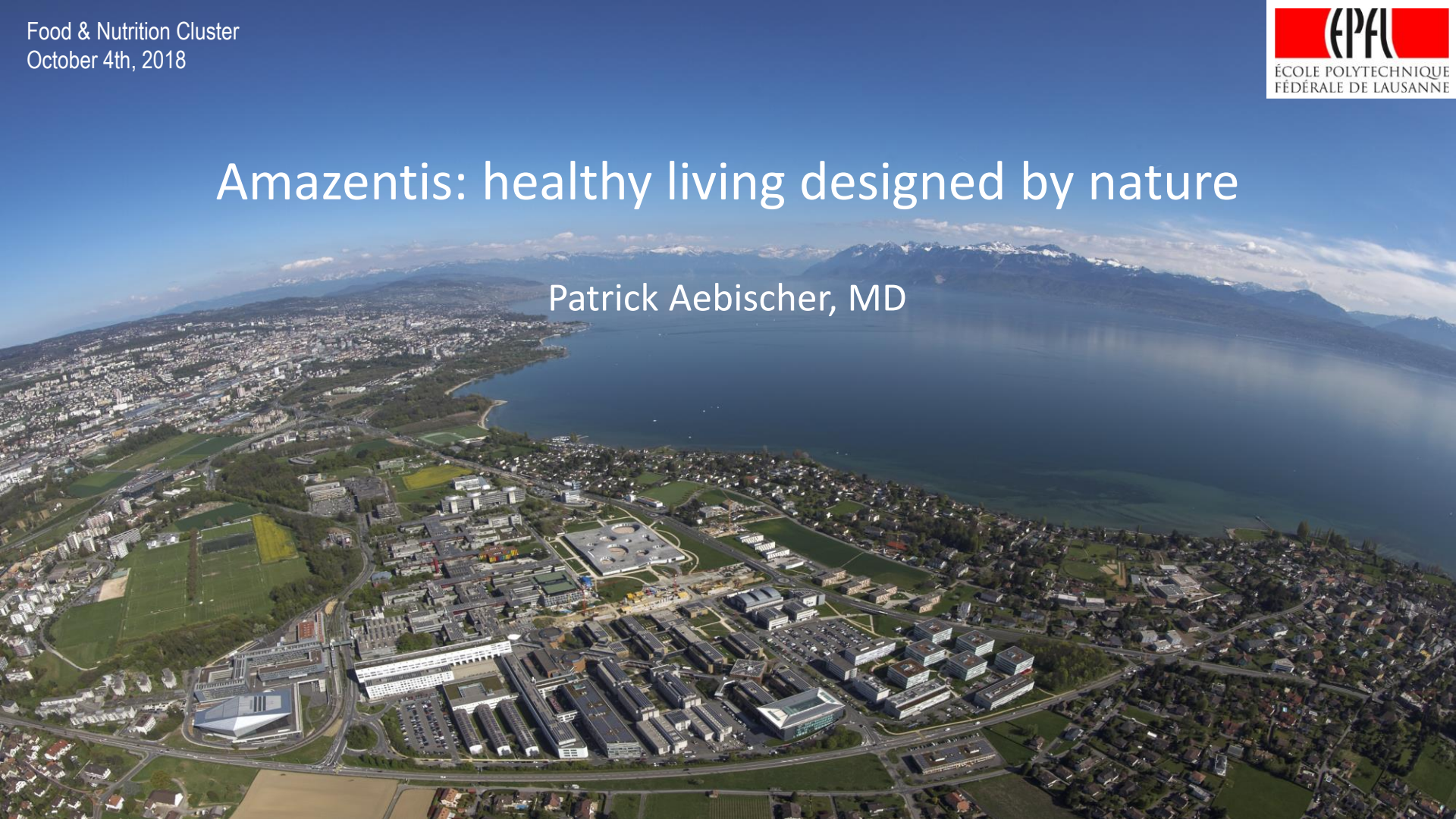
Food & Nutrition Cluster
October 4th, 2018

ÉCOLE POLYTECHNIQUE
FÉDÉRALE DE LAUSANNE

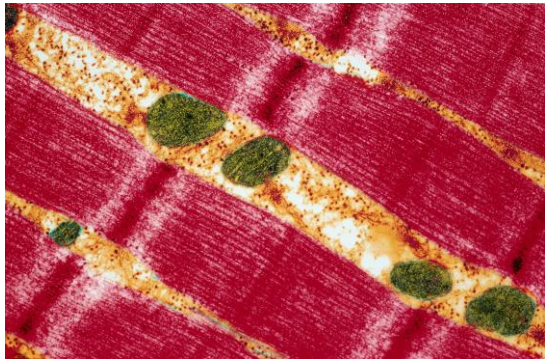
Amazentis: healthy living designed by nature

Patrick Aebischer, MD



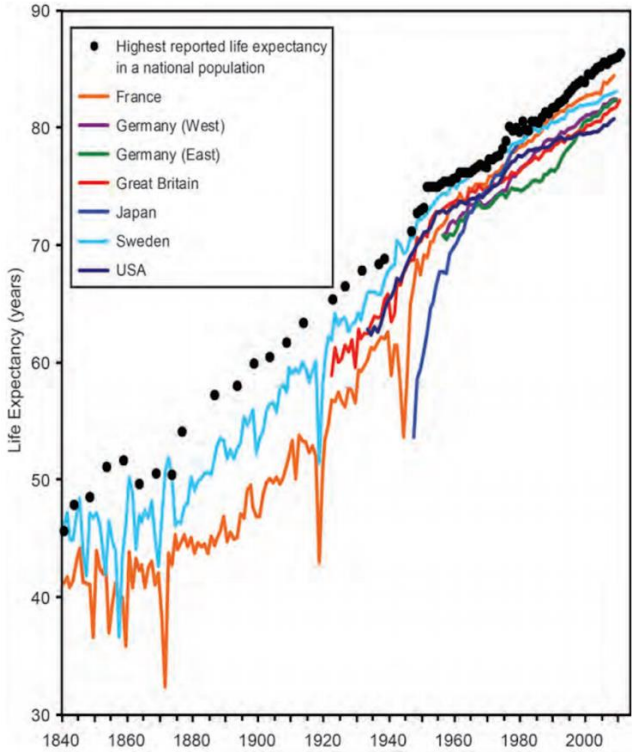
Combating Aging by Rejuvenating Mitochondria

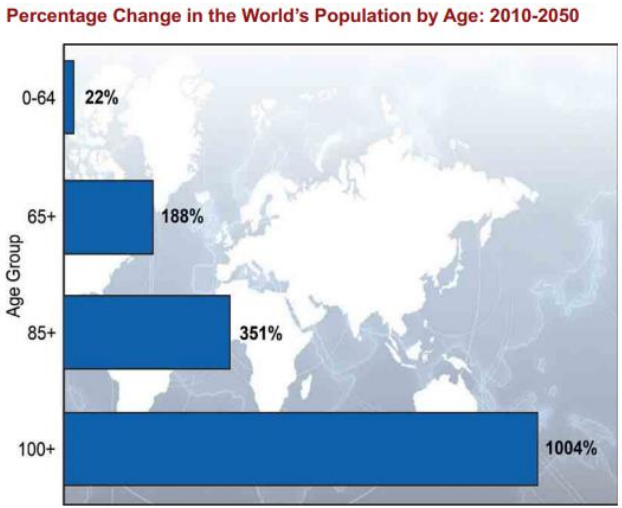
Amazentis is pioneering the next generation of natural compounds to manage and reverse age-related decline in cellular mitochondrial function



Developing products extending from
Consumer and Medical Nutrition to Pharmaceuticals

We are living twice as long as our forefathers





Source: United Nations, *World Population Prospects: The 2010 Revision.*

- 65+ population is projected to increase 188%
- 85-and-over population is projected to increase 351% between 2010 and 2050

National Institute of Aging, USA

Aging, a physiological decline

Brain

- Dementia -> AD
- Hearing & vision loss
- Depression

Fat

- Obesity
- Diabetes

Heart

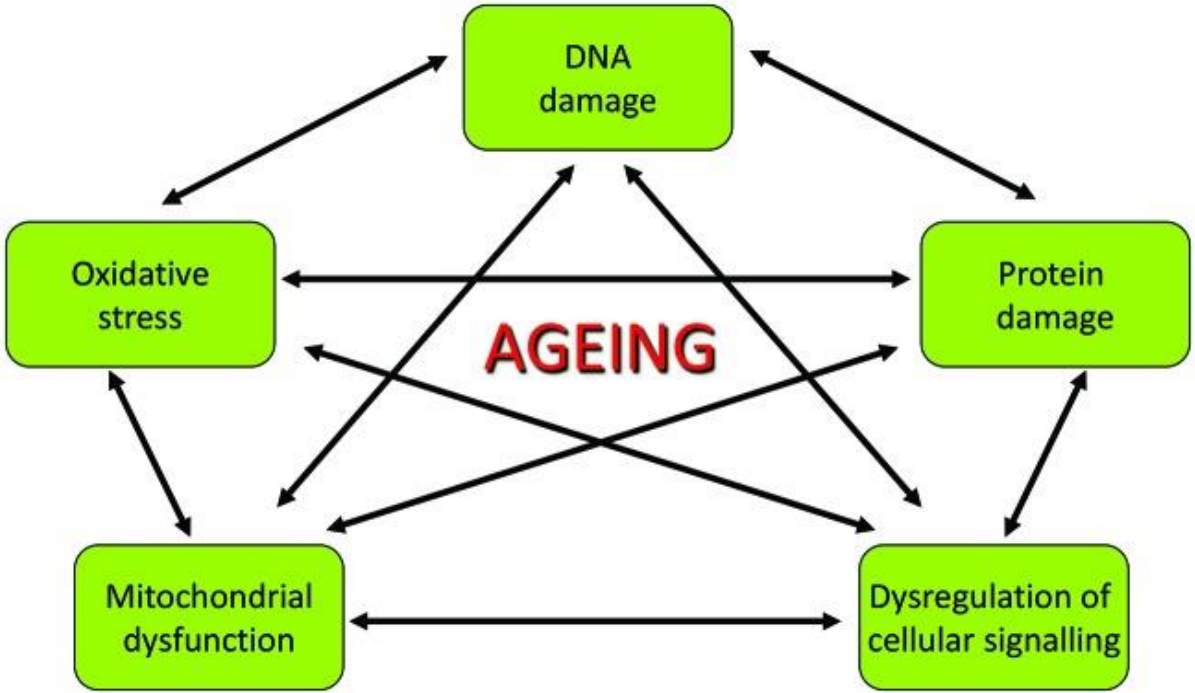
- Atherosclerosis
- Myocardial infarction

Muscle

- Sarcopenia
- Glucose intolerance

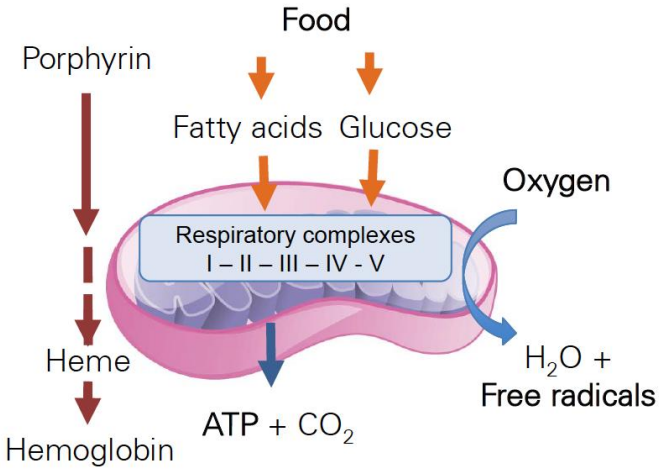
Key functions: mobility & cognition

Molecular mechanisms of aging



McAuley et al. Biosci Rep. 2017 37(1)

Mitochondria, the cell energy provider



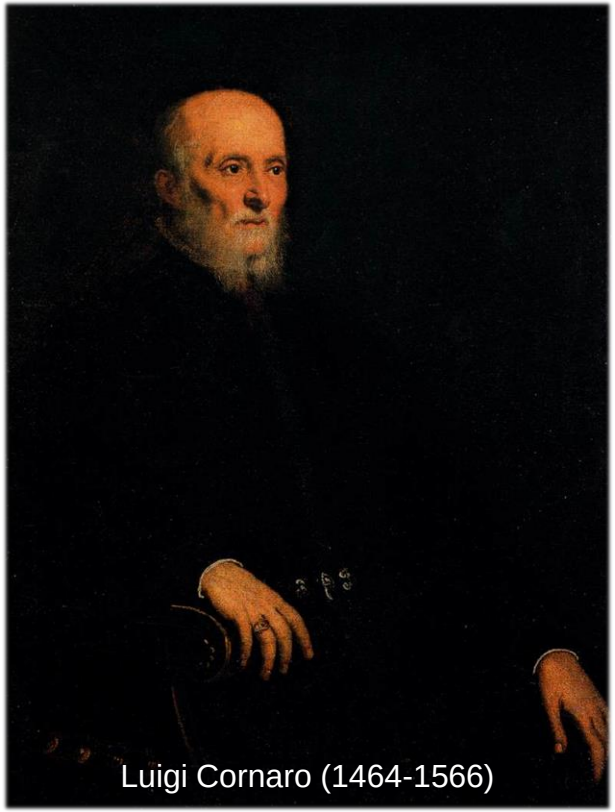
Mitochondria are the site of:

- Respiration
- Production of ATP
- Fatty acid burning
- Aerobic glycolysis
- Heme biosynthesis

But also the site of:

- Generation of free radicals damage mitochondrial protein, lipids and DNA
- Damaged mitochondria can initiate apoptosis

Boosting mitochondrial activity by caloric restriction



Luigi Cornaro (1464-1566)

LA SCOLA
SALERNITANA

Per acquistare, e custodire la Sanità,

Tradotta fedelmente dal verso Latino in Terza Rima piacevole volgare

Dall'Incognito Academico Vivo Morto.

CON LI DISCORSI
DELLA VITA SOBRIA
DEL SIG. LVIGI CORNARO.

C03

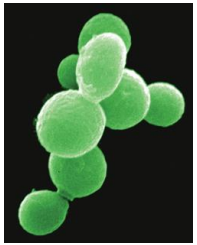
VENETIA

IN VENETIA, M. D C. LXII.
Presso Gio: Pietro Brigonci.

CON LICENZA DE' SVPERIORI.

Caloric restriction increases lifespan in many species

Yeast (7 days)



30-75% w/ glucose restriction

C. Elegans (20 days)

25-70% w/ bacterial dilution

Drosophila (40 days)

30-60% w/ yeast restriction

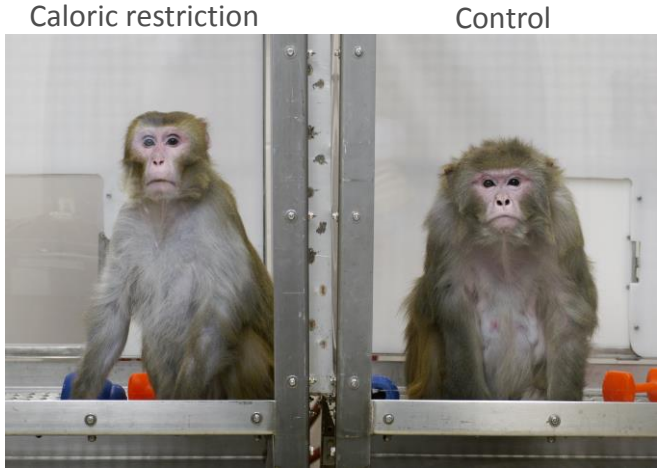
Mice (800 days)

20-60% w/caloric restriction

Caloric restriction in primates

The Wisconsin study : restriction of 30% over 20 years

- slow down the aging process
- ↓ incidence of diabetes, cancer, CV diseases
- ↓ cerebral atrophy



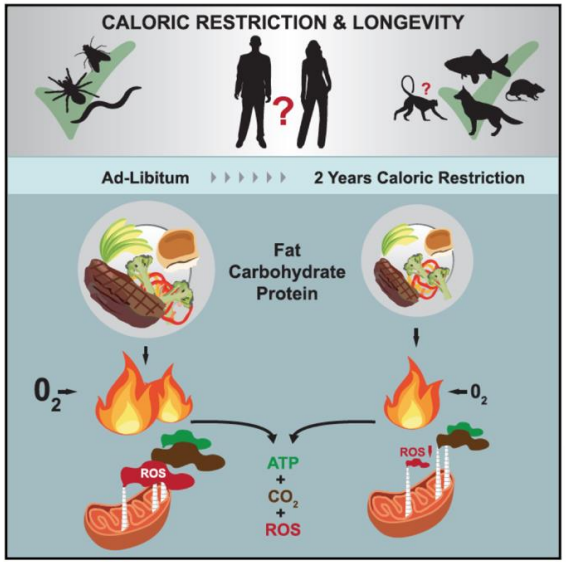
Colman et al., Science 2009

Caloric restriction in humans: accumulating evidence

Cell Metabolism
Clinical and Translational Report

Metabolic Slowing and Reduced Oxidative Damage with Sustained Caloric Restriction Support the Rate of Living and Oxidative Damage Theories of Aging

Graphical Abstract



Authors

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Correspondence

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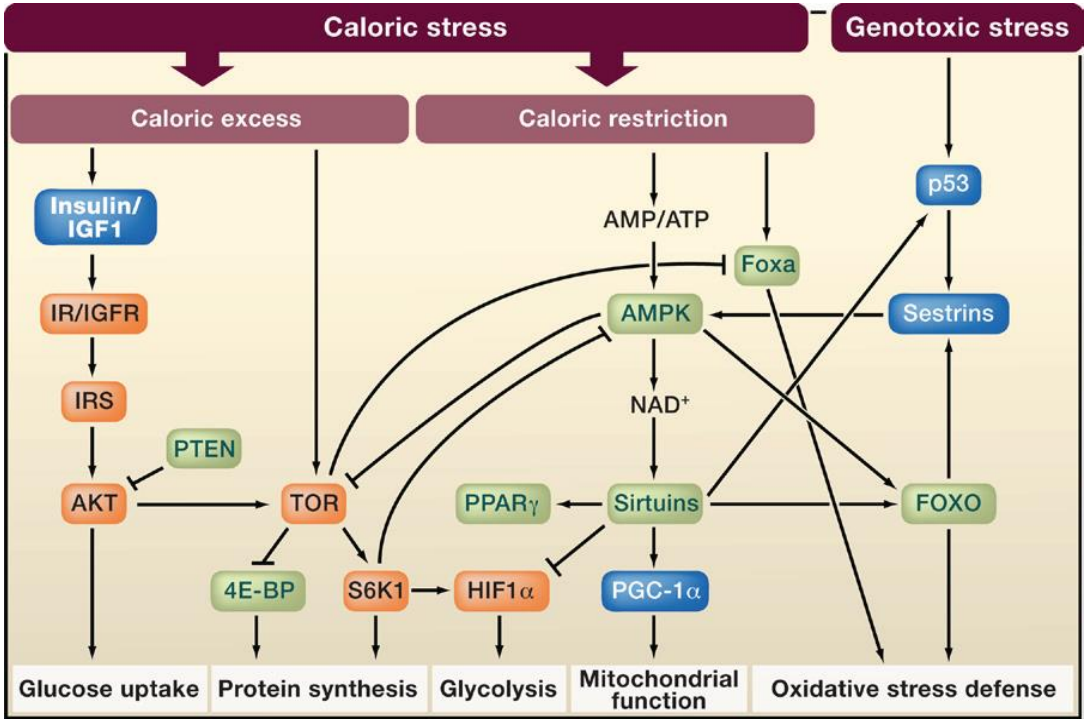
In Brief

Calorie restriction (CR) has been shown to have health benefits and to extend lifespan in diverse species.

Redman et al. conducted a 2-year CR trial in healthy, non-obese humans and found evidence that prolonged CR enhances resting energy efficiency, resulting in decreased systemic oxidative damage.

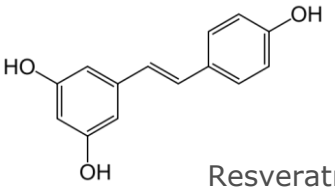
Caloric restriction pathways related to aging



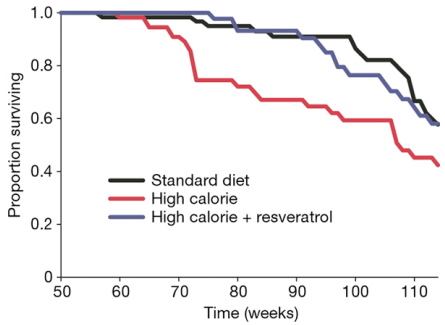
Source : Houtkooper RH, Williams RW, Auwerx J, Cell, 142(1) 2010

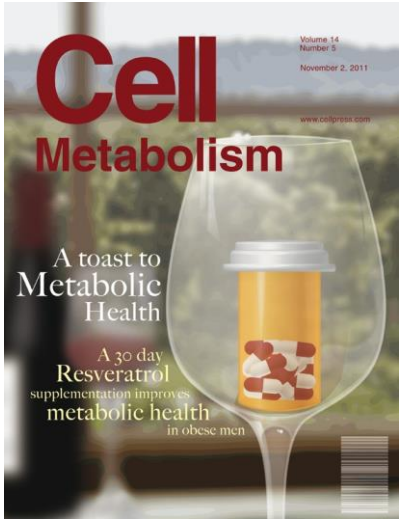
Resveratrol, a natural mimetic of caloric restriction?

Mice under high calorie diet



Resveratrol
(skin of red grapes)





Baur JA et al., Nature 2006

Nutritional bioactives that boost mitochondrial health

Resveratrol

Lagouge et al, Cell, 2006
Canto et al, *Nature*, 2009

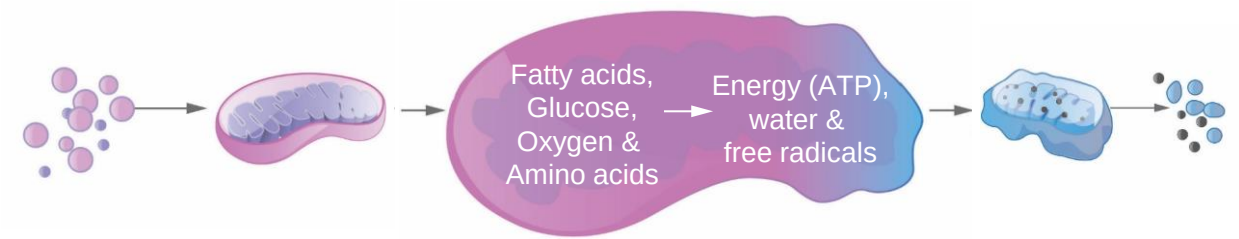
Nicotinamide Riboside

Canto et al, *Cell Metabolism*, 2012
Mouchiroud et al, *Cell*, 2013

Urolithin A

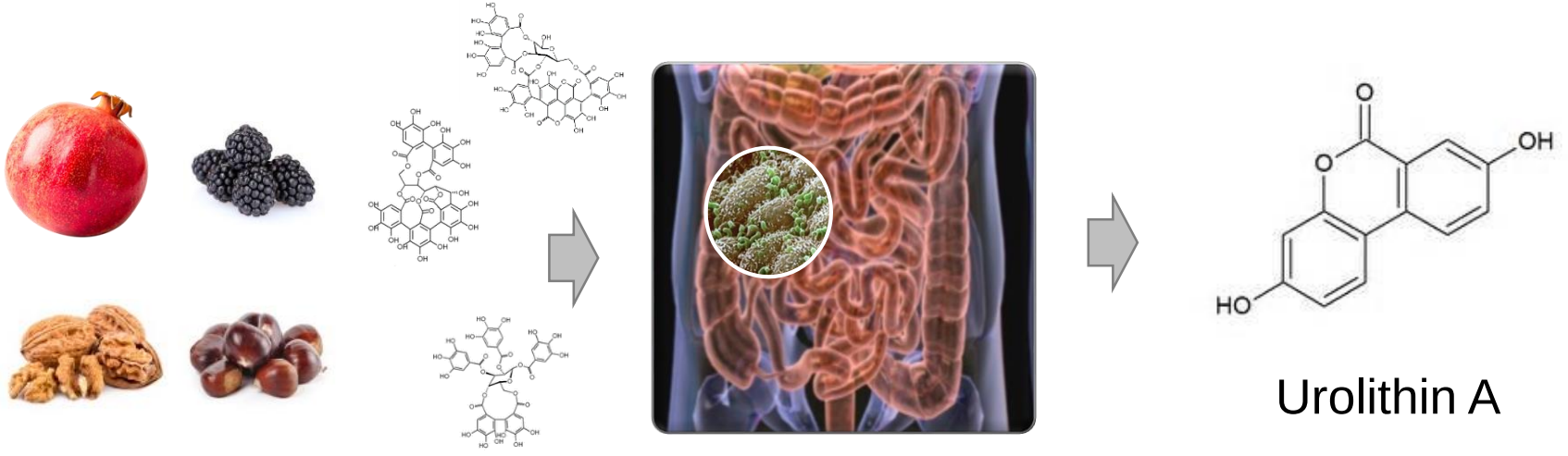
Ryu et al, *Nature Medicine*, 2016
Amazentis SA

Mitochondrial targets to improve muscle function



	Biogenesis	Energy Production	Mitophagy
Pathways to Target	Creation of new mitochondria	Optimal functioning of mature mitochondria	Clearance of damaged mitochondria
Nutrition Based Bioactives	Resveratrol Nicotinamide Riboside	CoQ10 L-Carnitine	Urolithin A

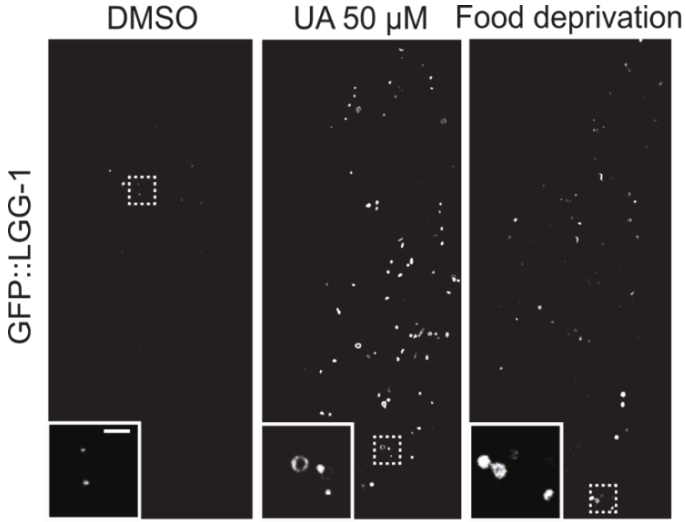
Dietary ellagitannins as a source of urolithins

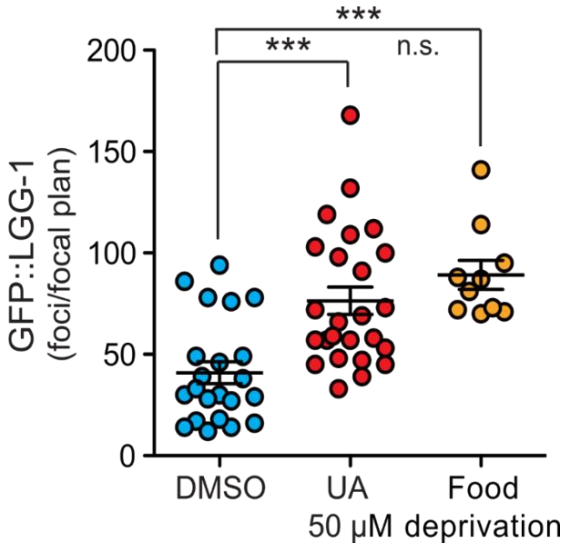


Only 30% of the population can perform this conversion and to varying degrees: microbiome dependent

Urolithin A induces autophagy in *C. elegans* similar to caloric restriction

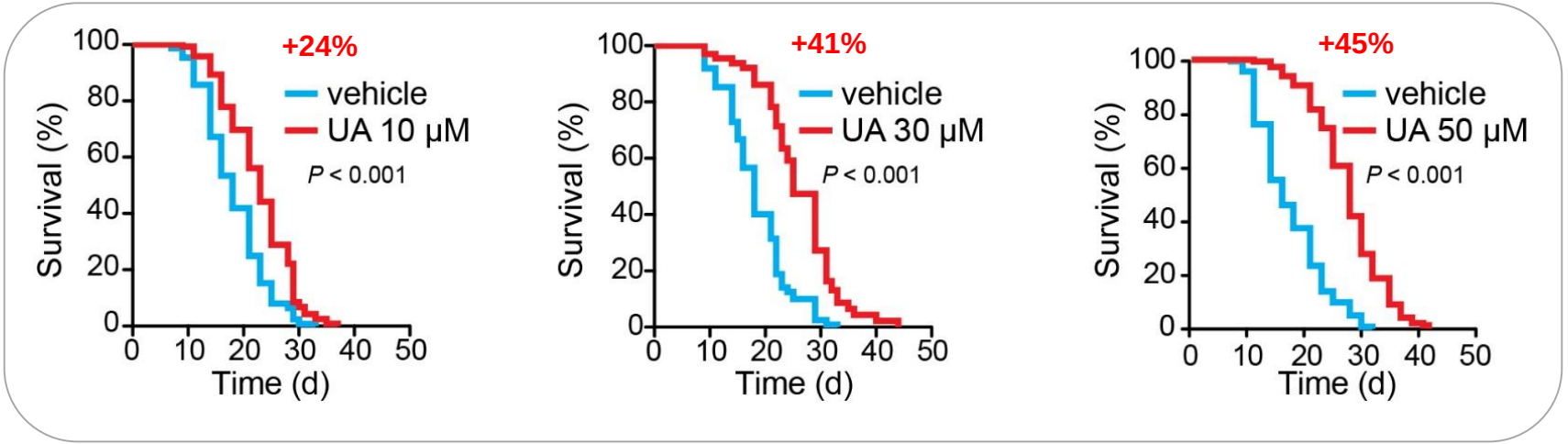
lgg-1 is the worm homolog of LC3B, a key protein involved in the autophagosome formation.





UA induces the formation of autophagosome in GFP::LGG-1 worm strain, similar to food deprivation, a well known inducer of autophagy

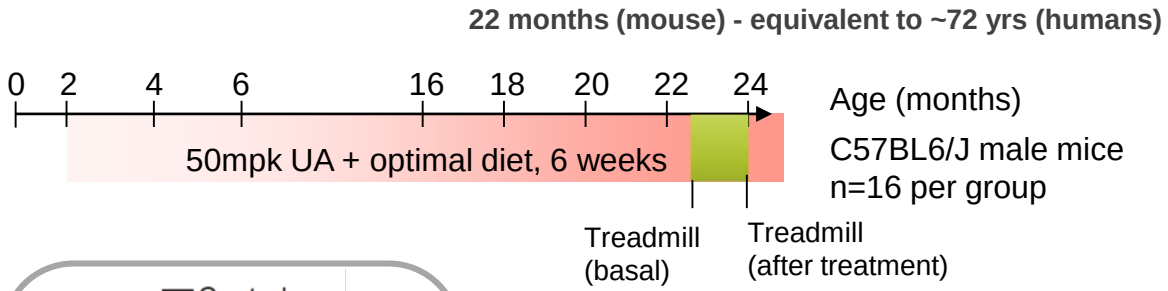
Urolithin A extends lifespan in *C. elegans*

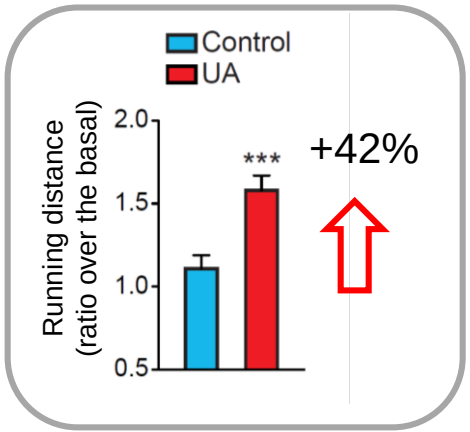


UA extends lifespan dose-dependently

Ryu et al, Nature Medicine, 2016

Short-term Urolithin A oral administration to aged mice dramatically improves running endurance capacity



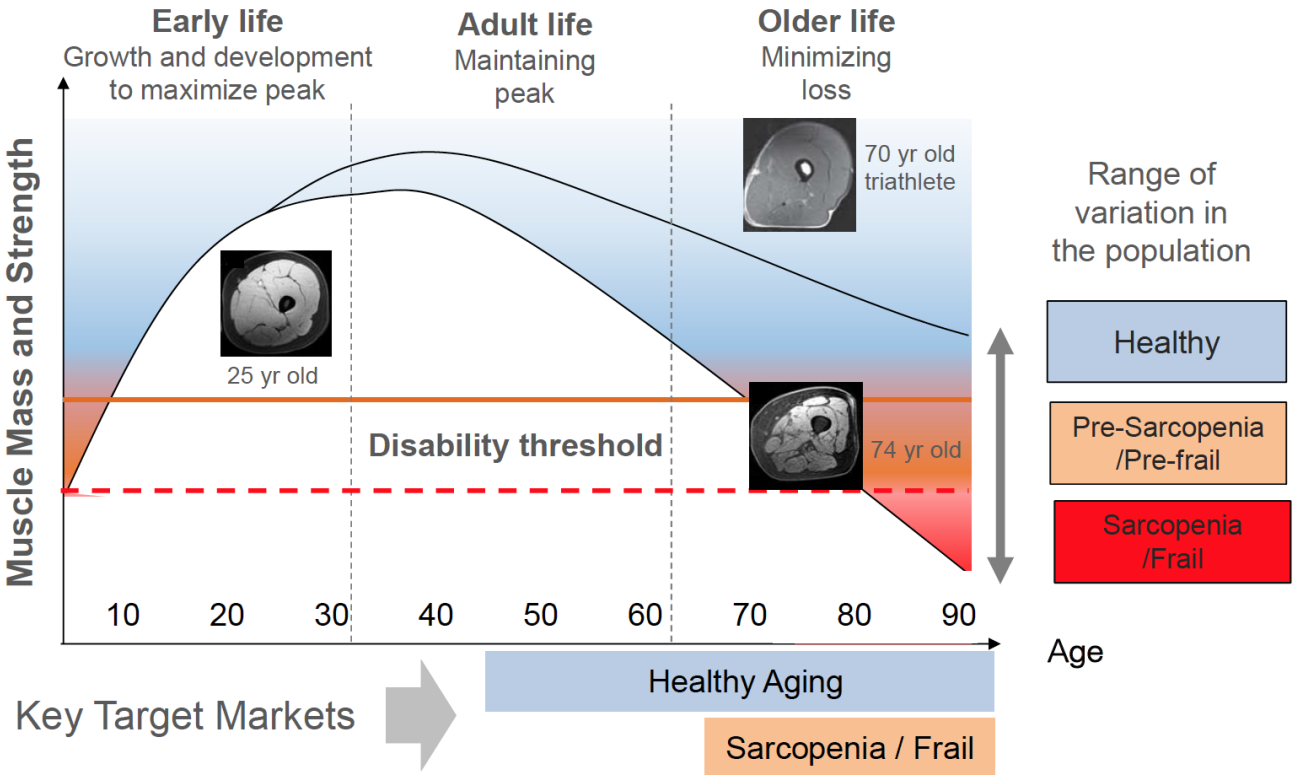


Older mice fed UA for 6 weeks, ***while on an optimal diet,*** *showed a marked improvement in running endurance levels.*

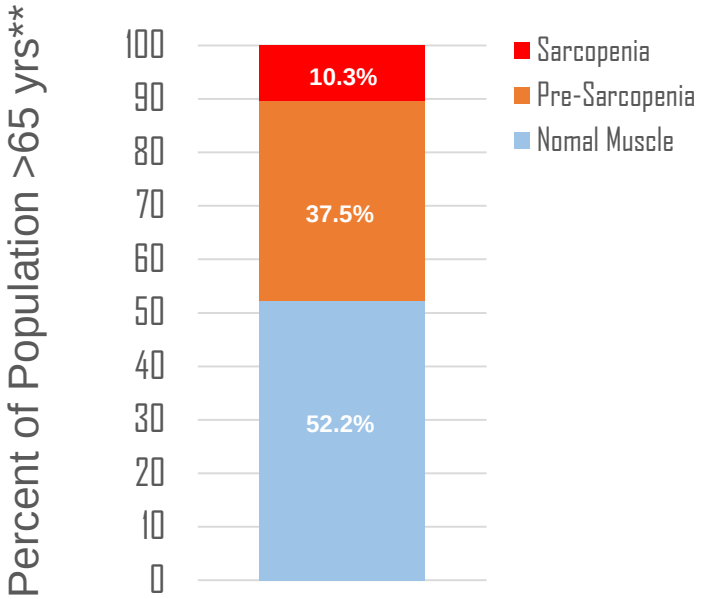
Values are mean ± s.e.m. *P ≤ 0.05, ***P ≤ 0.001; by Student's t-test

Ryu et al, Nature Medicine, 2016

Muscle decline during aging



Age-related decline in muscle function: A tremendous unmet need



There are ~56 million people 65 years and older projected by 2020 in the United States alone.

Worldwide, there will be more than 1 billion people over 65 years old by 2030.

*JAGS Vol 52, 80-85, 2004
** US Census 2014 est. in 2020

Urolithin A was evaluated in a Phase 1 Clinical Study

Key Outcomes

- Shown to be very safe and well tolerated at all doses tested
- Bioavailable and maintains steady state plasma levels
- Stimulates mitochondrial biogenesis in the skeletal muscle

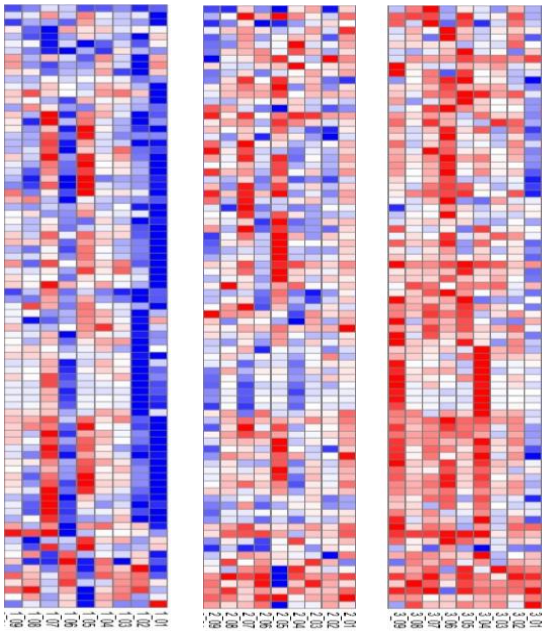
Double-blind, randomized, placebo controlled human trial

Urolithin A induced a molecular signature in human skeletal muscle mitochondria that resembles regular exercise

Heatmap represents the genes that are the most significantly changed by the treatment within the GO_MITOCHONDRION geneset

Interventional Study in Sedentary Adults
28 days with Urolithin A

Placebo | 500mg | 1000mg

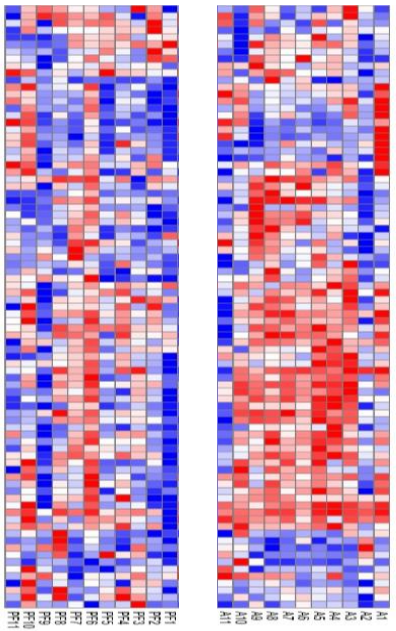


N=9

Average for both studies was ~70 yrs old

Non-interventional study

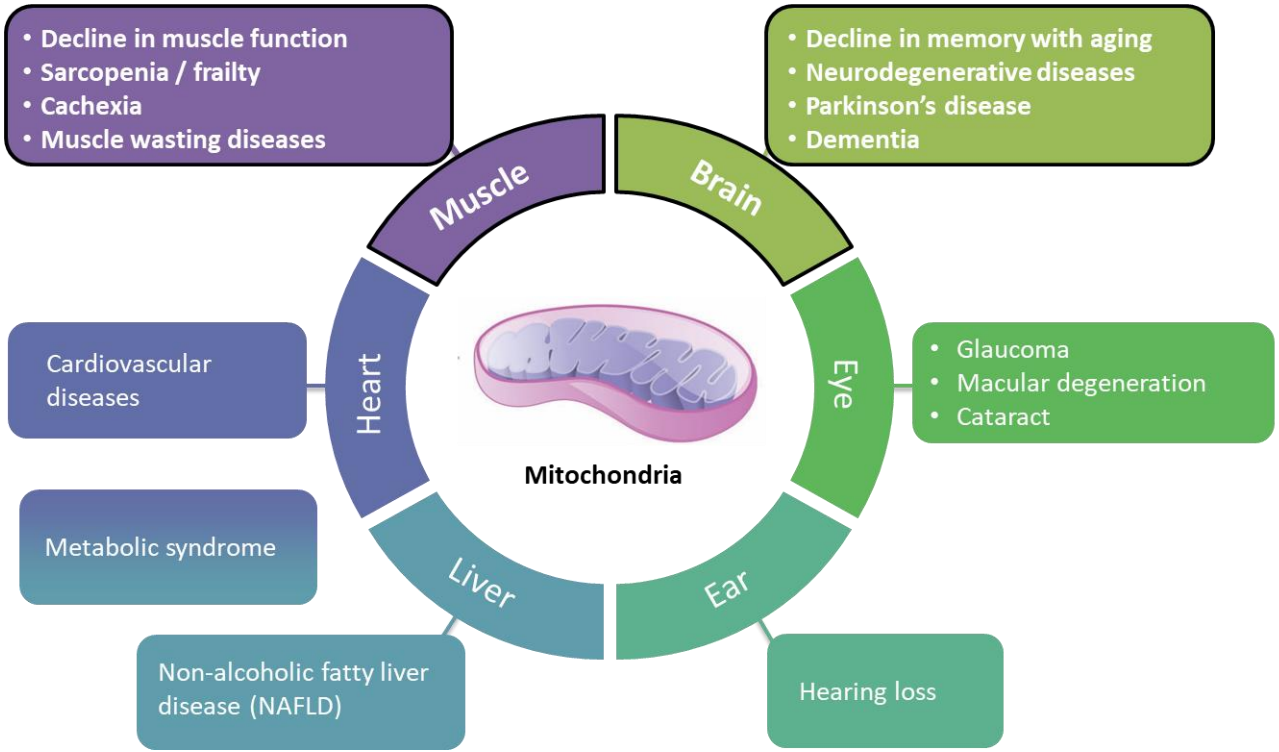
Sedentary & Pre-frail | Active



N=11

row min max

Mitochondrial Health is at the heart of most age-related conditions



Acknowledgments

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LGC – Behavioral Genetics Laboratory

Nagi Bioscience

Amazentis

C. Rinsch, PhD

A. Singh, MD

W. Blanco, PhD

P. Andrieux, PhD

Amazentis' board members

Patrick Aebischer, MD, Chairman
- Co-founder of Amazentis
- President emeritus, EPFL
- Board of Directors: Nestlé, Lonza, Logitech
- Chairman, Novartis Venture Fund
- Senior partner of NanoDimension-III

Chris Rinsch, PhD
- CEO & Co-founder, Amazentis
- Inventages Venture Capital (Nestlé Fund)
- Modex Therapeutics / Isotis SA
- MBA (INSEAD)

Eric Lohrer
- Investment professional at Loreda Holding, a large single family office
- Formerly, director level executive at Johnson & Johnson (10+ yrs)
- Board member/advisor: portfolio of biotech & medical device companies.

Pierre Landolt
- Co-founder, Amazentis:
- Landolt & Cie SA; Chairman
- AxialPar Ltda, Brazil; Chairman
- Past board member of Novartis, Sandoz Family foundation

Thierry Lombard
- Partner, Landolt & Cie
- Former Senior Partner in Lombard Odier (42yrs)
- Former President of the Family Business International Foundation (FBIF)
- Member of the ICRC

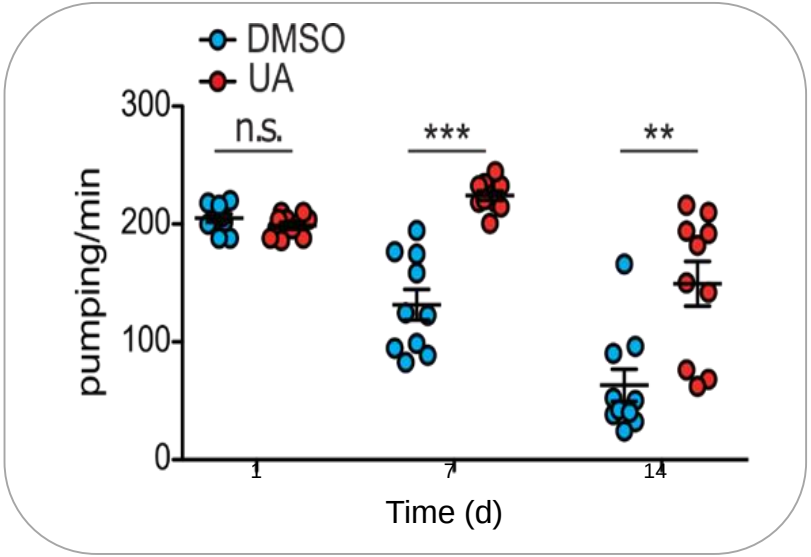
Odile Rundquist, PhD
- Senior Scientific Advisor representing Mr. André Hoffmann, vice-chairman of Roche
- Former Senior Pharmaceutical Analyst at leading investment banks (10yrs)

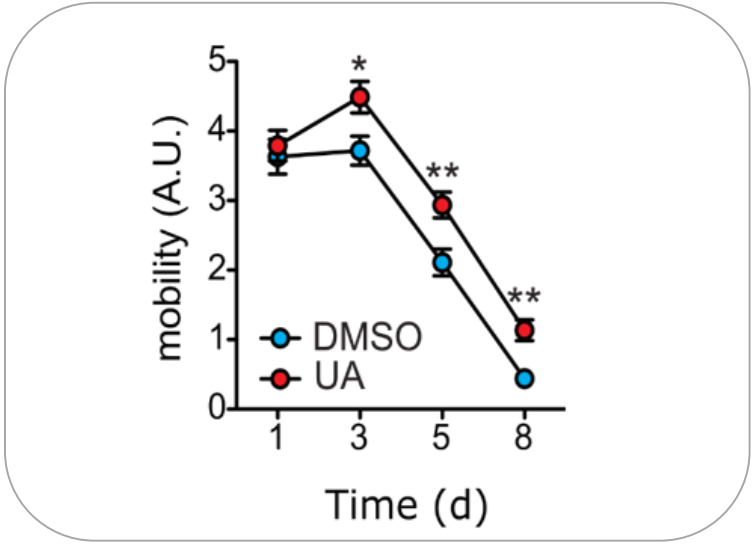
Goal: die young as late as possible

Madonna della Melagrana, Sandro Botticelli, 1487
…simbolo di fecondità, abbondanza e regalità…


ÉCOLE POLYTECHNIQUE
FÉDÉRALE DE LAUSANNE
Thank you for your attention

Urolithin A improves fitness in *C. elegans*

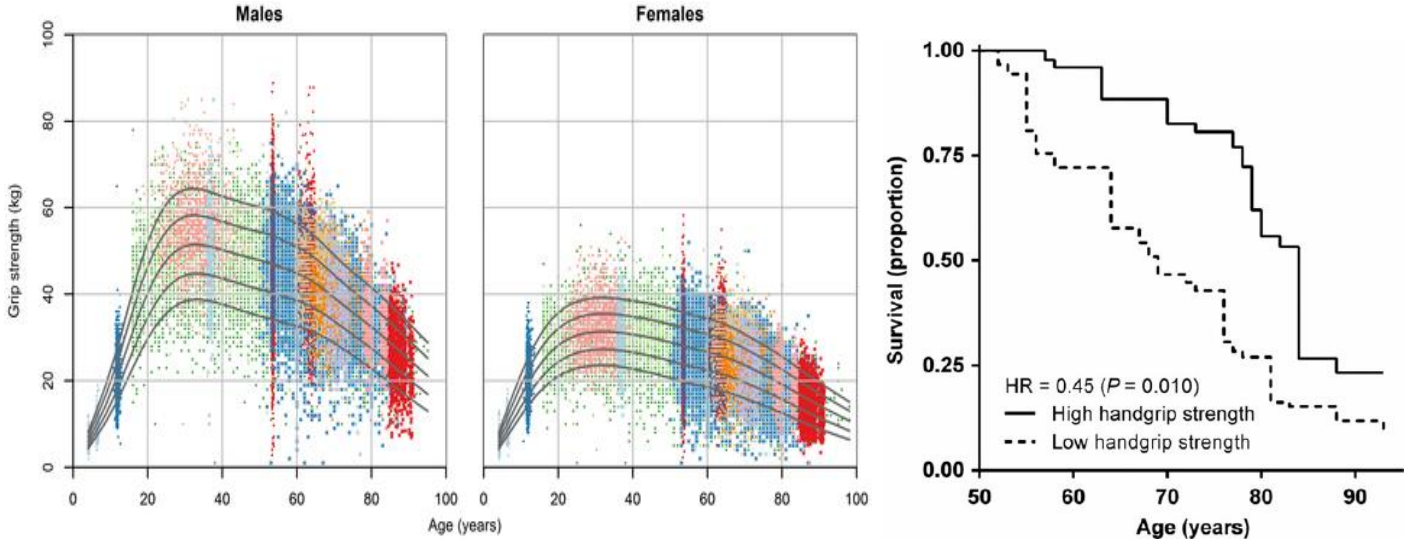




Improved pharyngeal pumping & mobility is indicative of better muscle function in aged worms

Ryu et al, Nature Medicine, 2016

Hand Grip Strength is closely linked to human lifespan and mortality



Better hand muscle strength correlates with longer life expectancy and vitality

Dodds RM, et al. (2014). PLOS ONE 9(12): e113637.
Koopman et al., (2015).Age and Ageing 44(3):465-470