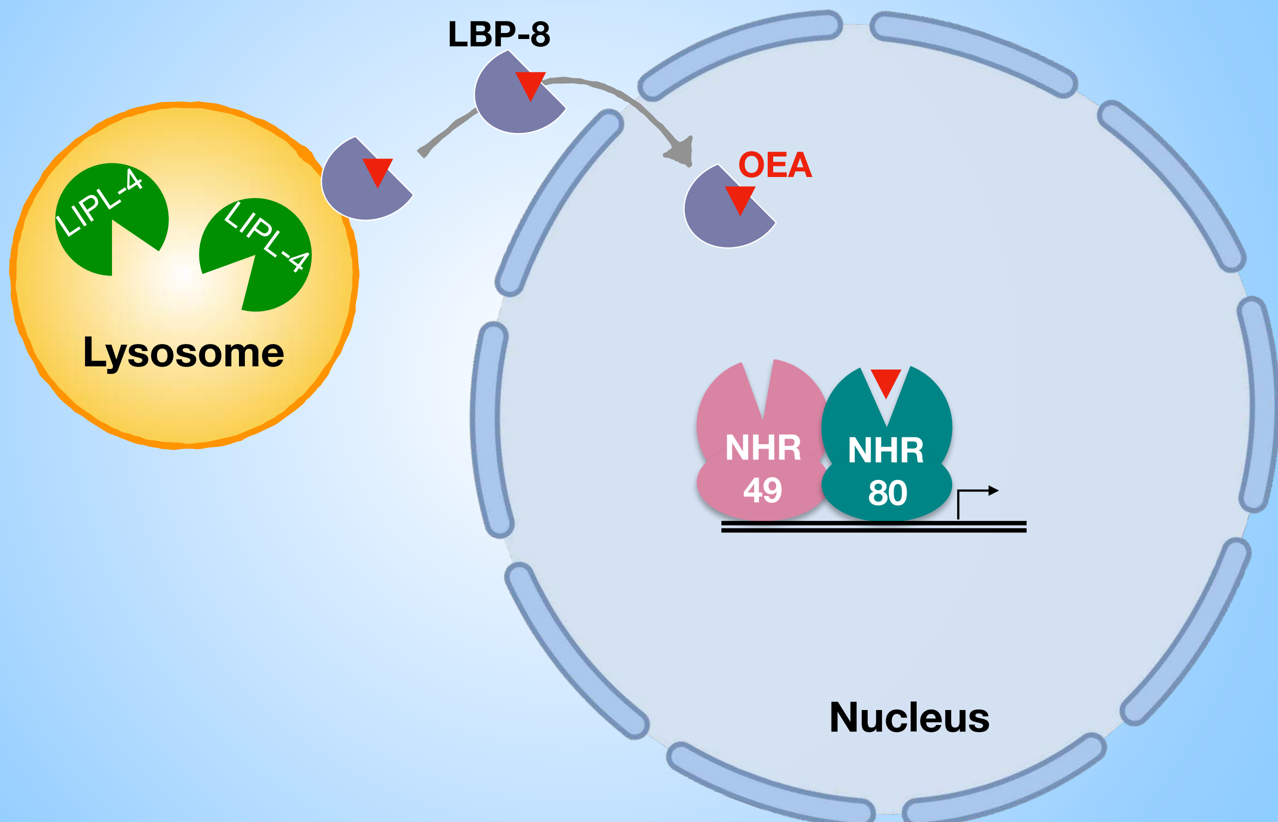
OEA: Oleoylethanolamide

LBP-8: Fatty acid binding protein

Folick et al. Science 2015; Tillman et al. Sci Rep 2019


Intestine/Fat Storage Cells
LBP-8
LIPL-4
LIPL-4
Lysosome
Nucleus
LBP-8: Fatty Acid Binding Protein

Intestine/Fat Storage Cells



David Moore Group

LBP-8: Fatty Acid Binding Protein
OEA: Oleoylethanolamide
NHR-49: PPAR-alpha
NHR-80: HNF4-alpha

- **Power of collaboration**

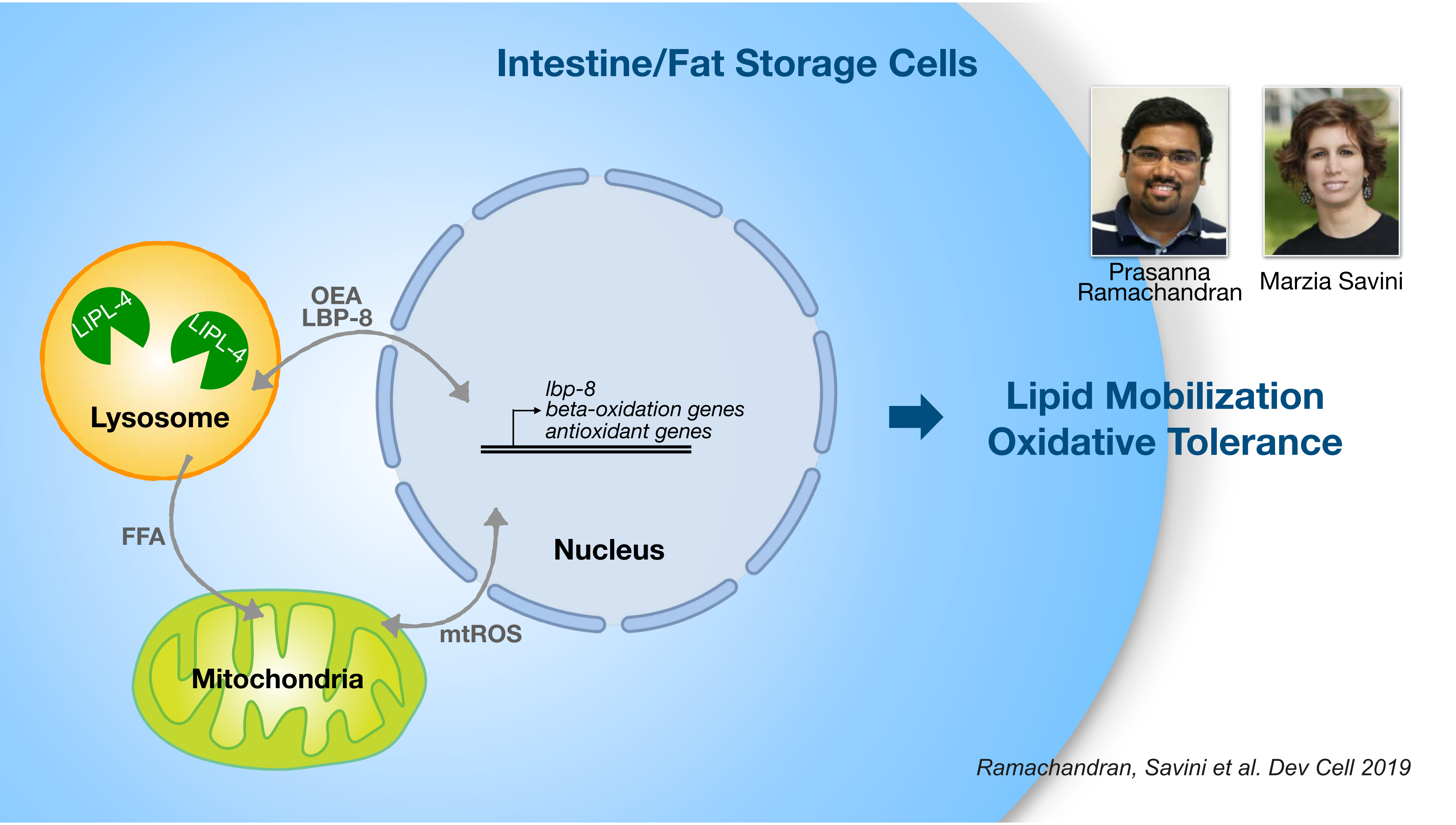
  Learn from experts in different fields.

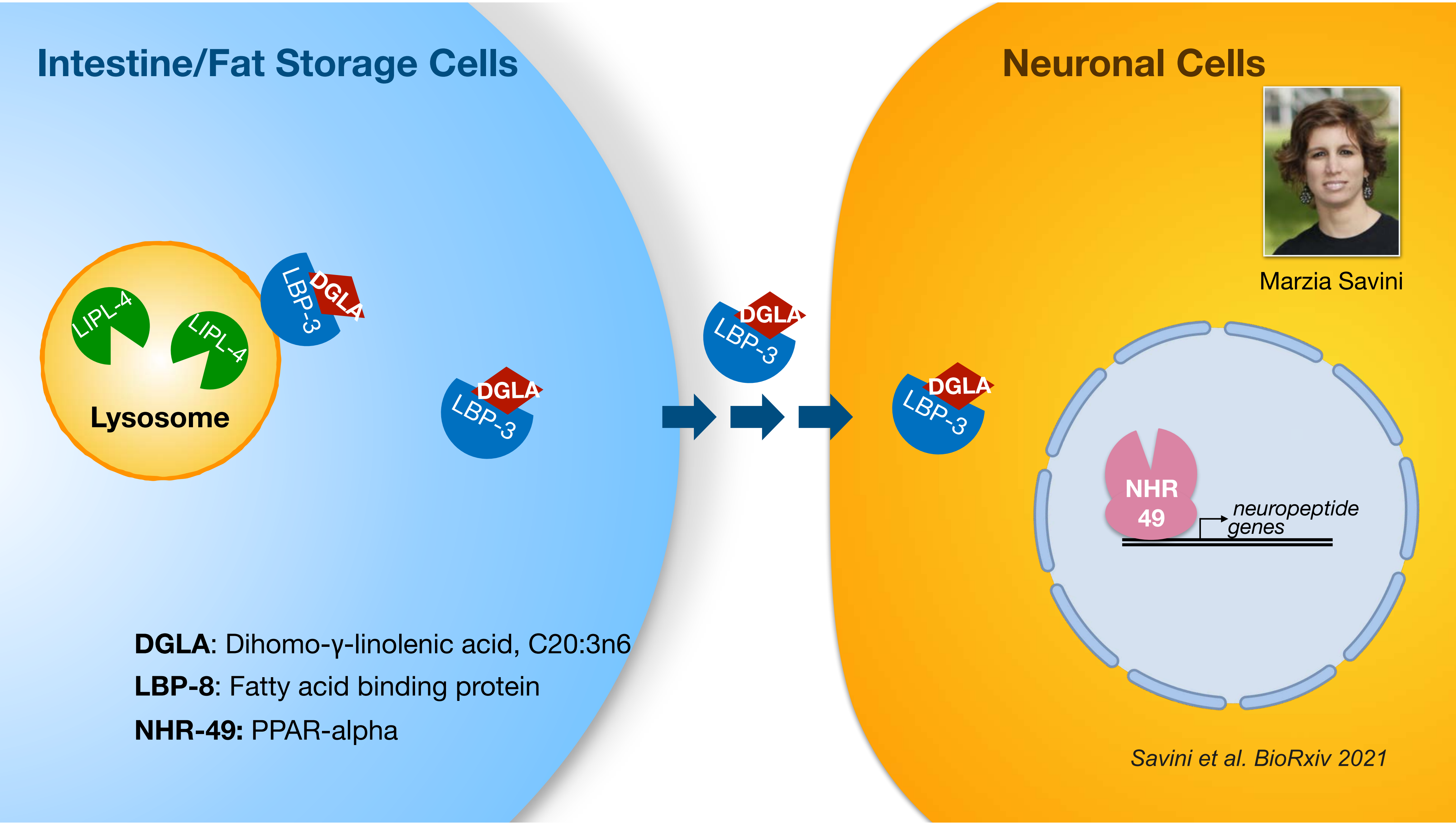
  Advance mechanistic inquiry in a deeper manner.

David Moore Group

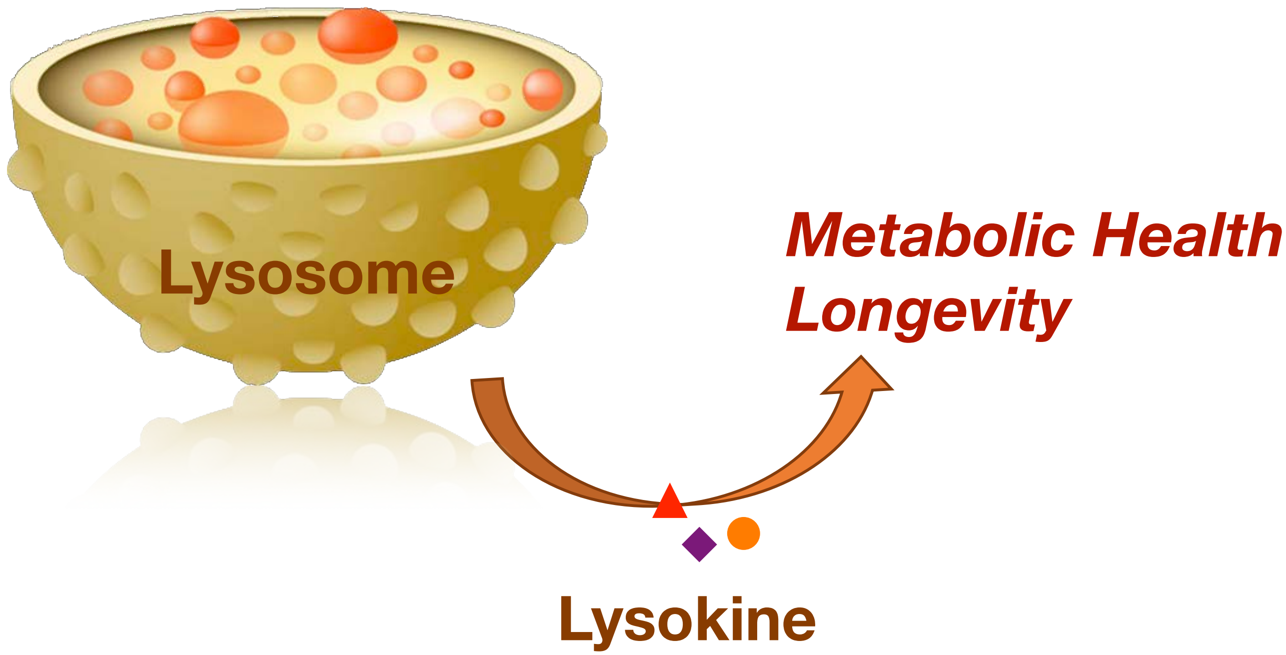
Rudy Zechner Group

Eric Ortlund Group

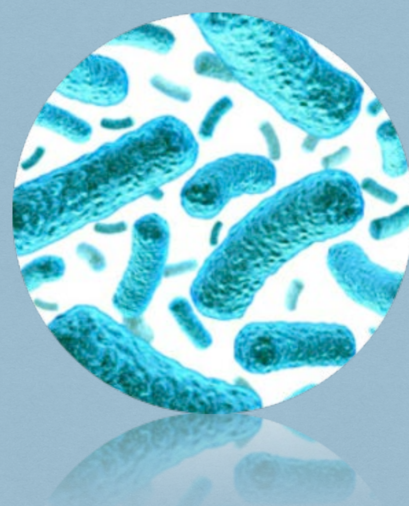

Intestine/Fat Storage Cells
LIPL-4
LIPL-4
Lysosome
OEA
LBP-8
lbp-8
beta-oxidation genes
antioxidant genes
FFA
Nucleus
mtROS
Mitochondria
Prasanna Ramachandran
Marzia Savini
Lipid Mobilization
Oxidative Tolerance
Ramachandran, Savini et al. Dev Cell 2019

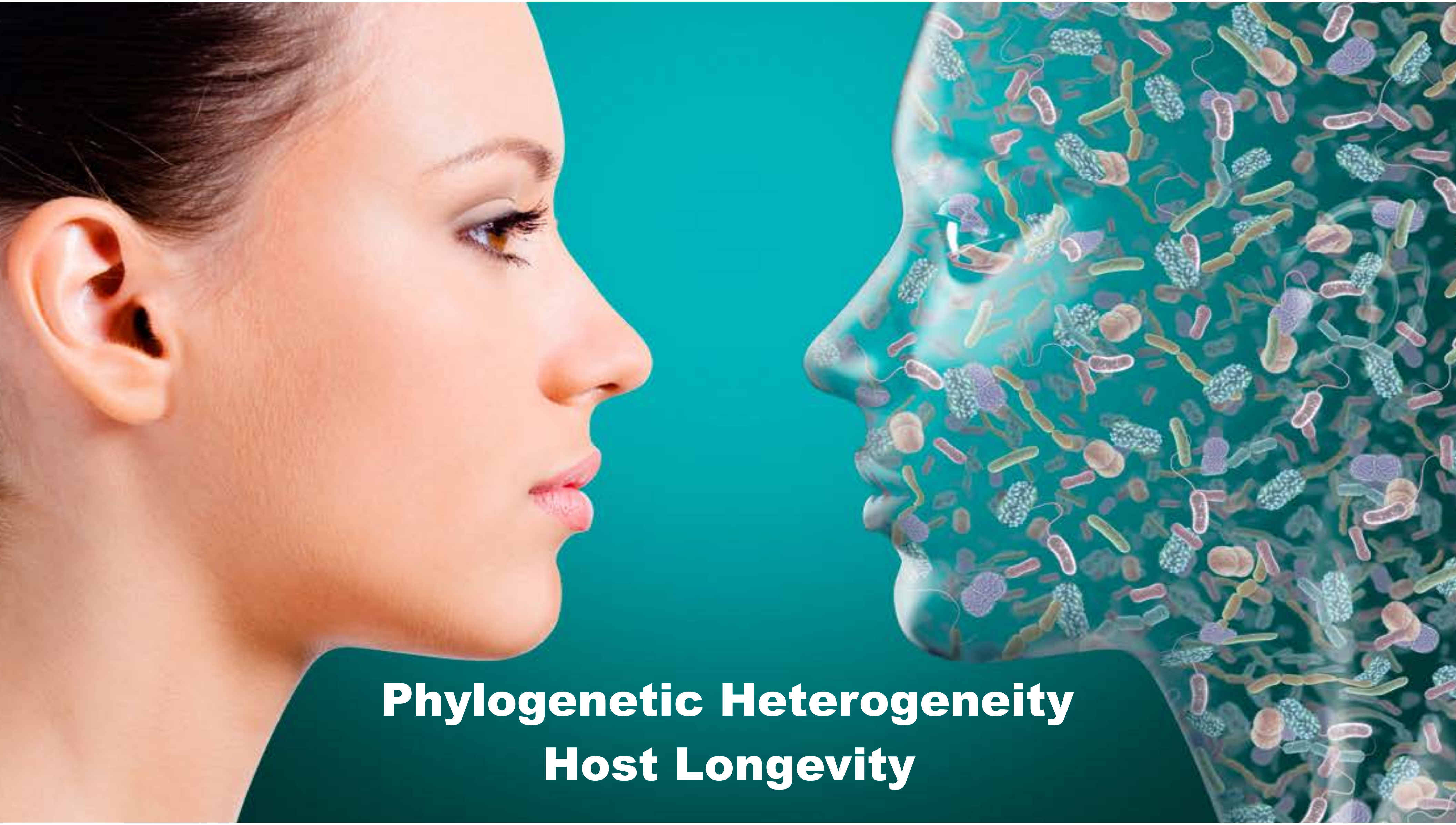


Intestine/Fat Storage Cells
Neuronal Cells
Marzia Savini
LIPL-4
LIPL-4
Lysosome
LBP-3
DGLA
NHR 49
neuropeptide genes
DGLA: Dihomo-γ-linolenic acid, C20:3n6
LBP-8: Fatty acid binding protein
NHR-49: PPAR-alpha
Savini et al. BioRxiv 2021

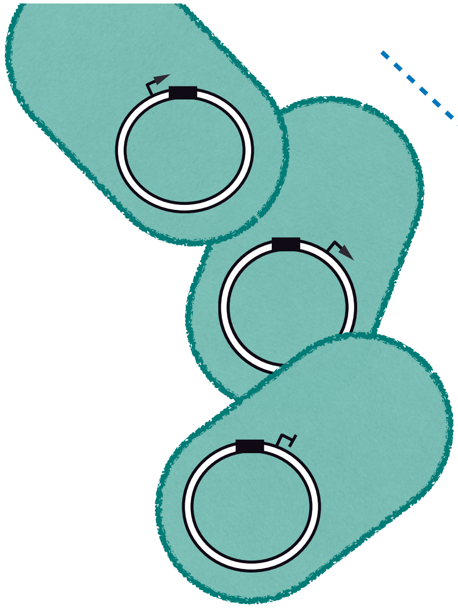

Lysosome
Metabolic Health
Longevity
Lysokine

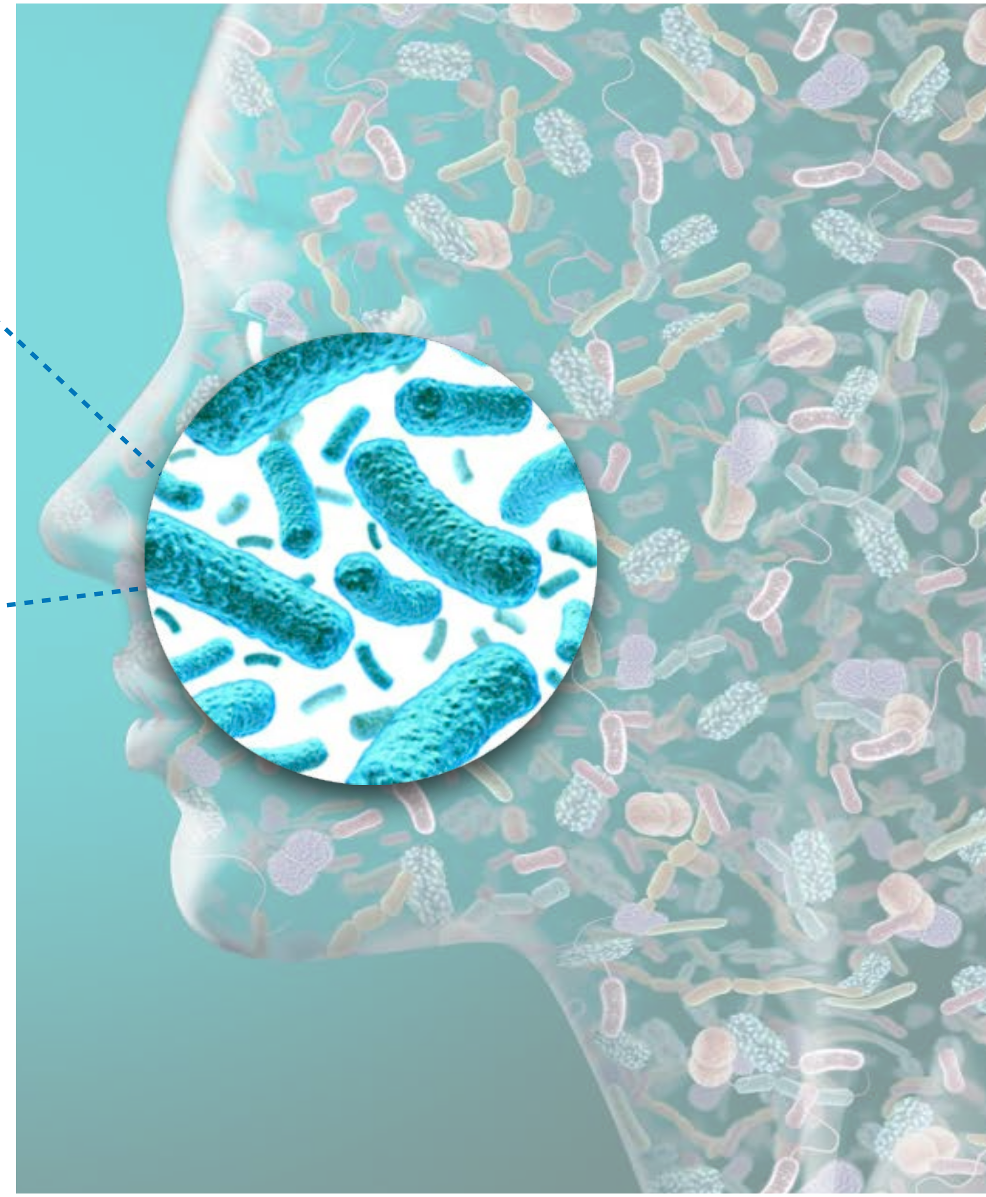
Microbial Metabolism
&
Longevity




Phylogenetic Heterogeneity
Host Longevity

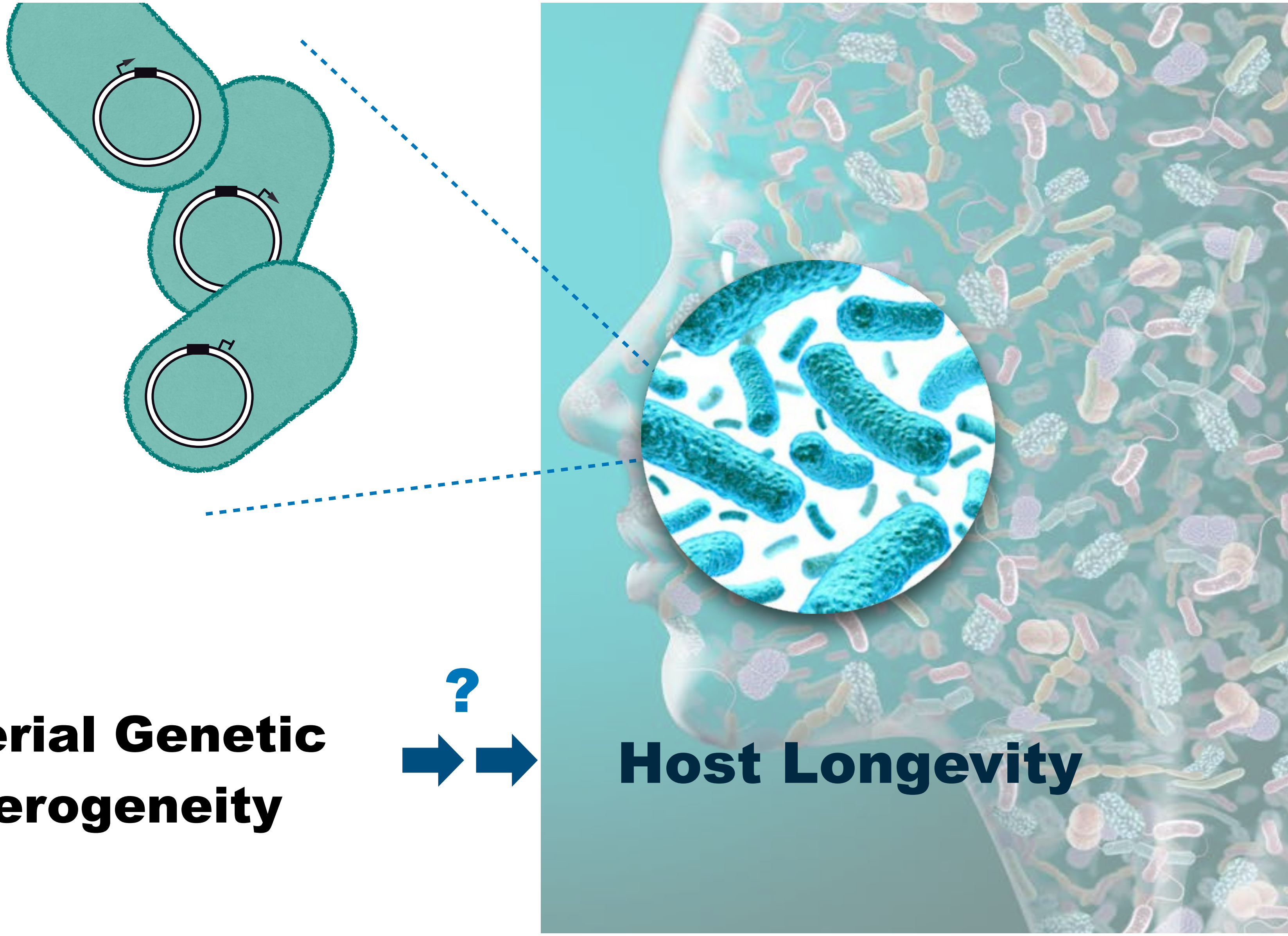
Christophe Herman
Group



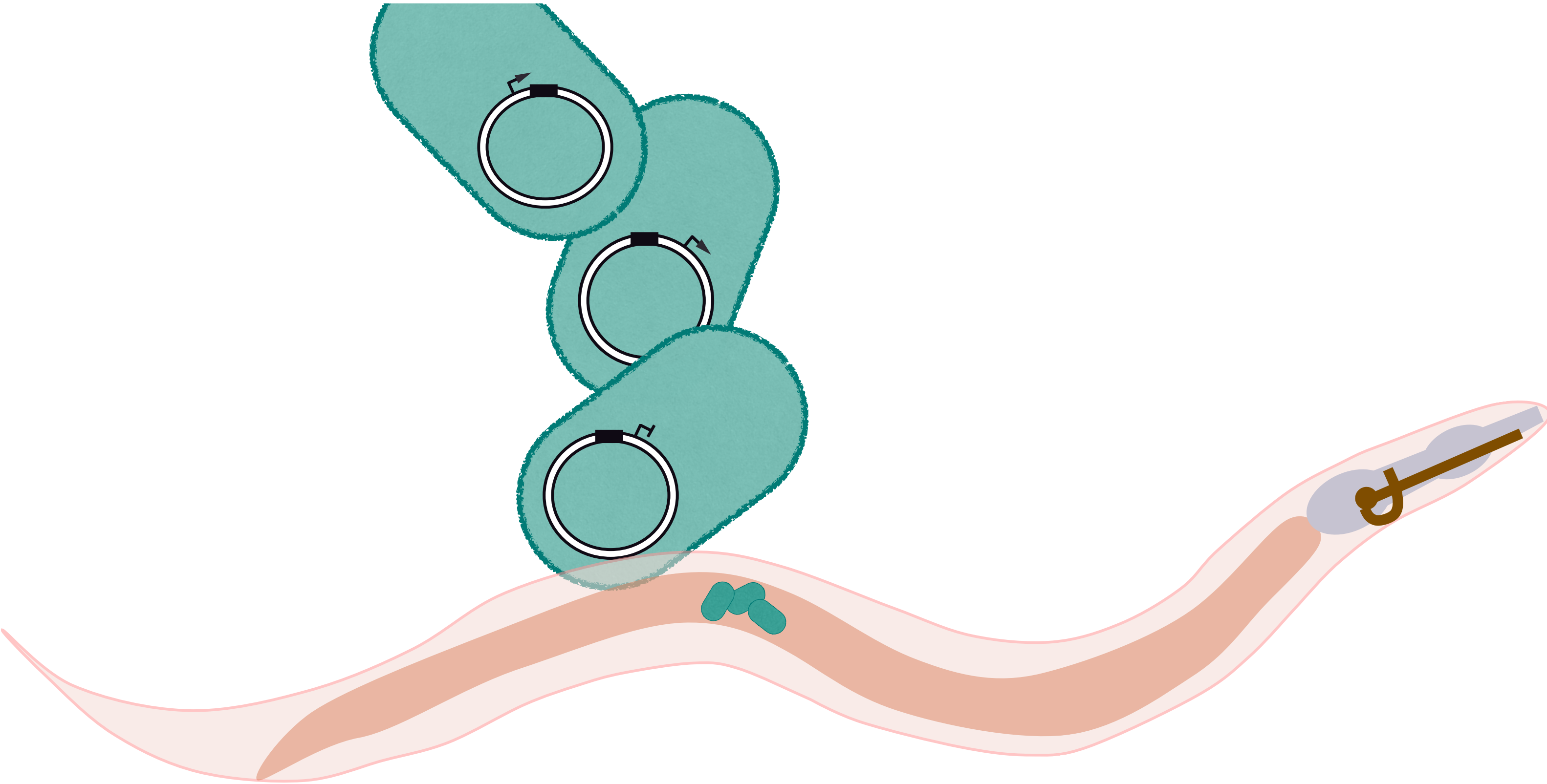


How about different genes in same bacteria?

Christophe Herman Group



Bacterial Genetic Heterogeneity → ? → **Host Longevity**



Bing Han

Bacterial Genetic Heterogeneity ? → → **Host Longevity**

29 bacterial deletion mutants promote *C. elegans* longevity

pabB	hns	lon	ycbJ	ygjV	pbl	yfdG	pdxA
lipB	gmhA	ycgL	yfiB	hyfR	rplY	skp	
lpp	ihfB	ynjE	nrfG	sapD	recC	ycgN	
aroG	aroD	secB	purE	uidC	psuK	trxA	

Host Longevity

Han et al. Cell 2017

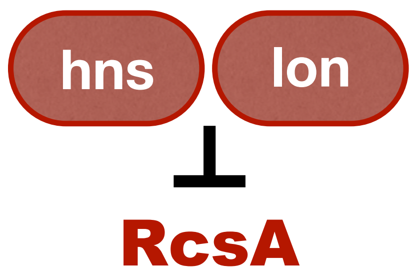
29 bacterial deletion mutants promote *C. elegans* longevity

pabB	hns	lon	ycbJ	ygjV	pbl	yfdG	pdxA
lipB	gmhA	ycgL	yfiB	hyfR	rplY	skp	
lpp	ihfB	ynjE	nrfG	sapD	recC	ycgN	
aroG	aroD	secB	purE	uidC	psuK	trxA	

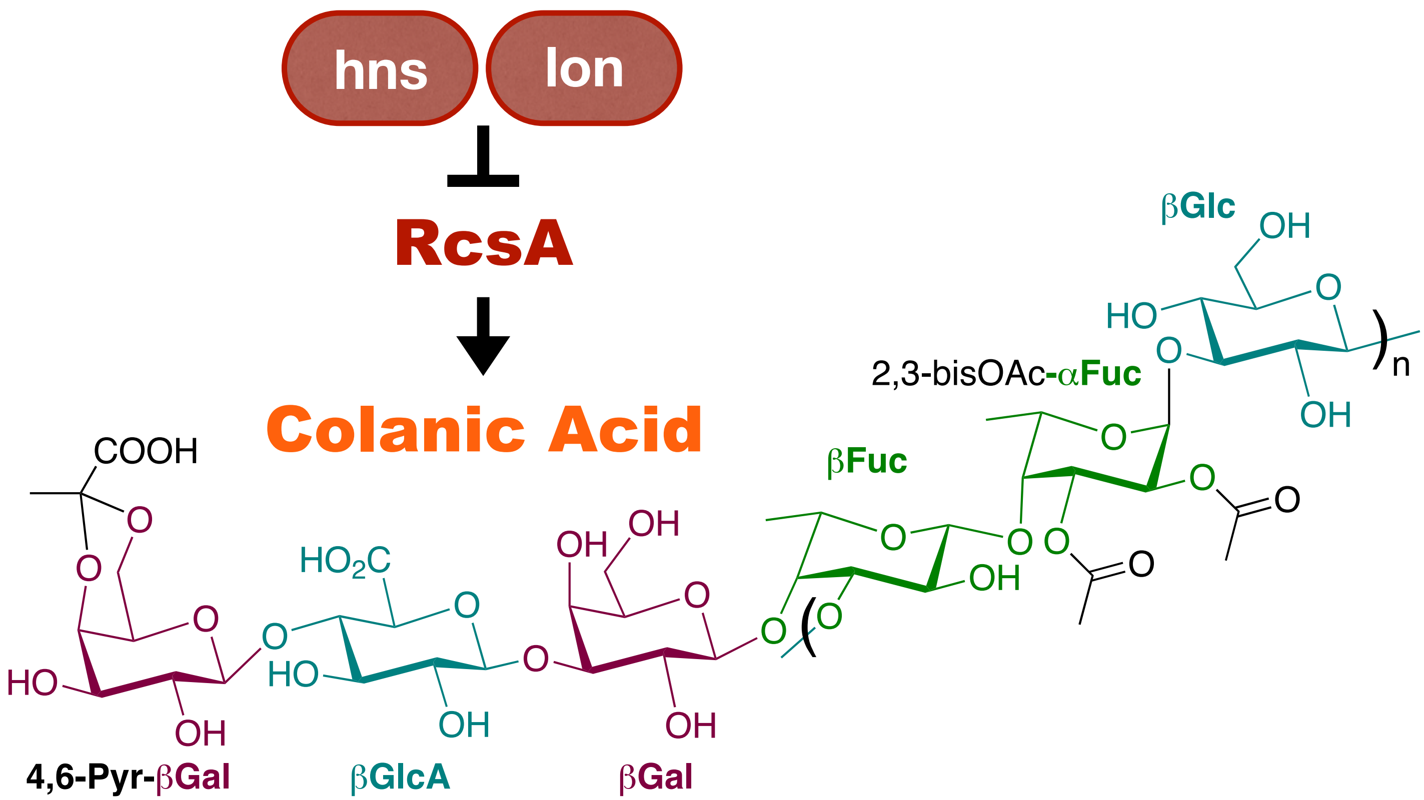
Host Longevity

Han et al. Cell 2017

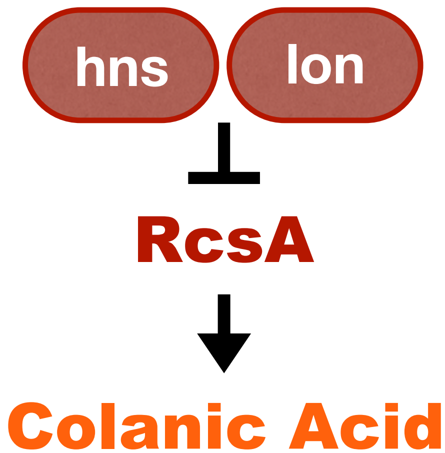
H-NS & LON inhibit RcsA that controls Colanic Acid (CA) synthesis

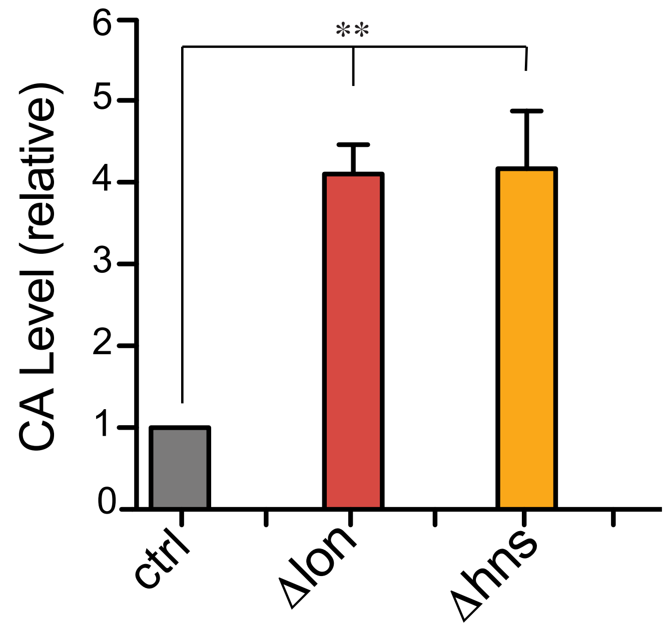


H-NS & LON inhibit RcsA that controls Colanic Acid (CA) synthesis

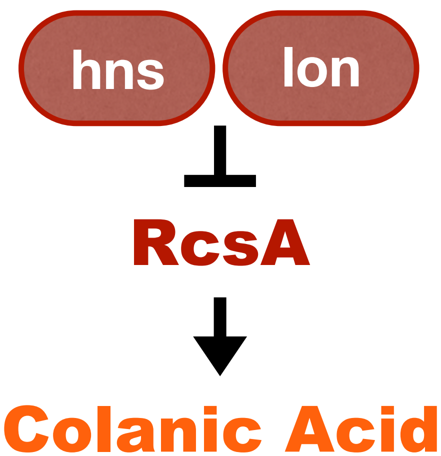


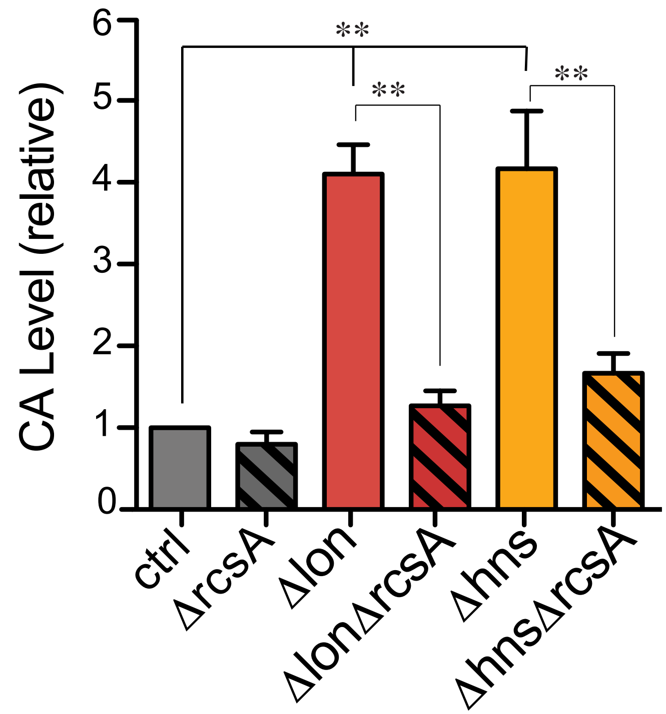
Δhns/Δlon deletion increases CA production from bacteria



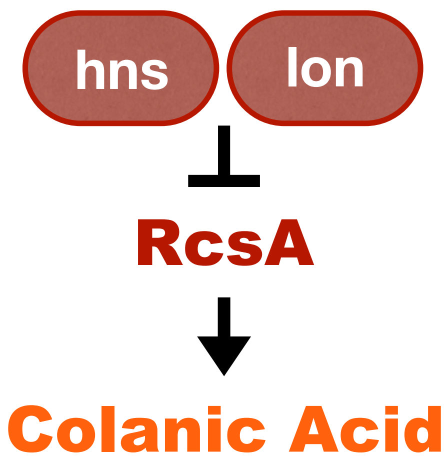


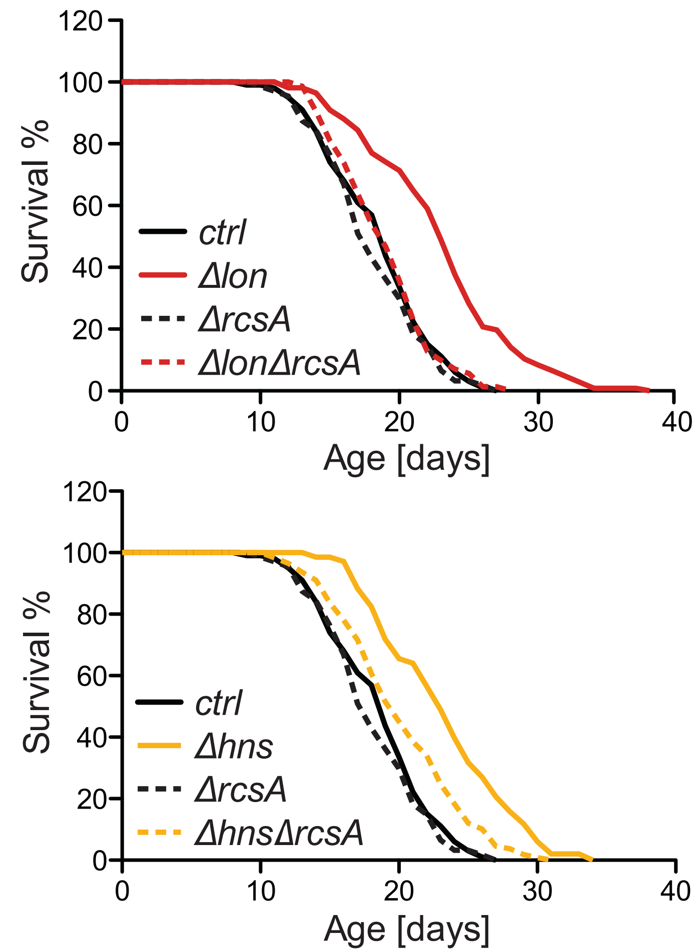
Δhns/Δlon deletion increases CA production from bacteria



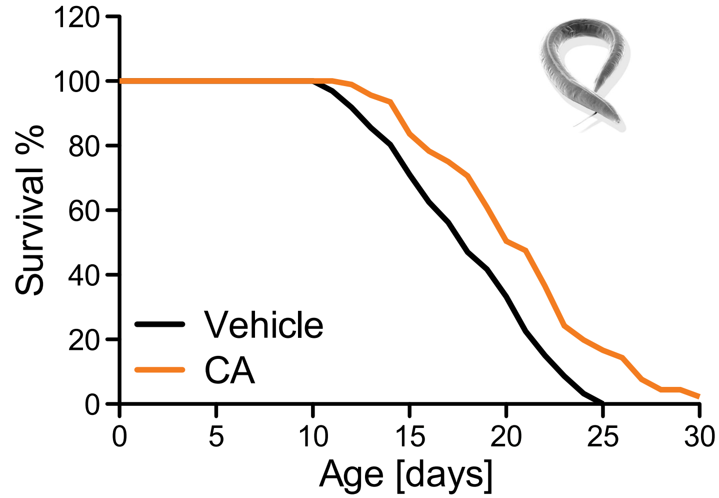


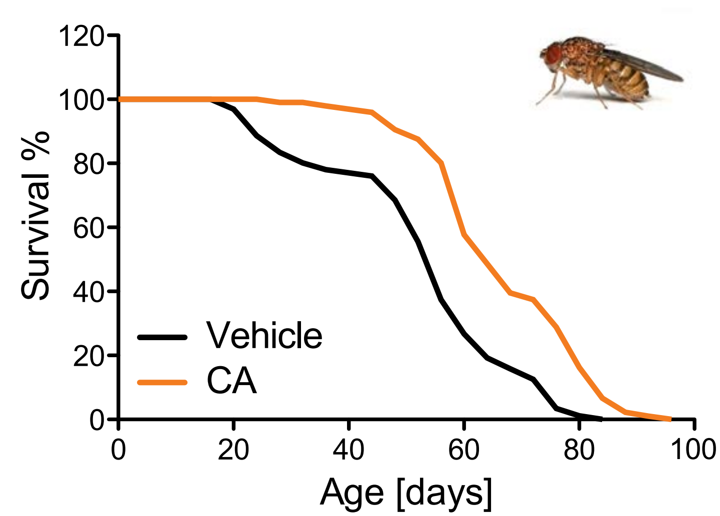
Δhns/*Δlon* deletion requires CA overproduction to promote longevity

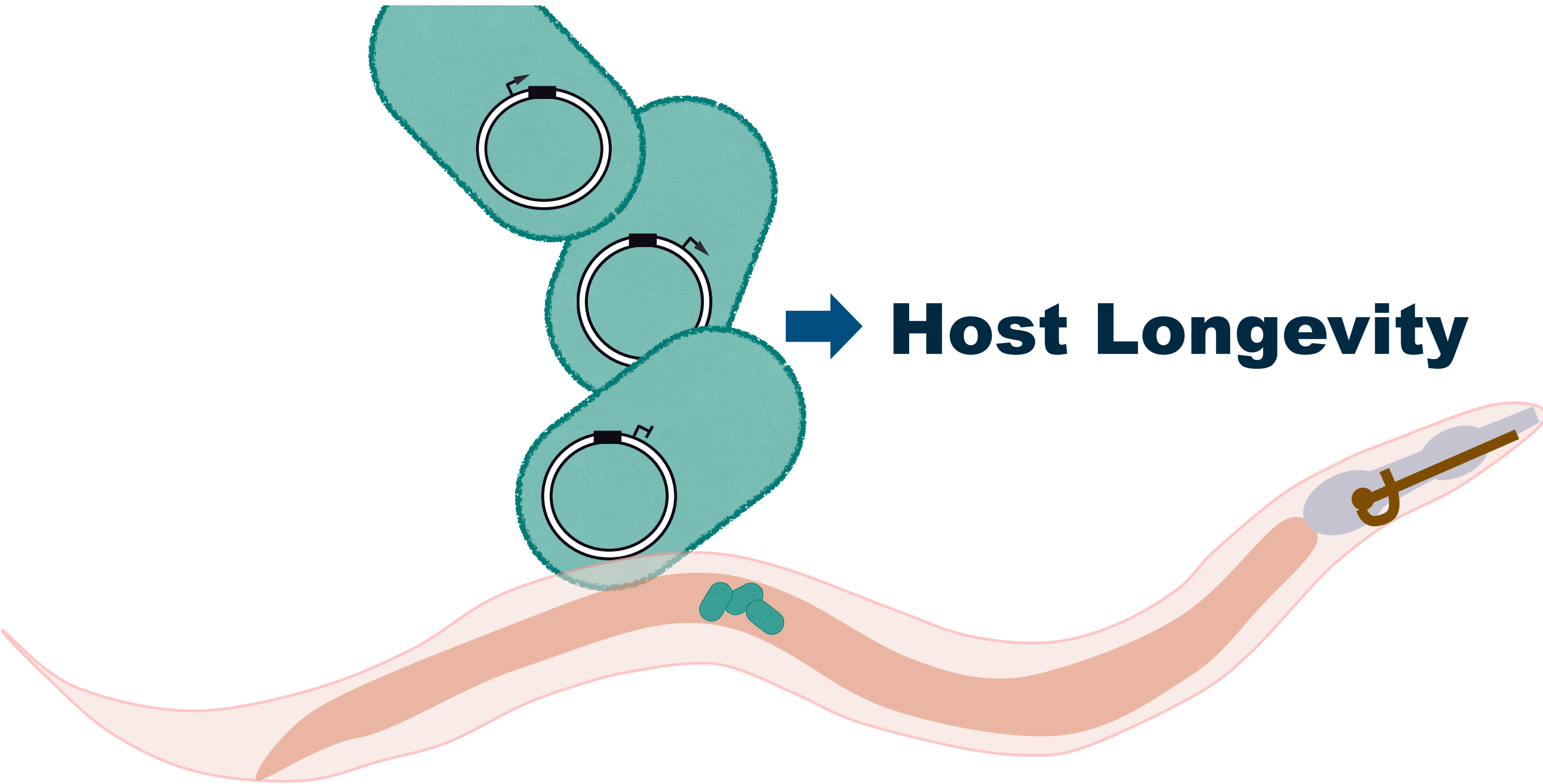




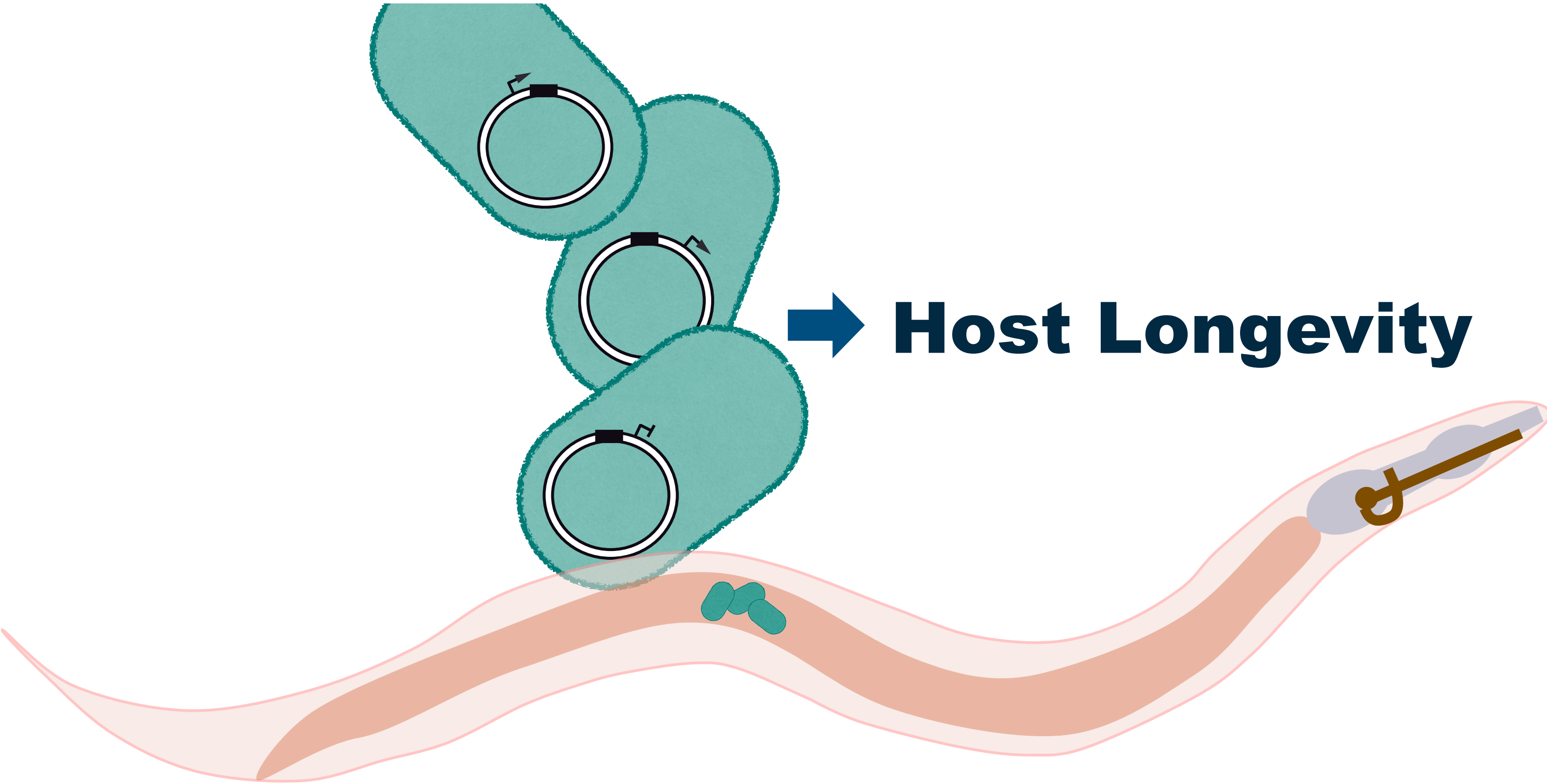
Purified CA sufficiently promotes longevity in the host







How to fine-tune bacterial metabolite production in the host gut?



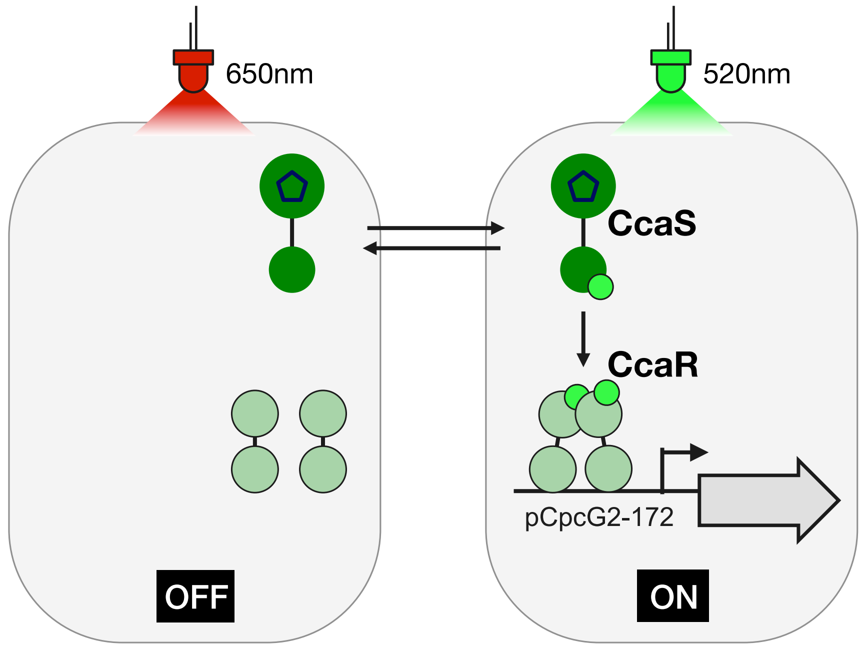
Lucas Hartsough

Mooncheol Park

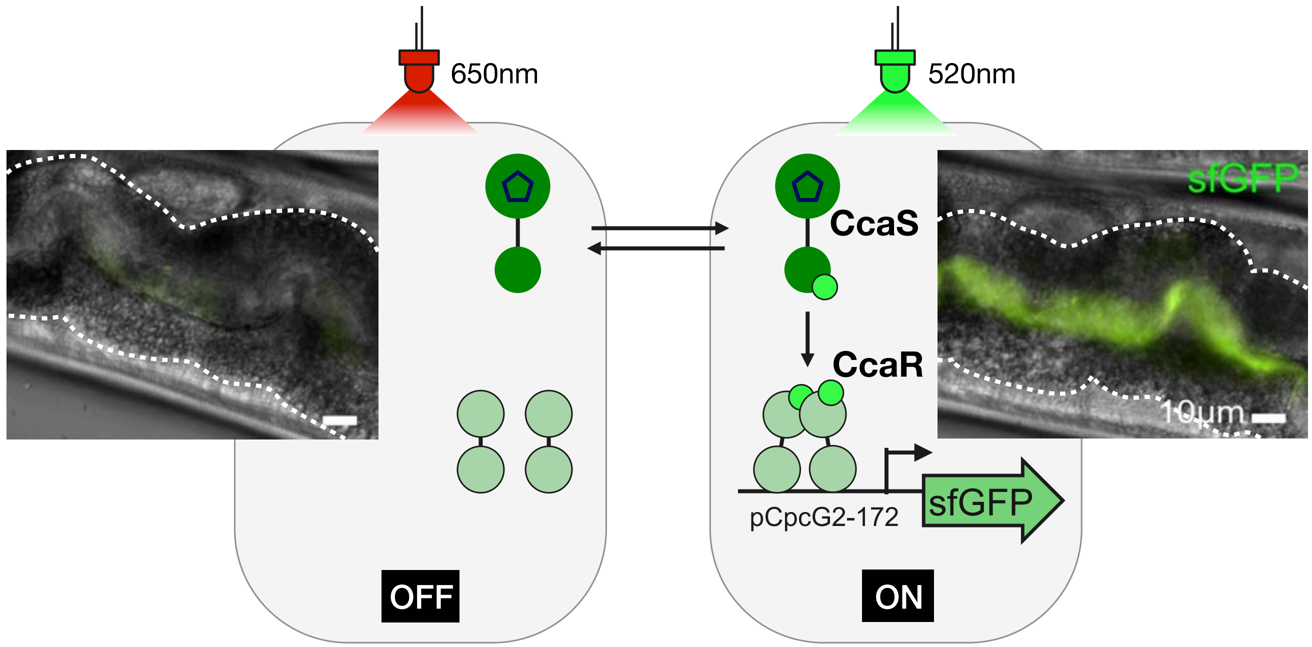
Jeff Tabor Group

How to fine-tune bacterial metabolite production in the host gut?

Optogenetic control of bacterial gene expression

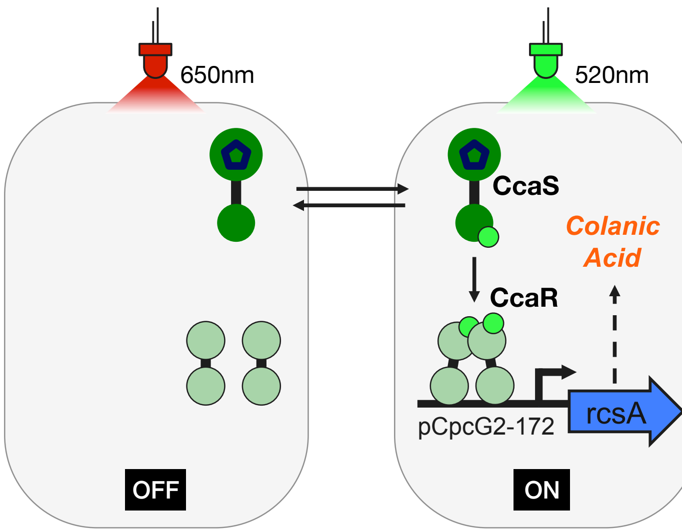


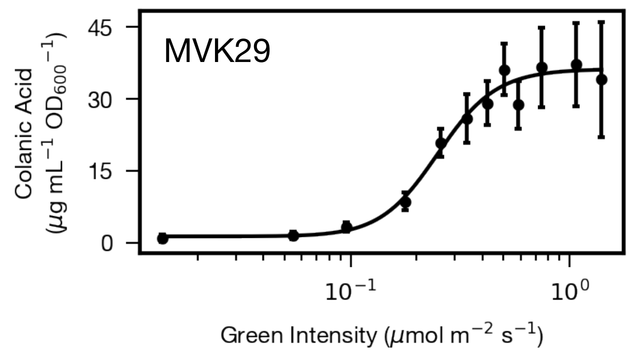
Light can switch ON/OFF bacterial gene expression in the gut



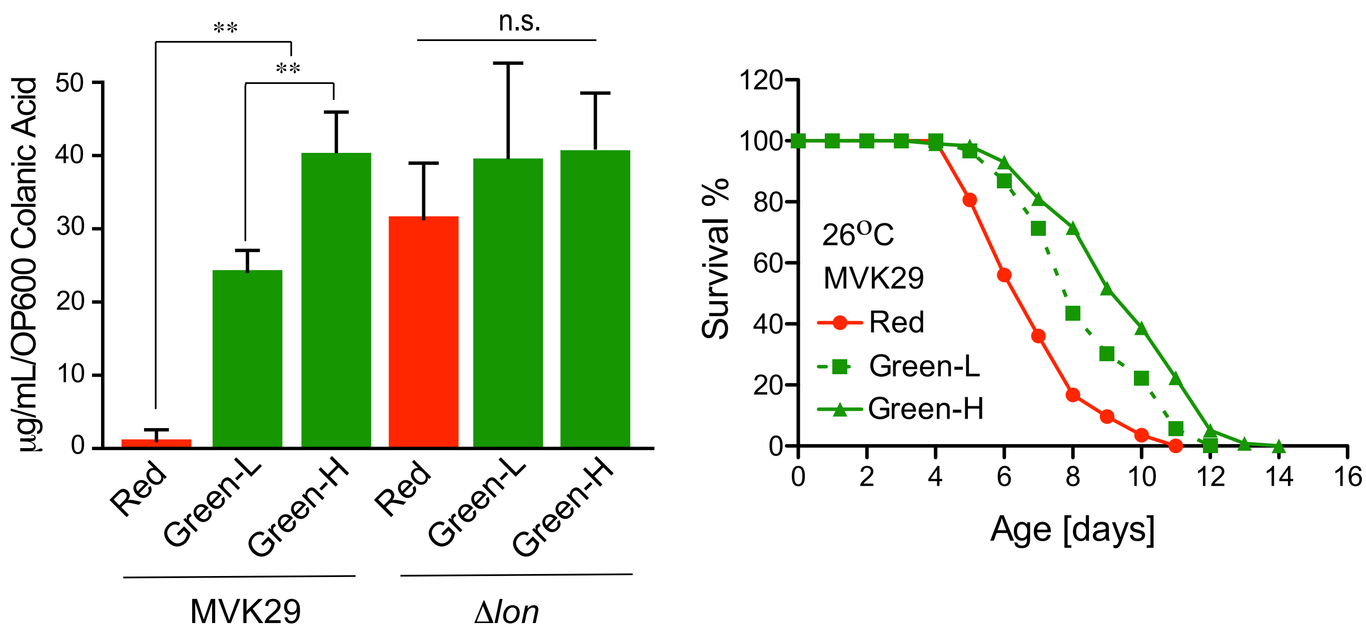
Hartsough et al. eLife 2020

Engineer light-inducible CA-producing bacteria

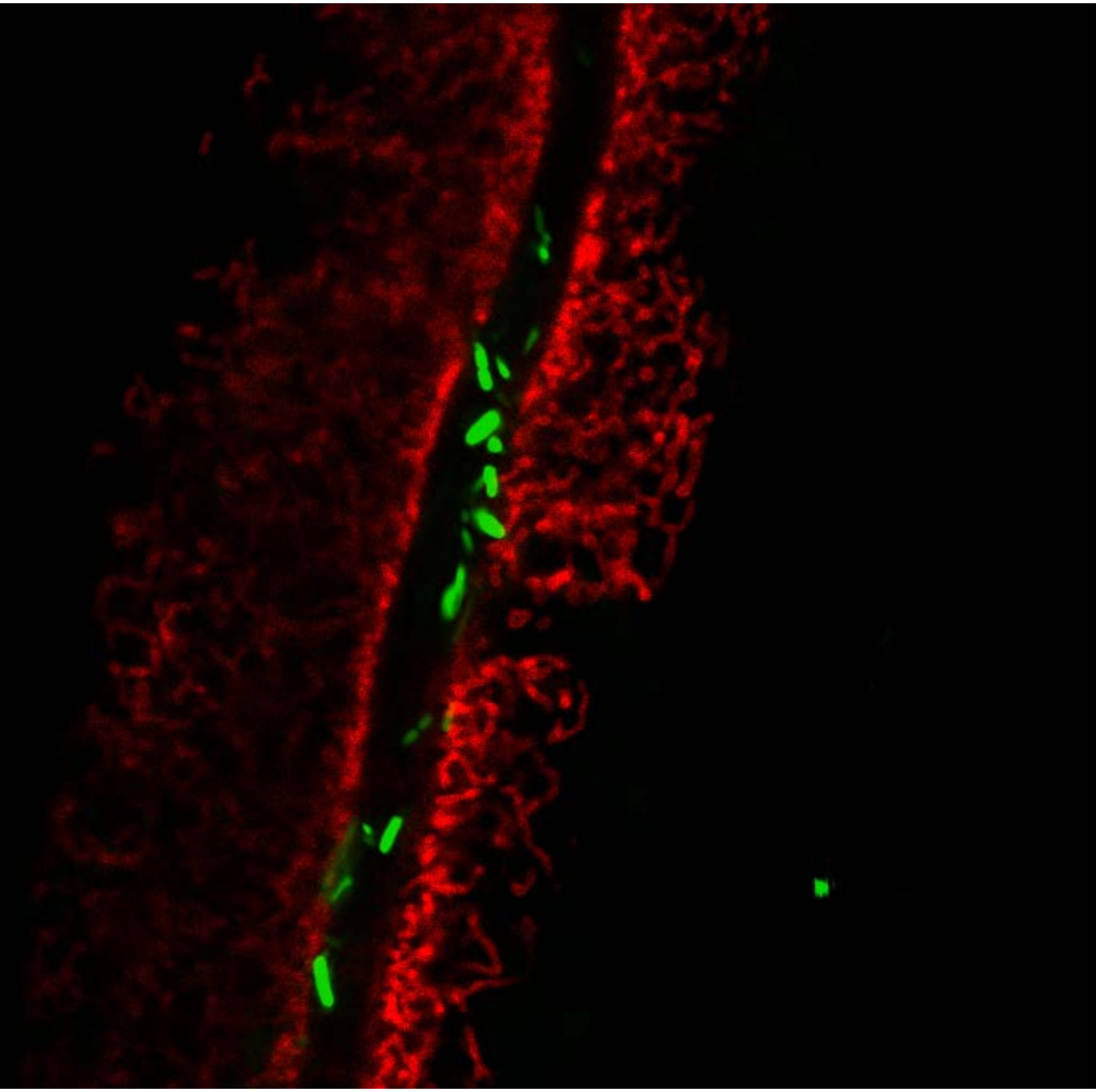


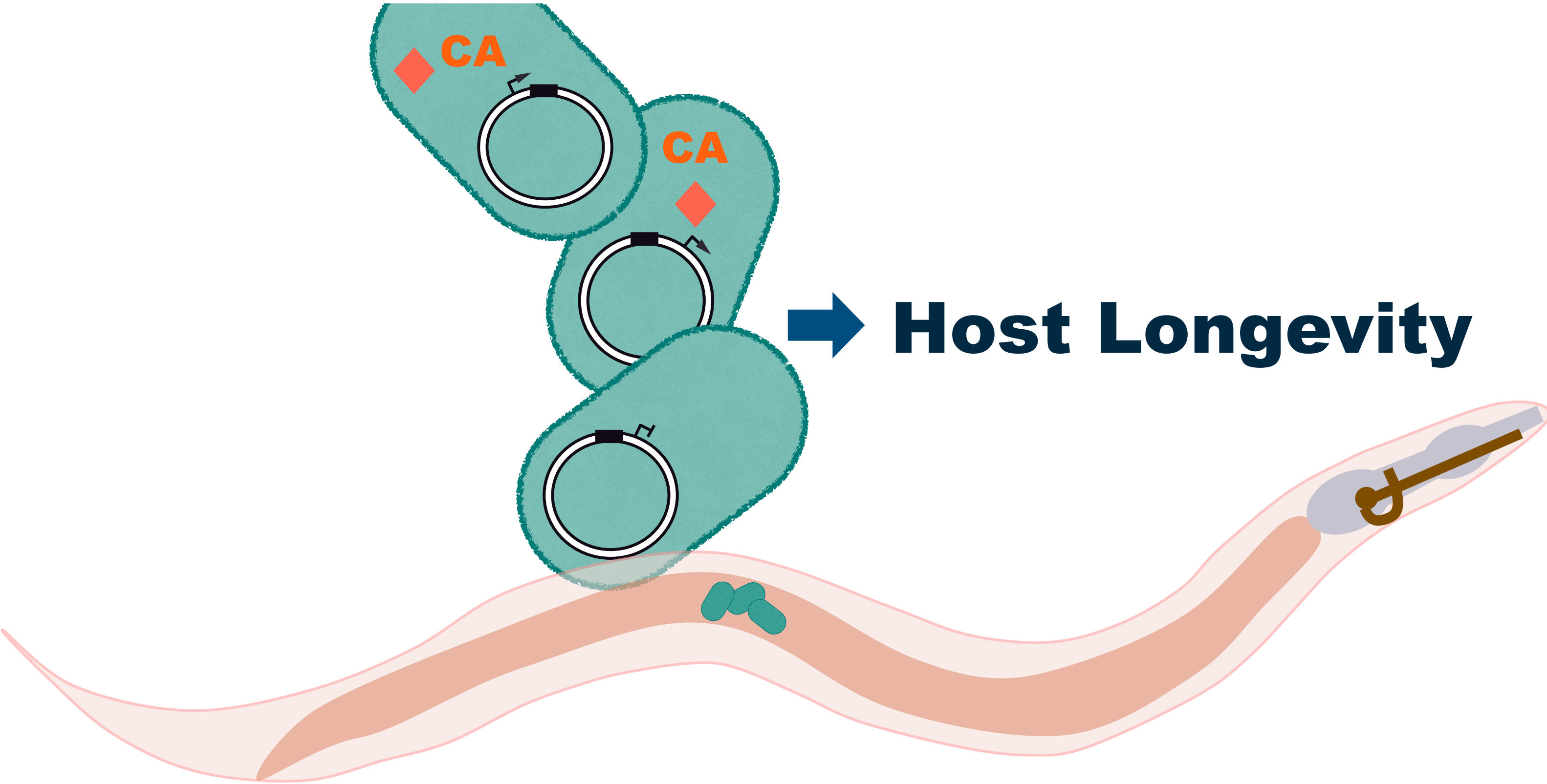


Promote longevity with light-inducible CA-producing bacteria



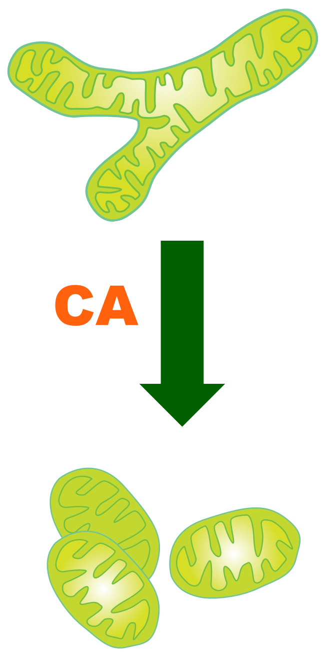
- Quantitative
- Reversible
- Rapid Time Control
- Fine Spatial Resolution

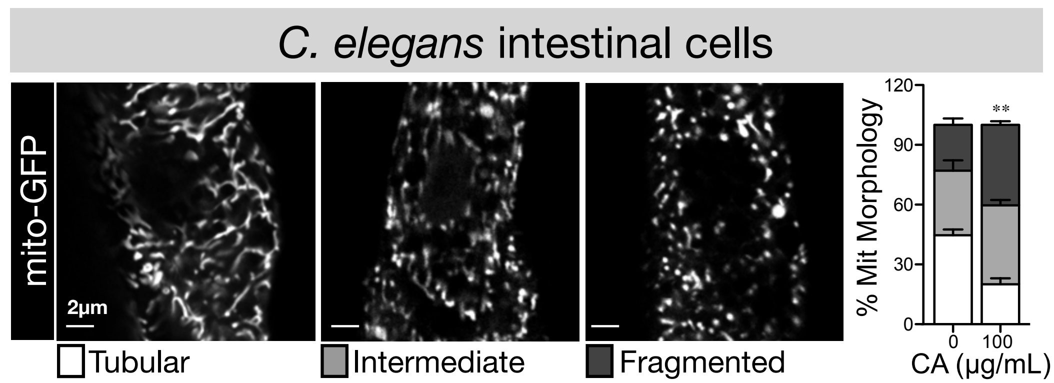




How does CA exert beneficial effects on the host?

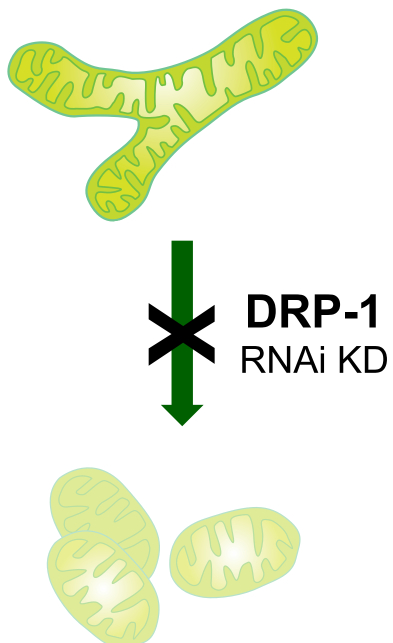
CA increases mitochondrial fragmentation in intestinal cells

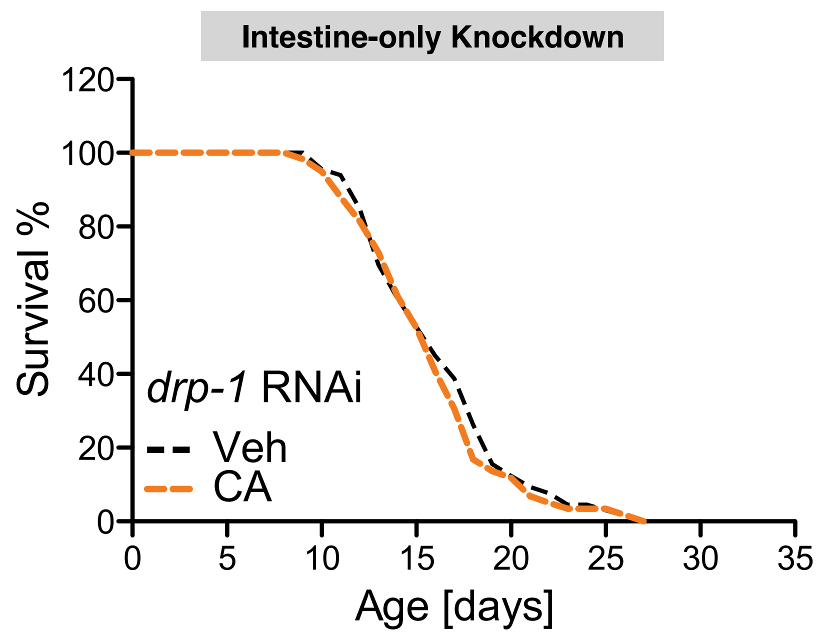




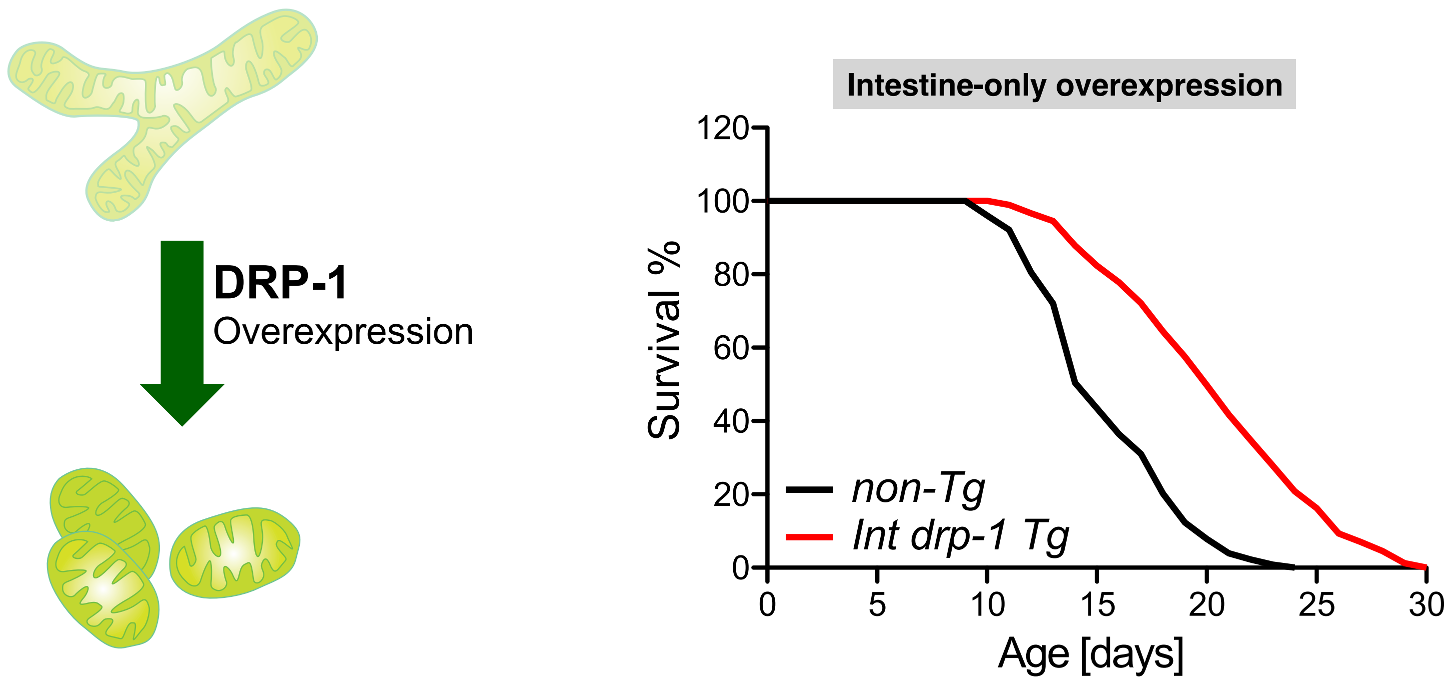
Han et al. Cell 2017

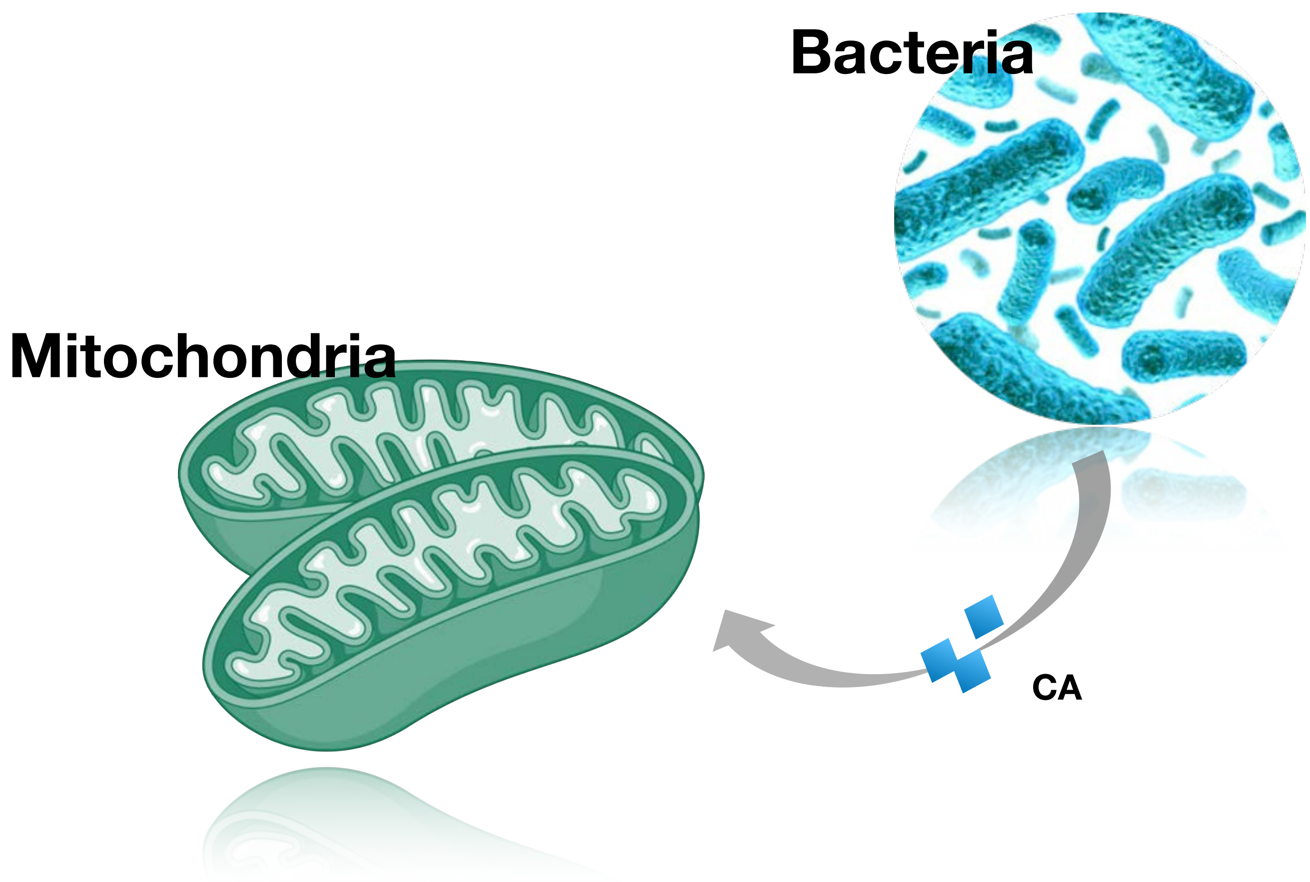
CA-induced longevity requires mitochondrial fission in the gut



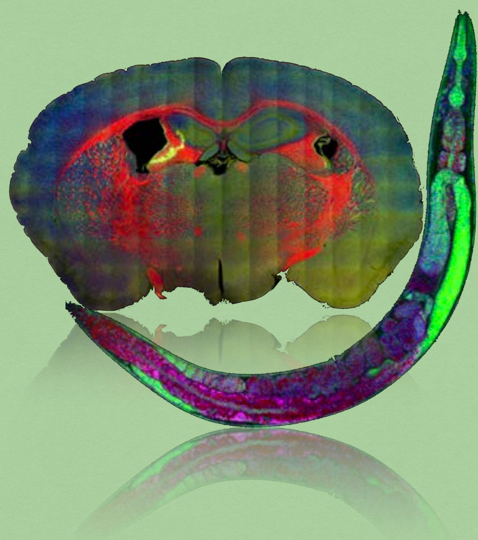


Increasing intestinal mitochondrial fission promotes longevity

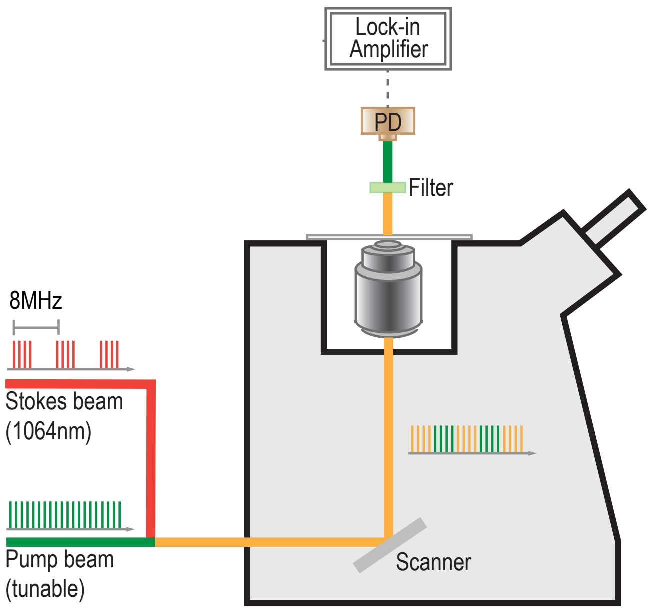


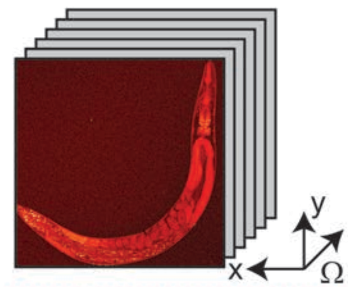

Bacteria
Mitochondria
CA

Metabolic Imaging
&
Longevity

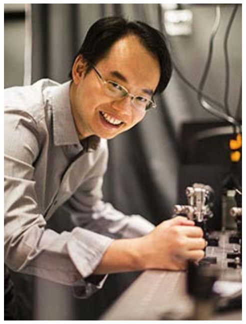


Stimulated Raman Scattering Microscopy





Sunney Xie

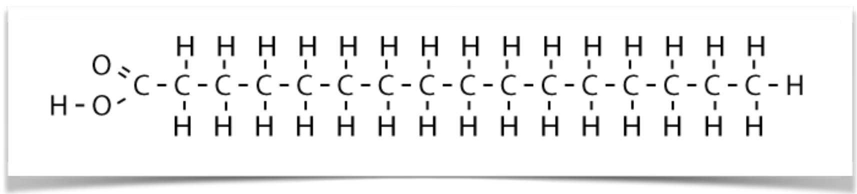


Wei Min

Imaging Vibrational Energy of Chemical Bonds

- **Spatial resolution:** ~300nm
- **Chemical sensitivity**: > μM
- **3D capacity:** ~500μm in depth
- **Imaging speed**: 1μs/pixel

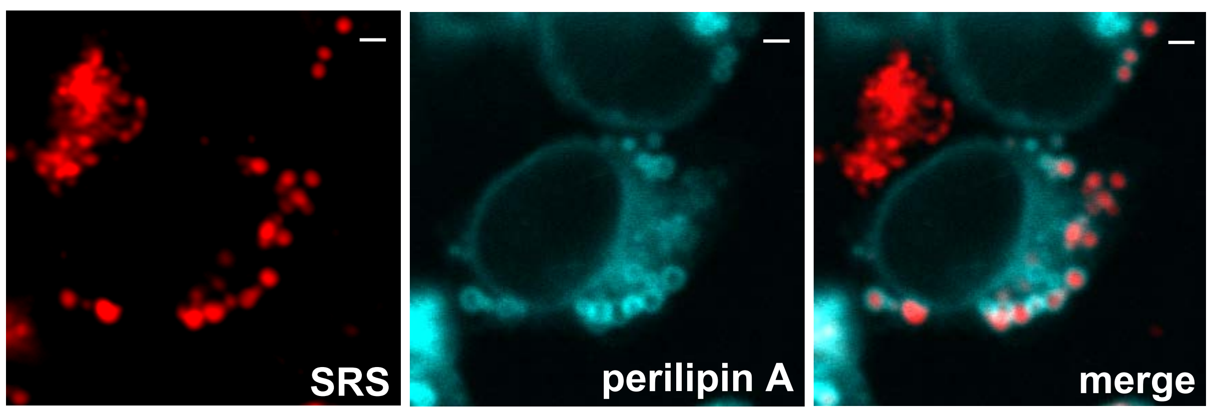
Imaging lipid molecules at sub-cellular resolution



Fatty acid chain

H-C-H, Ω = 2845cm^{-1}

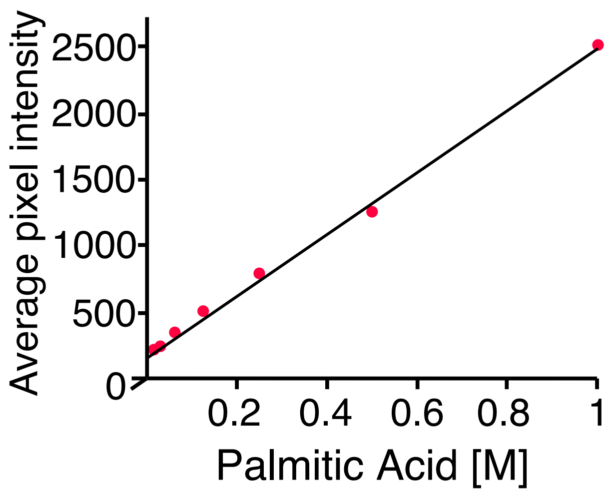
Pump beam = 817nm
Stokes beam = 1064nm

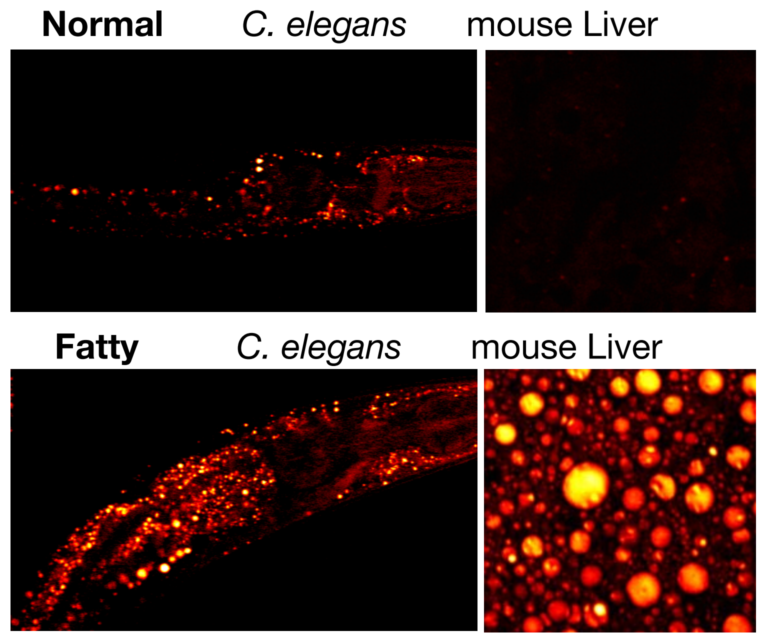


Wang et al, Nature Methods 2011

Imaging lipid molecules in a quantitative manner

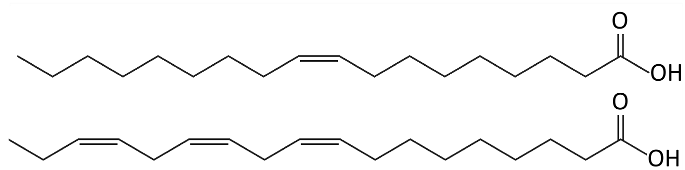
$$\mathbf{SRL} \propto \mathbf{[c]} \bullet \sigma_{molecule} \bullet I_{stokes} \bullet I_{pump}$$



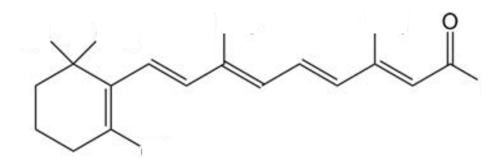


Wang et al, Nature Methods 2011
Yu et al, Biochim Biophys Acta 2014

Imaging lipid molecules with chemical specificity

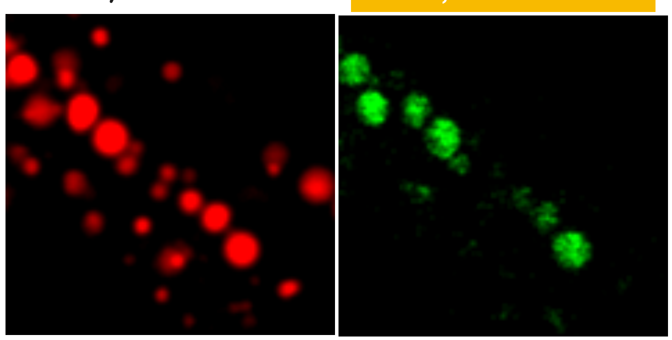


Unsaturated fatty acids

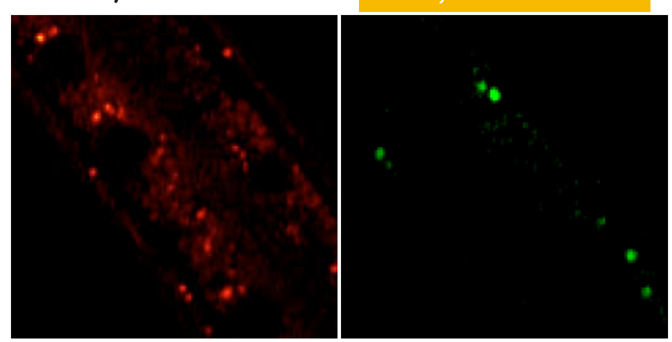


Retinoid

H-C-H, Ω=2845cm^{-1} | =C-H, Ω=3015cm^{-1}

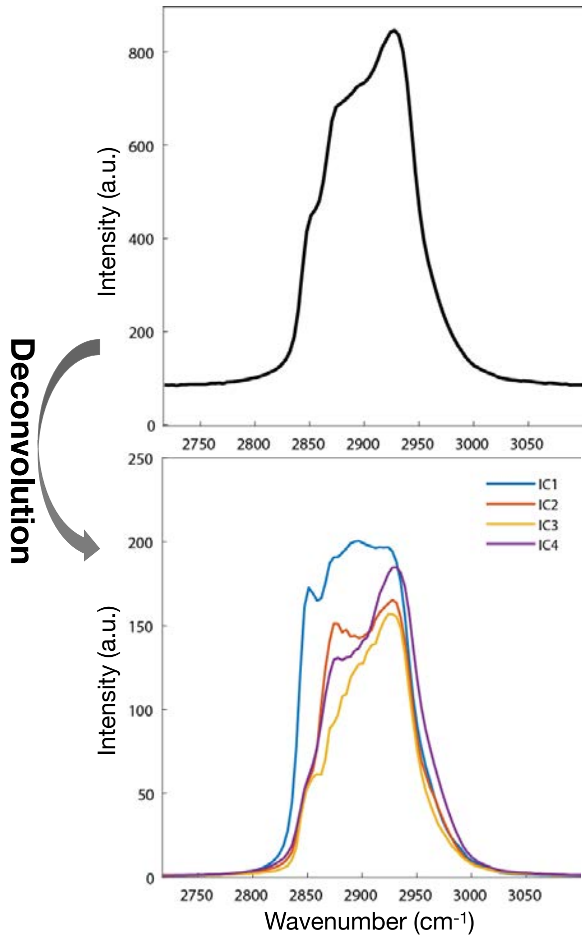


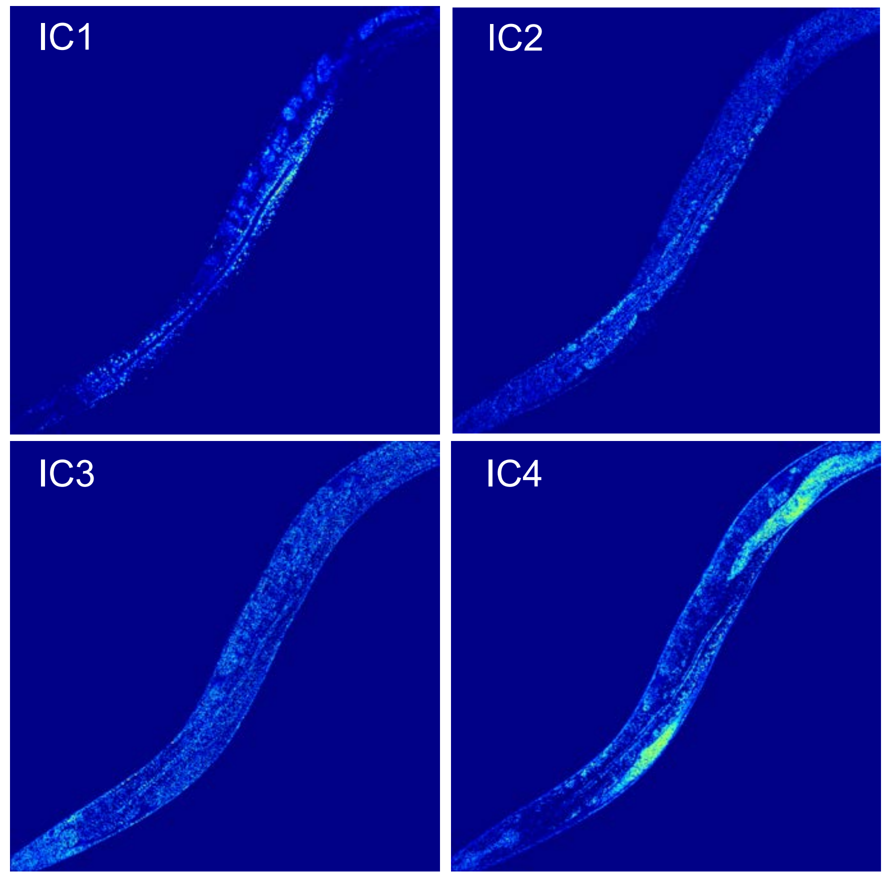
H-C-H, Ω=2845cm^{-1} | C=C, Ω=1580cm^{-1}



Chen et al Chemphyschem 2018

Untargeted hSRS imaging of metabolic features in live worms

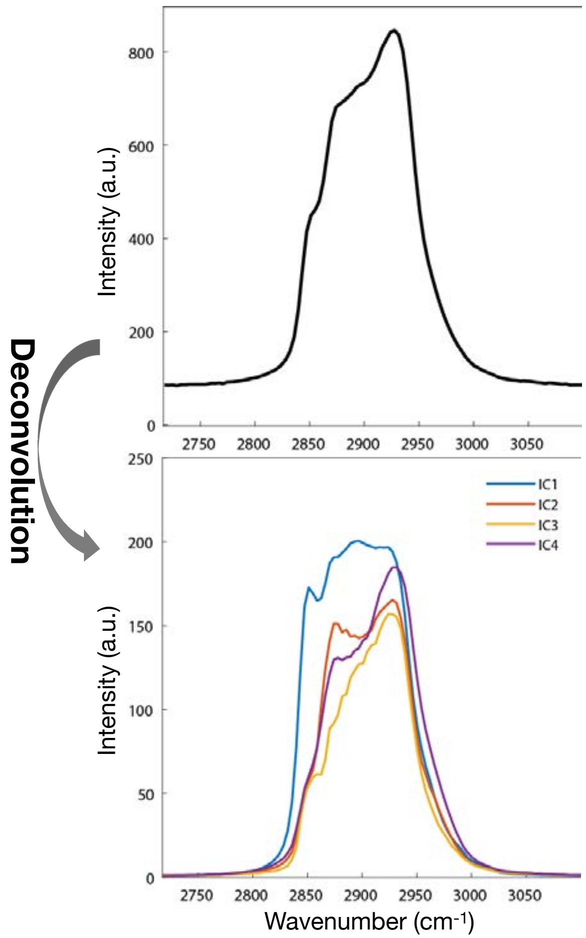


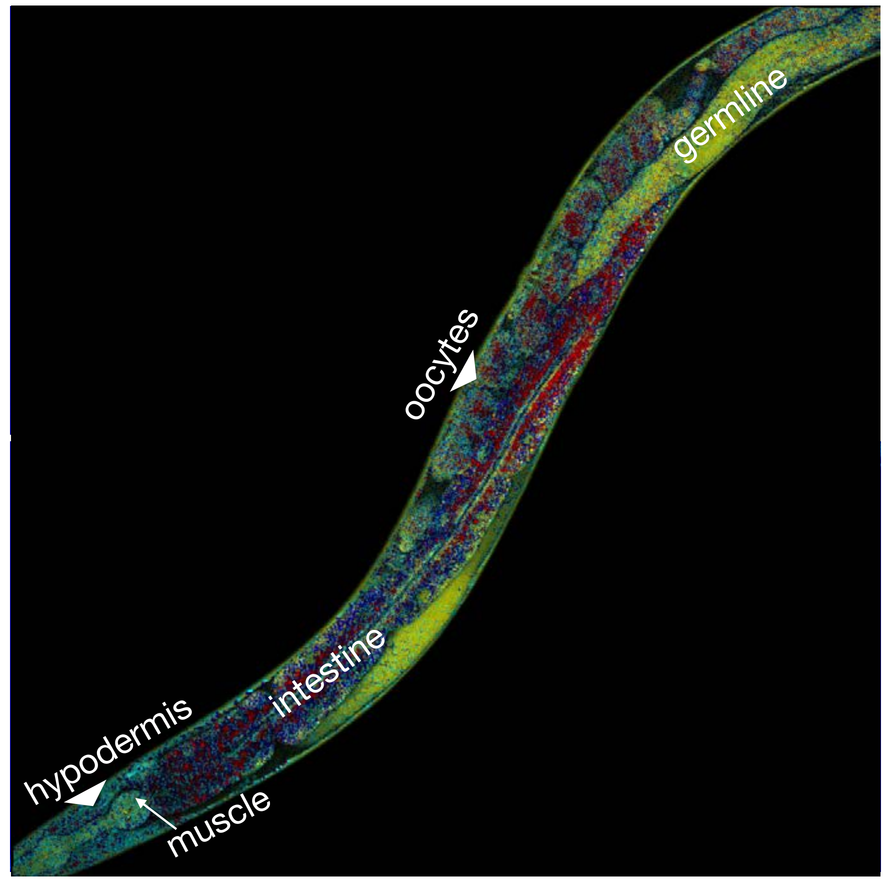


Tao Chen

Unpublished

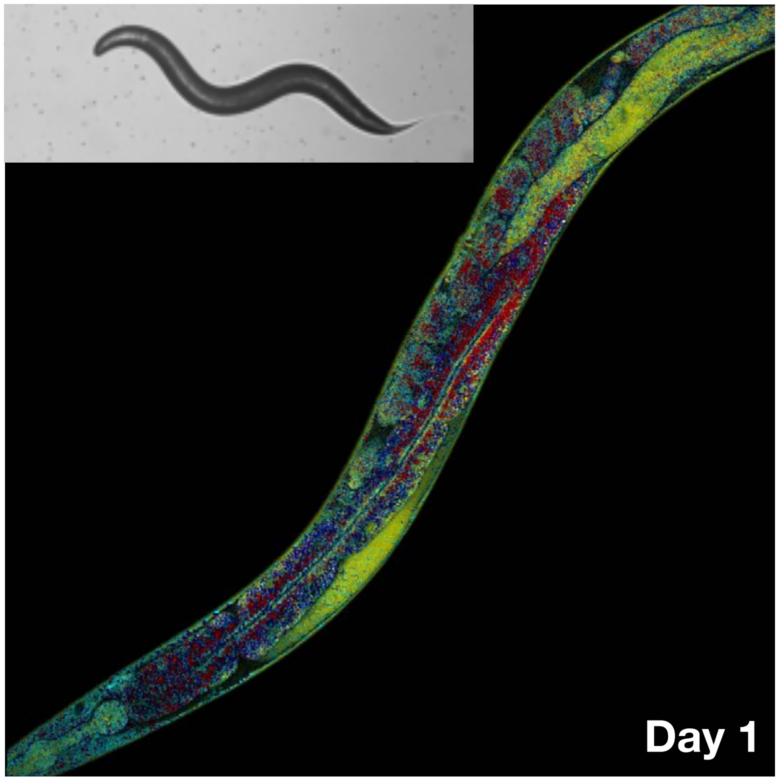
Untargeted hSRS imaging of metabolic features in live worms

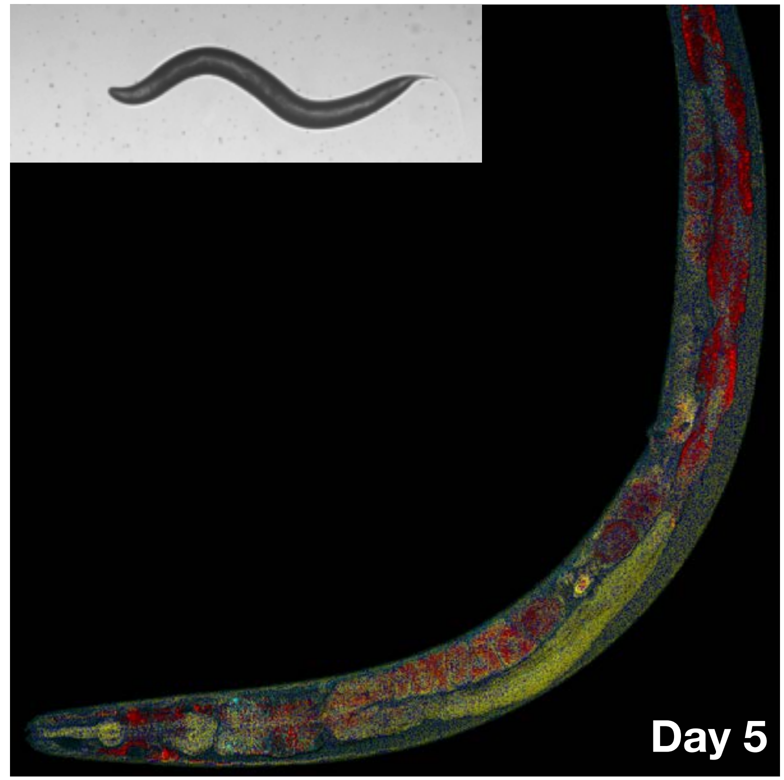




Unpublished

Untargeted hSRS imaging of metabolic features during aging

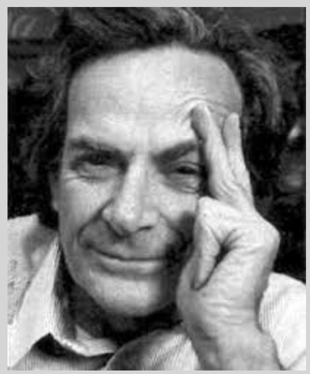




Unpublished

- **Power of new technology**

  Offer new lens to view new mechanisms.



"to answer many of these fundamental biological questions, you just look at the thing!"

- Richard Feynman

Former Members: Bing Han (Fudan), Yong Yu (Xiamen), Andrew Folick (UCSF), Prasanna Ramachandran (Boston Children), Chih-Chun Lin (Cornell), Isaiah Neve (Norton Rose Fulbright), Peiwen Hu (Astellas Pharma), Yusi Fu (Creighton), Ahmet Yavuz (Known Medicine), Jessica Sowa (West Chester), Louis Mak (Baylor Genetics), Tim Mahoney (BCM), Holly Oakley (MD Anderson), Lucas Sanor (Yale), Ravi Medikonda (Johns Hopkins), Tyler Finamore (U of Notre Dame), Kuang Hu (UT Austin), Jie Ye (MD Anderson)

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Mentors: Dirk Bohmann (UR), Henri Jasper (Genentech), Gary Ruvkun (MGH)

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