Insights into Healthspan and Neurodegeneration in C. elegans

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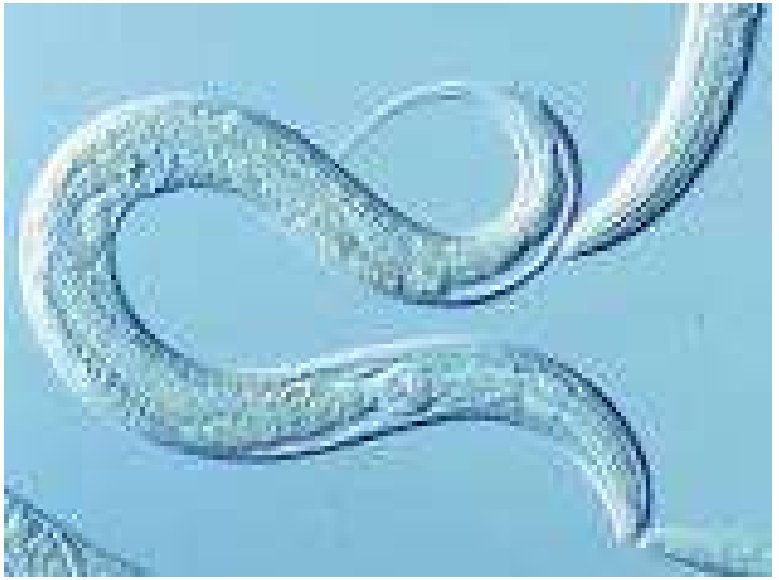


Nelson A232 Bush **driscoll@biology.rutgers.edu**

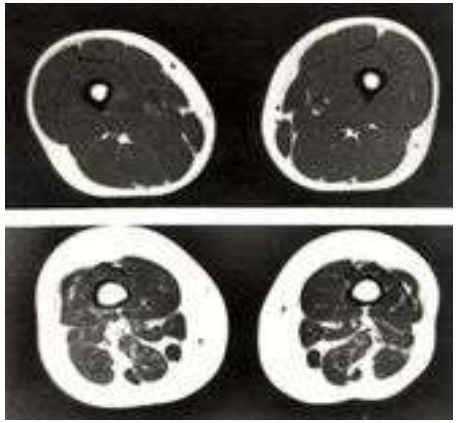
A talk in two parts:

1) Basic research as the key to healthy aging

2) New biology in neuronal health

Aging involves physical decline

Sarcopenia is an inevitable component of human aging



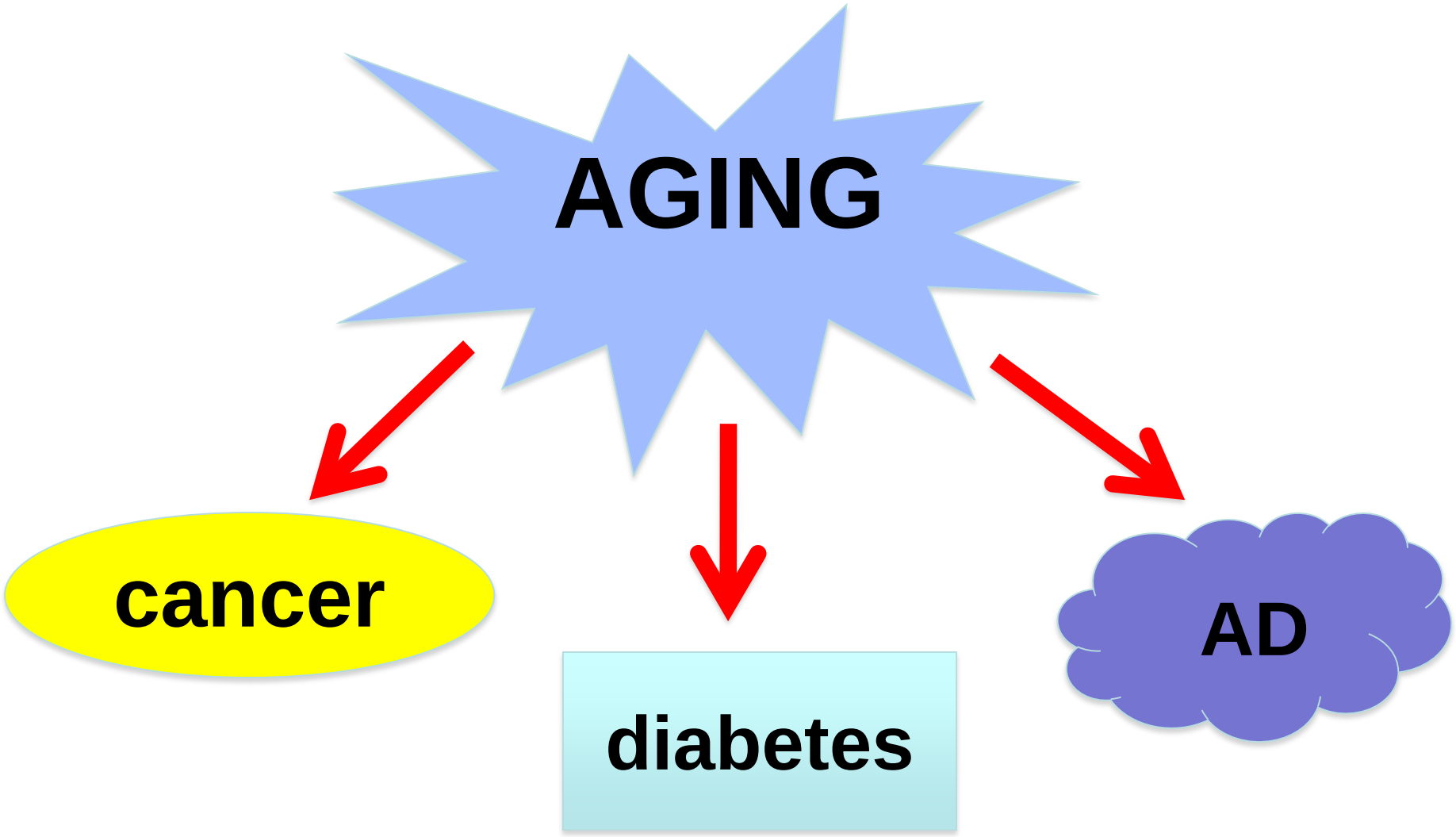
progressive loss of muscle mass and strength

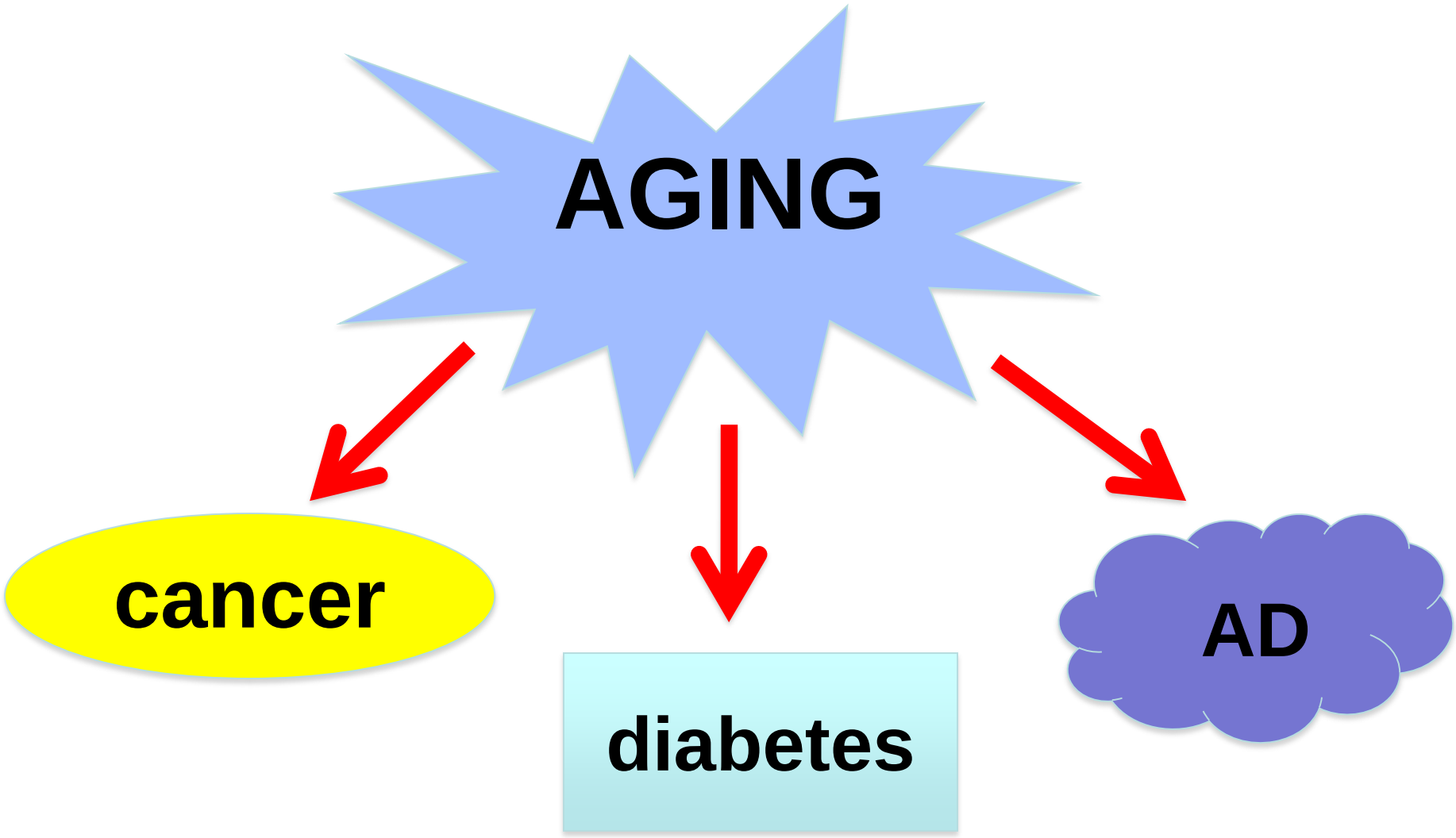
-midlife onset

need for institutional ca
falls and consequent in

Major quality of life issue; major economic issue

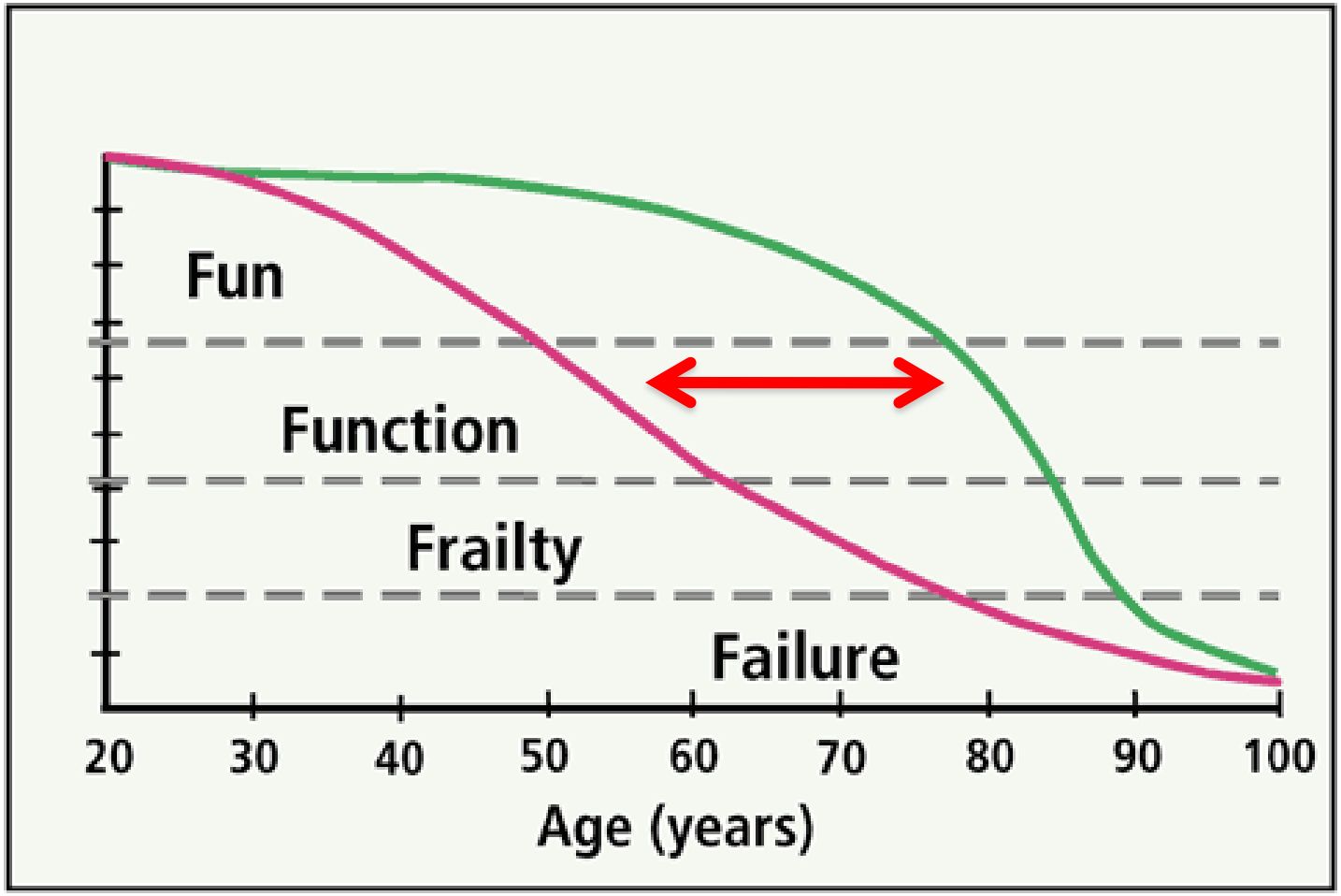
Aging is the primary risk factor for cancer, diabetes, Alzheimer's disease, and more…





decrease aging consequences
improve quality of life and delay disease

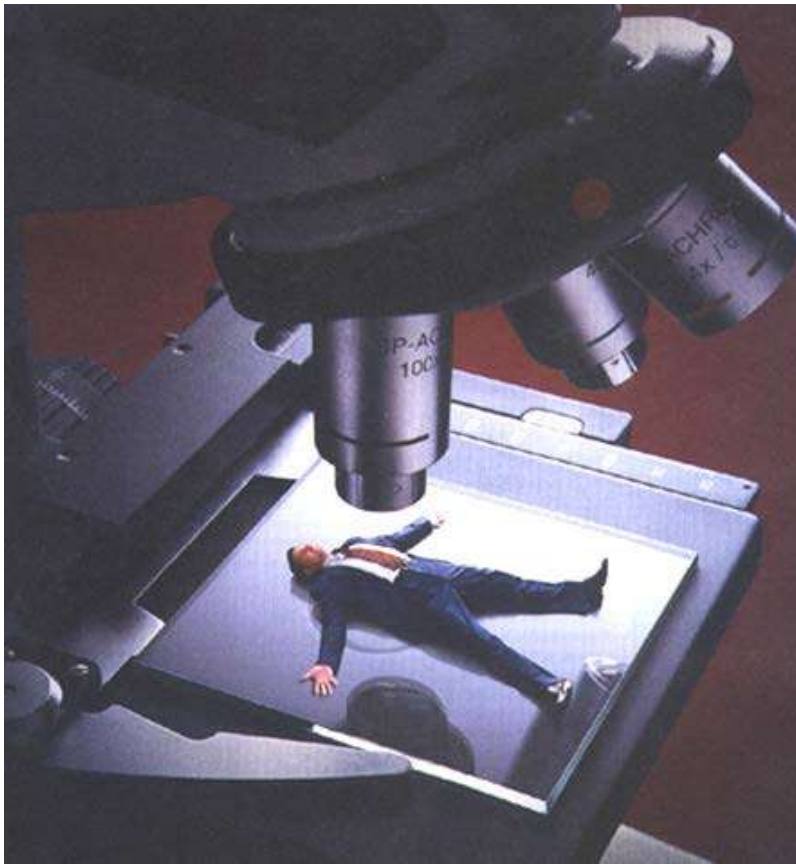
Functional ability with age



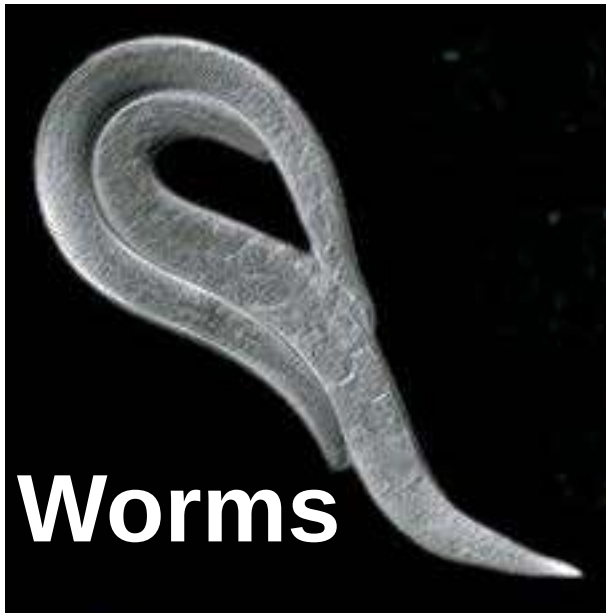
Extending healthspan is an important objective for the field

Humans make lousy experimental subjects

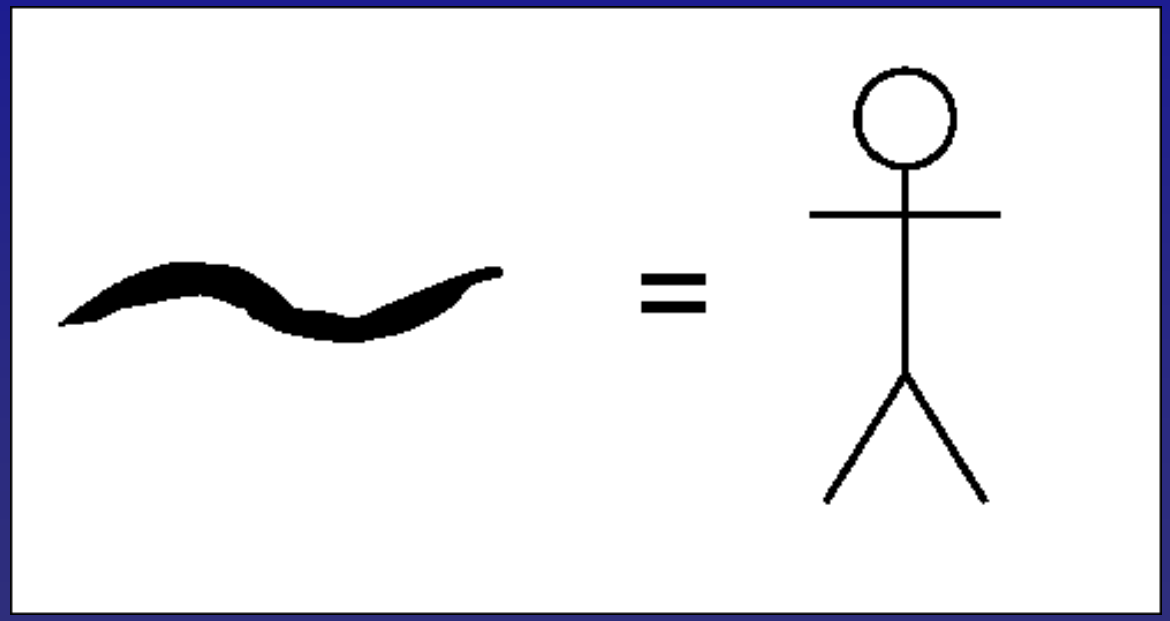
- genetically heterogeneous
- environmental differences
- slow reproduction, few offspring
- live too long
- reluctant to give up tissues



Model systems are invaluable in biology



Basic Biological Mechanisms Are Conserved



The *C. elegans* model

--959 cells

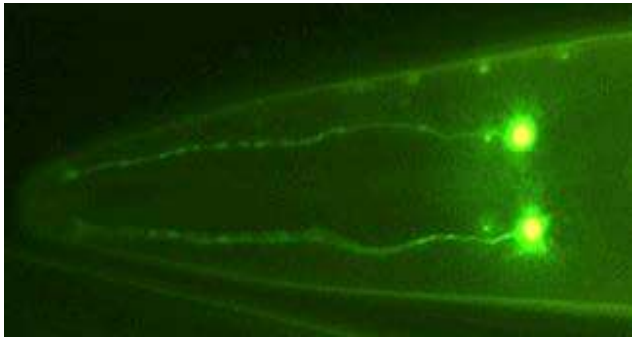
--transparent

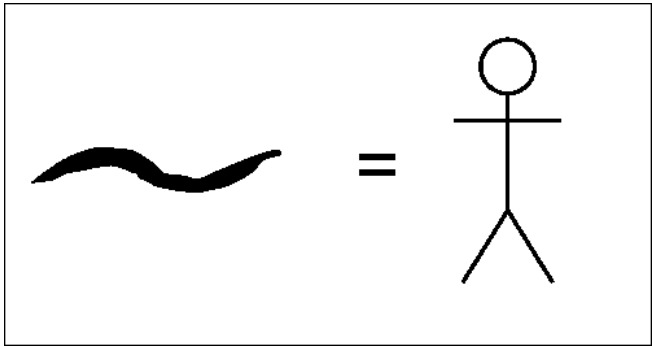
--strong genetics

--easy transgenic generation

--lives 3 weeks

Basic biological mechanisms are conserved



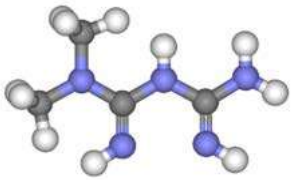


genes

diet

exercise

healthspan

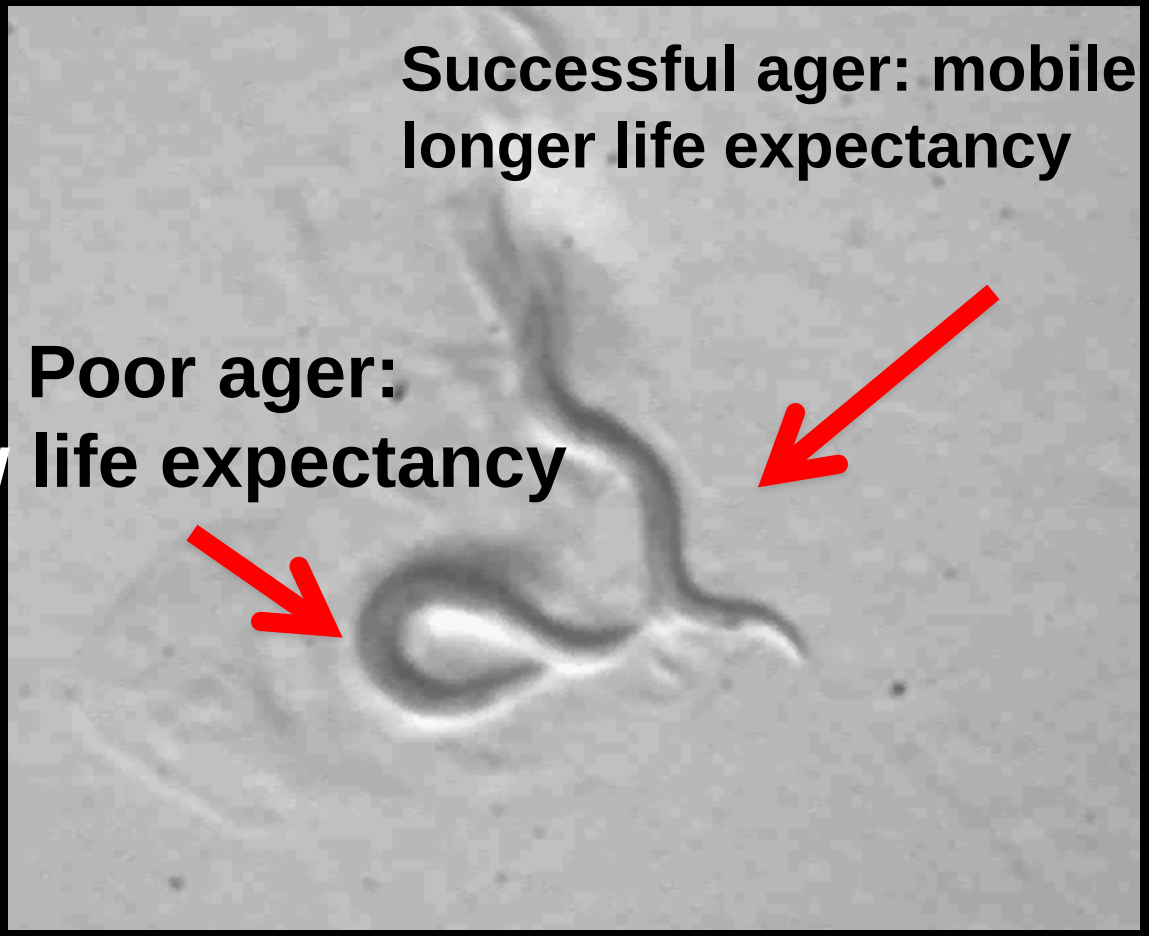


natural products

environment

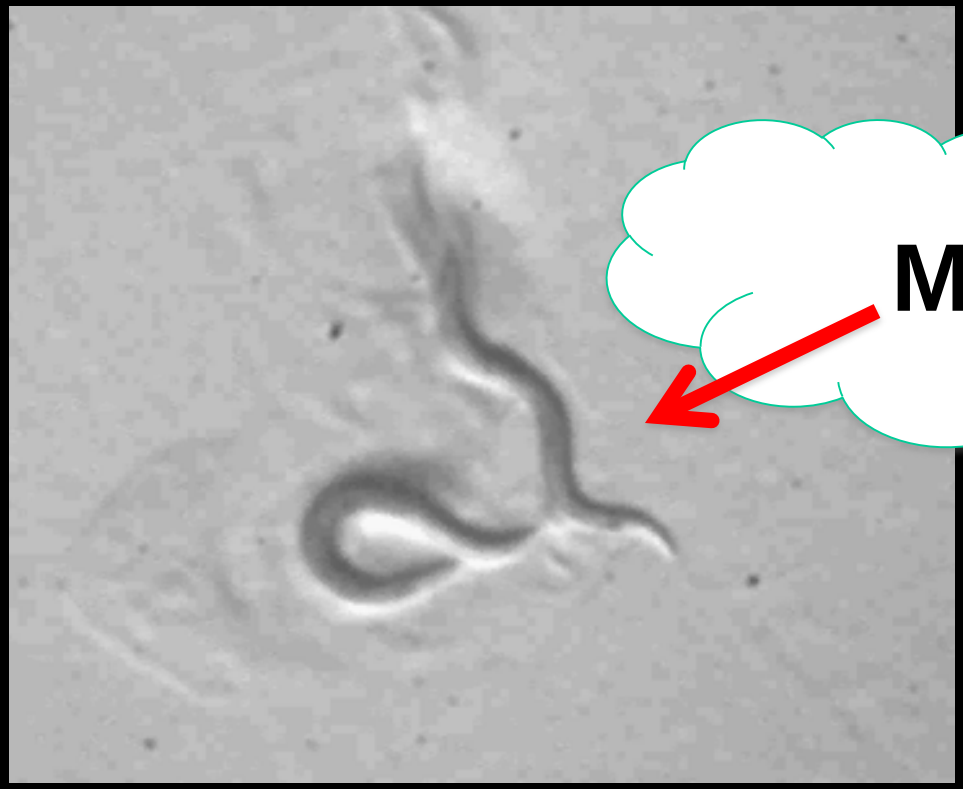
chance

Animals of the same chronological age, same genotype and same environmental experience can “age” differently



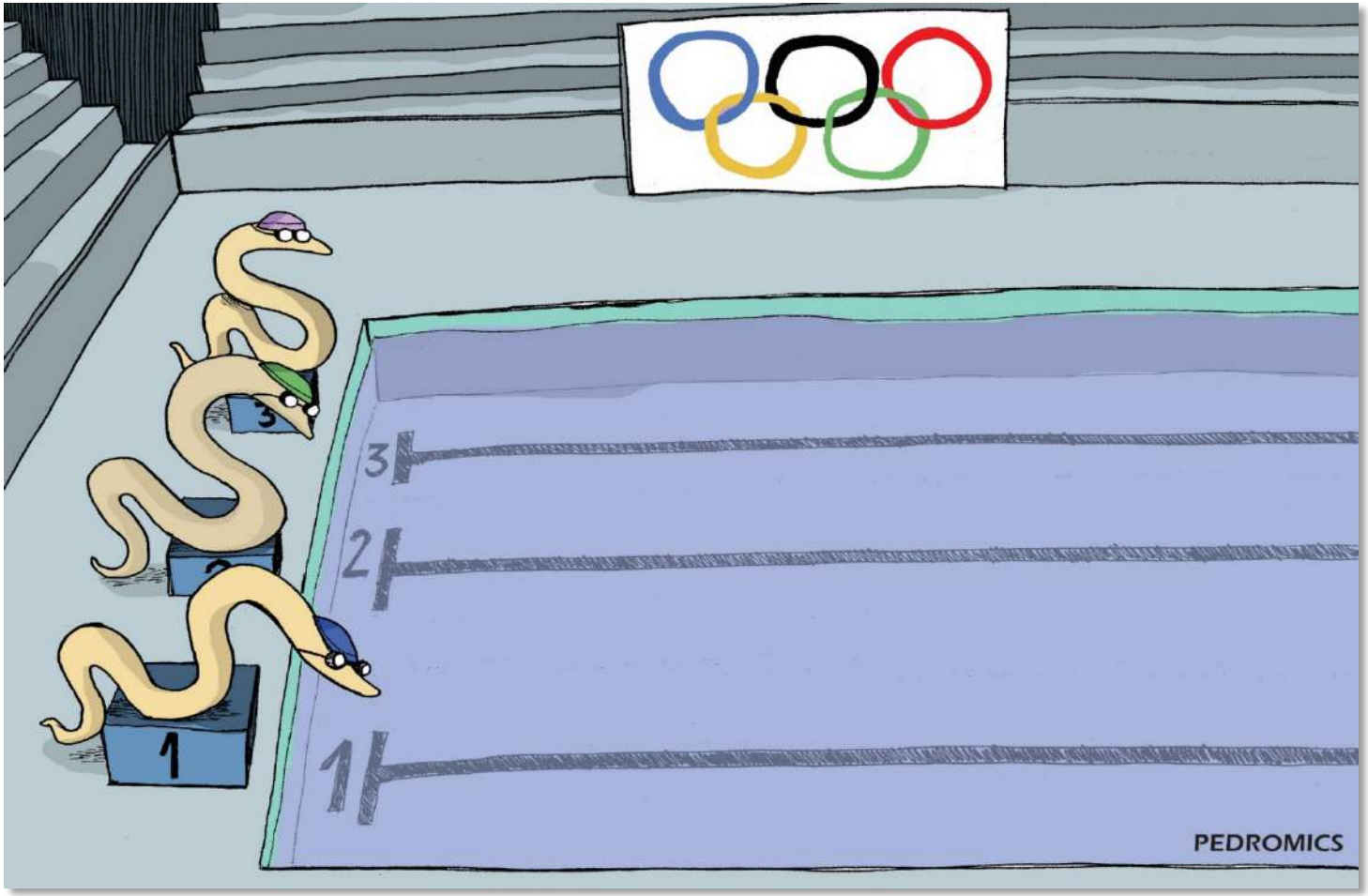
same age animals

C. elegans can age gracefully or age poorly

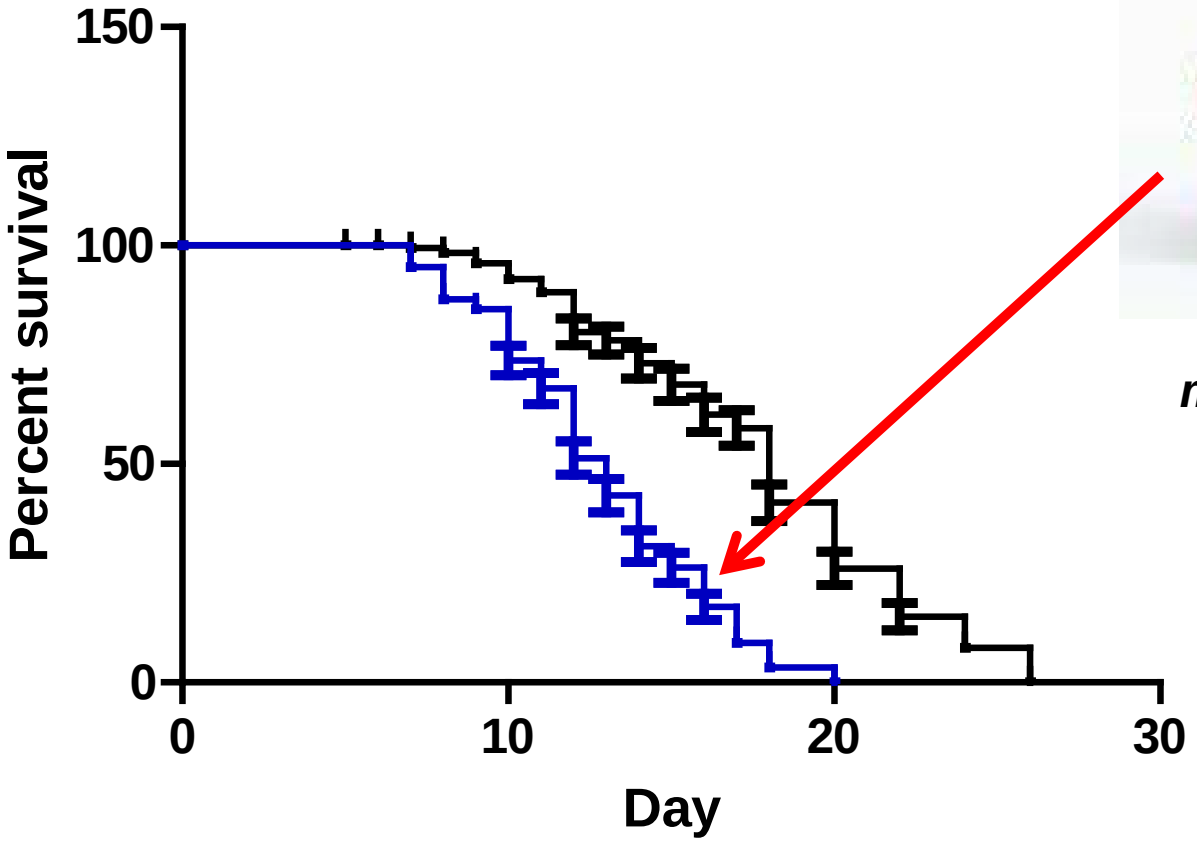


--Identifying the differences is of interest

Exercise and healthy aging

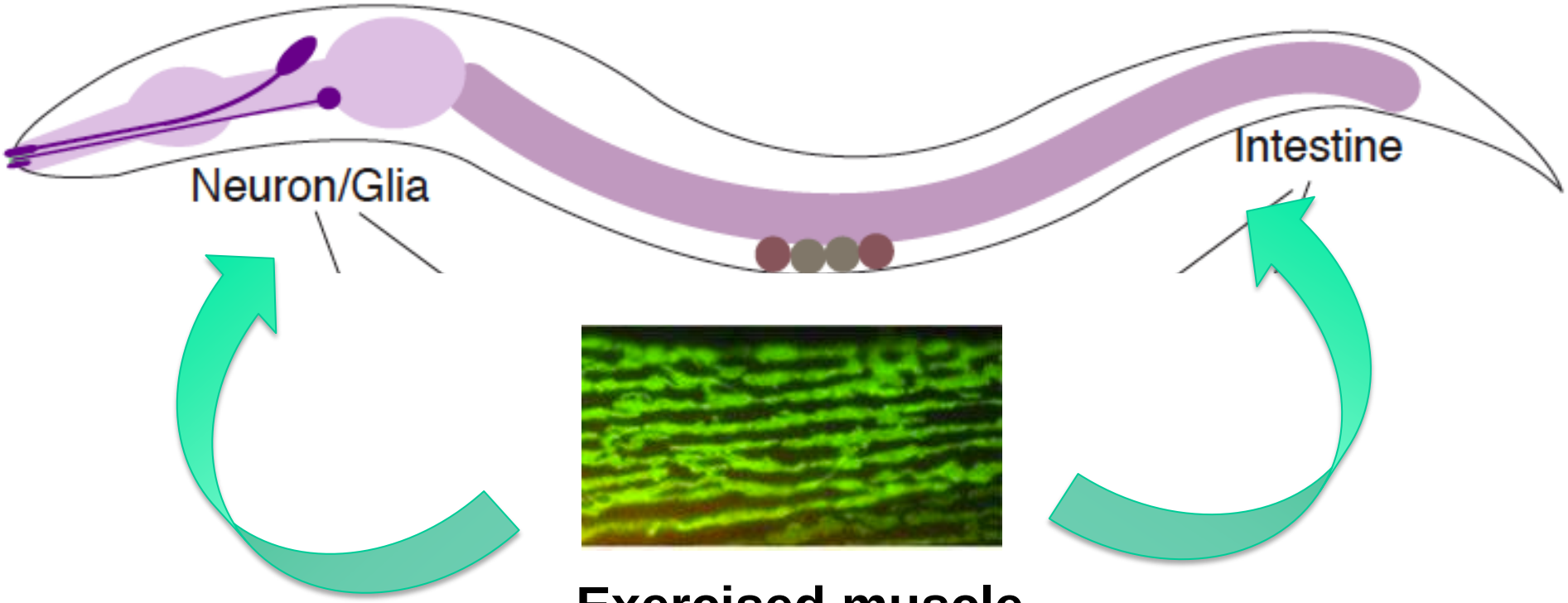

3
2
1
3
2
1
PEDROMICS

Lethargic worms that do not train have lower life expectancy

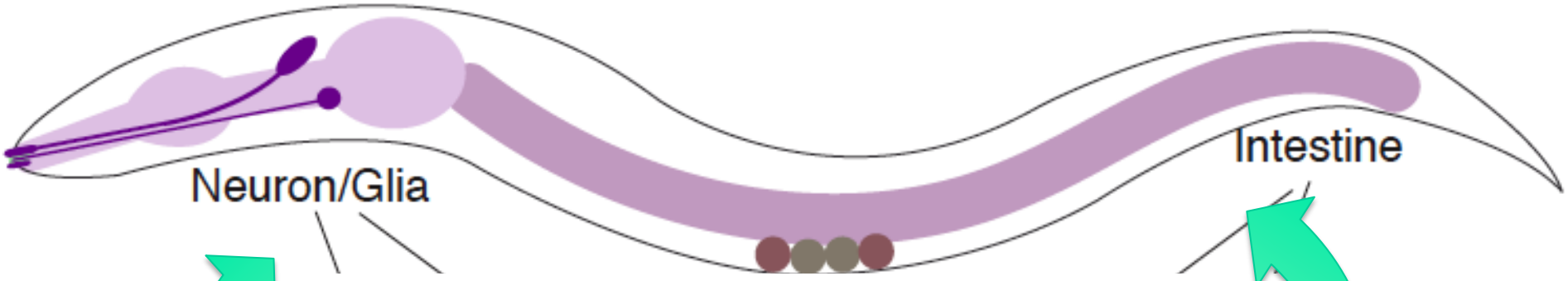


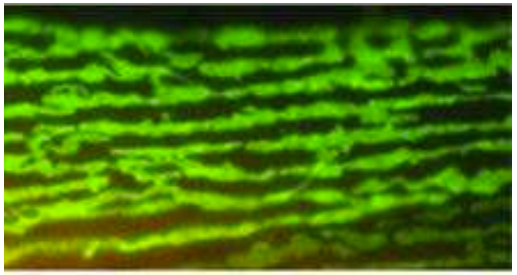
mec-10 mec-4 **mutant**

Key Question: What exercise-induced molecules dictate whole animal health?



Key Question: What exercise-induced molecules dictate whole animal health?

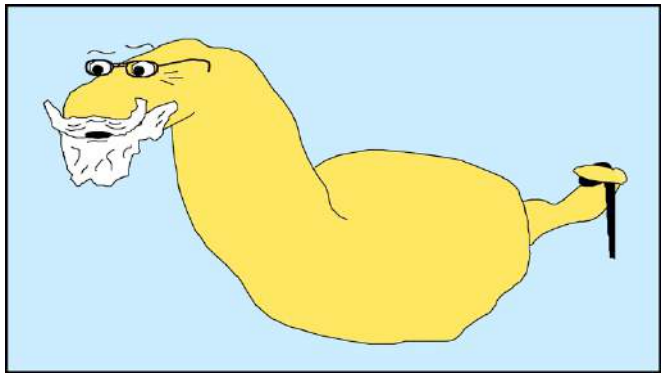




Exercised muscle

CITP

Caenorhabditis Intervention Testing Program



Our mission: **Identify pharmacological interventions that increase lifespan and/or healthspan in a robust manner using *Caenorhabditis***

The CITP Team:

- **Monica Driscoll Rutgers University, NJ**
- **Gordon Lithgow Buck Institute, CA**

- **Patrick Phillips University of Oregon**

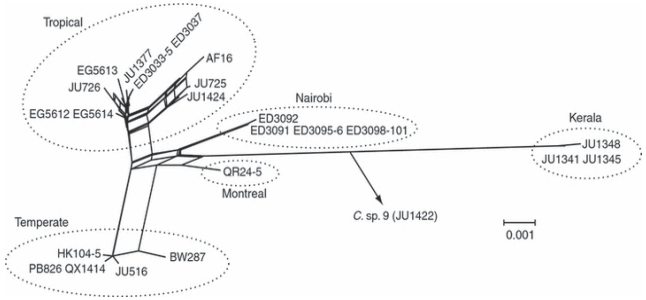
- **Max Guo NIA Project Scientist**

- **Ron Kohanski NIA Program Officer**

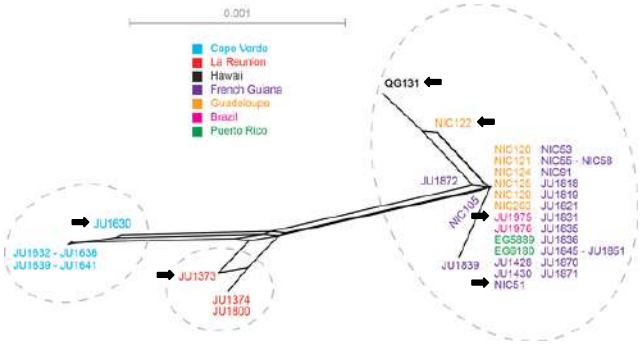
The CITP strains

maximize genetic diversity

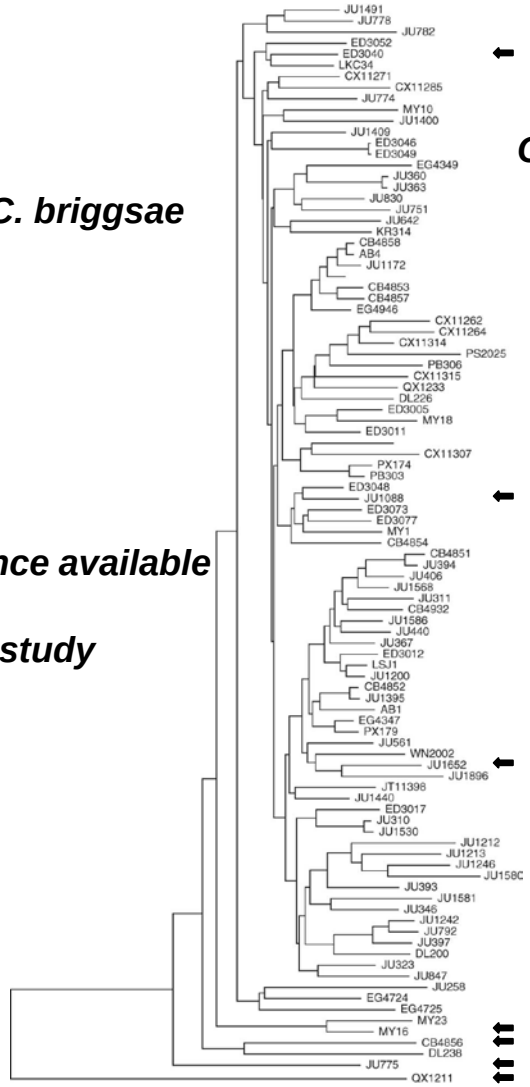
4-8 strains per species



C. tropicalis (sp. 11)



C. briggsae



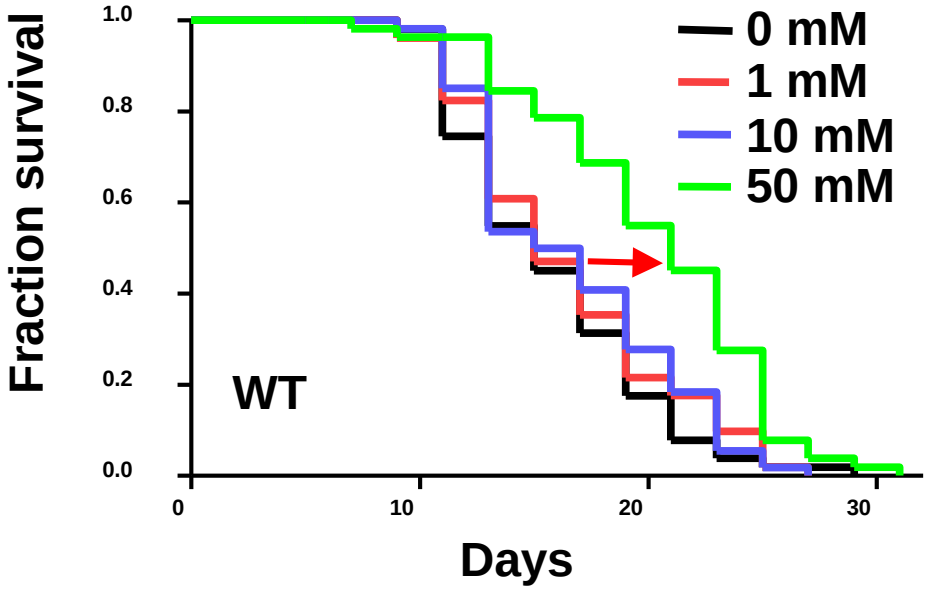
C. elegans

-genome sequence available

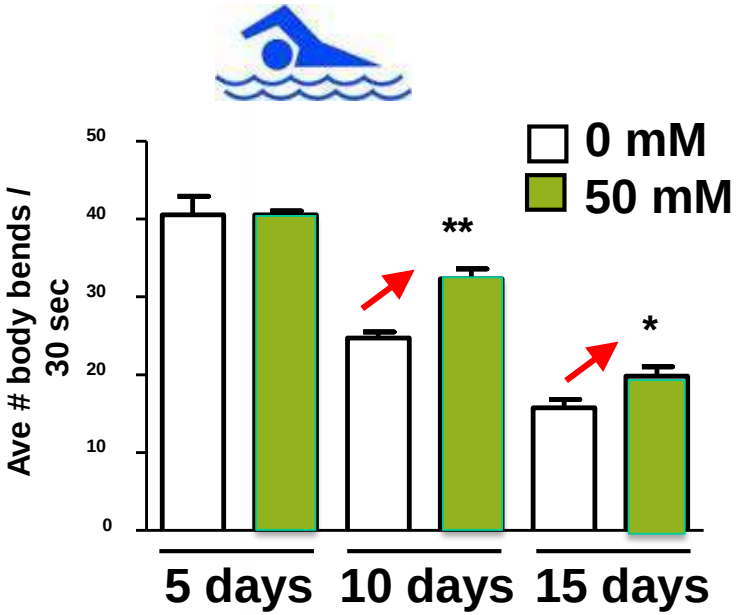
-some previous study

TAME project summary

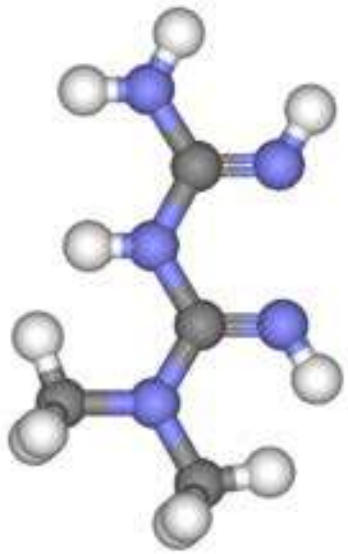
Metformin can extend *C. elegans* median lifespan..

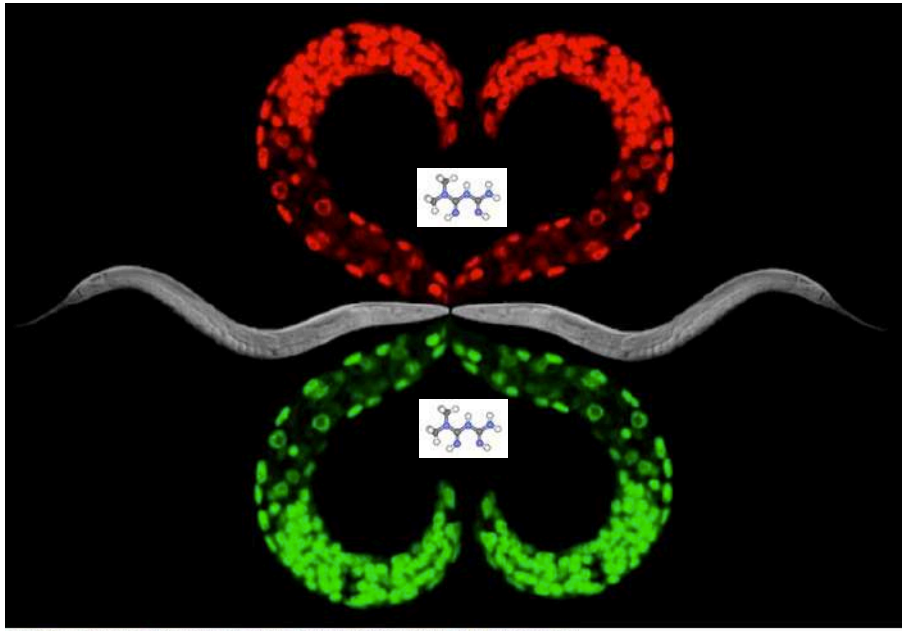


Metformin treatment improves late age swimming prowess



Metformin





C. elegans art by Ahna Skop and Tri Nguyen. Stay tuned for a #Worm17 Art Show recap.

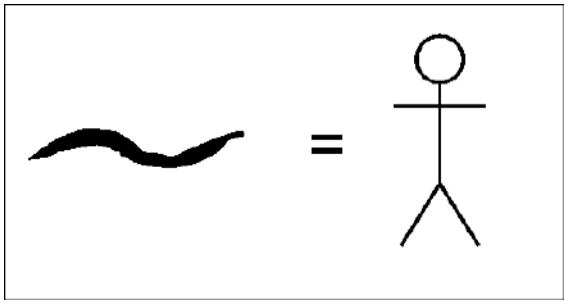
CITP

A talk in two parts:

1) Basic research as the key to healthy aging

2) New biology in neuronal health

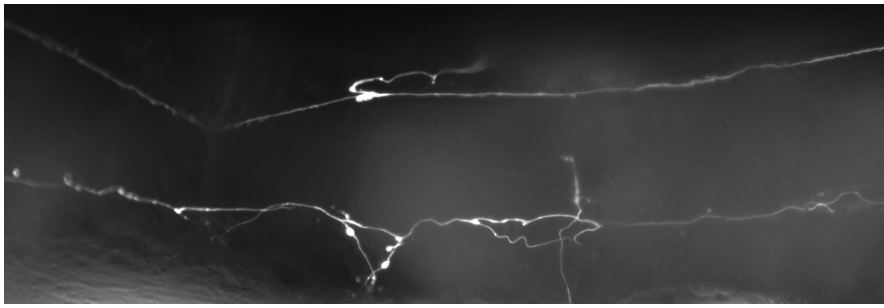
C. elegans age like humans



C. elegans **NS aging is similar to human brain aging**

--little loss of neurons by cell death

--synaptic decline



--dendrite restructuring

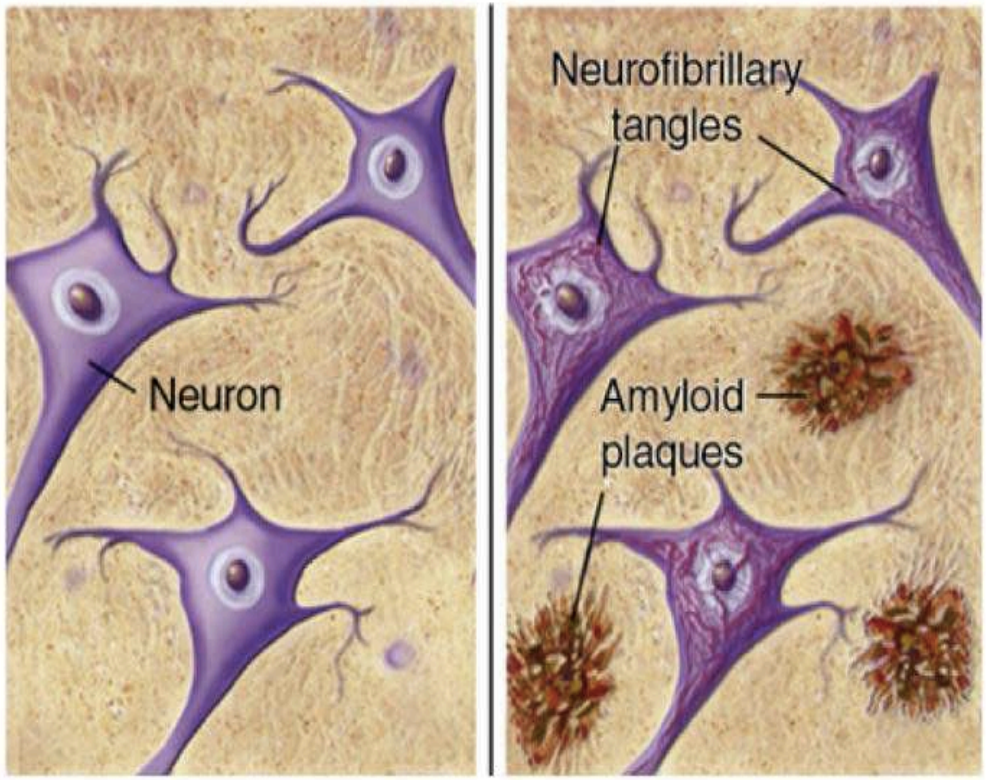
--differential susceptibility for different neurons

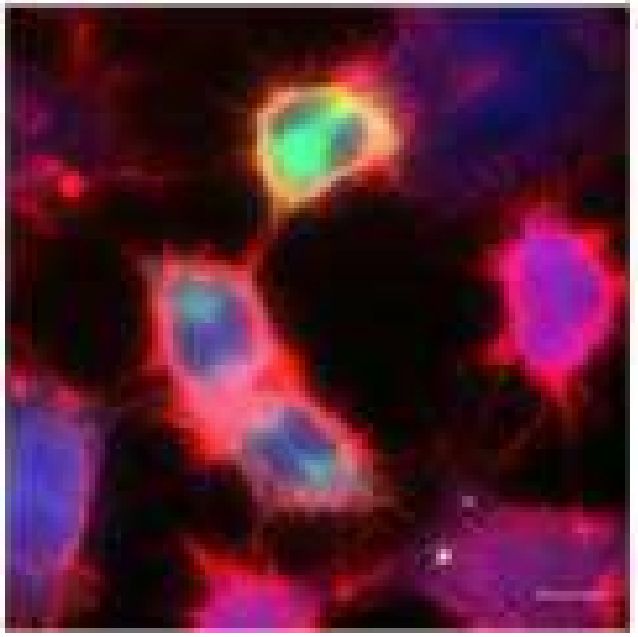
--proteostasis is important

In aging systems, trash management becomes an increasing problem

Major challenges for an aging neuron

1) Protein Aggregation





Aggregate Transfer=
worse than we thought!!

Major challenges for an aging neuron

2) Mitochondrial Dysfunction

Healthy

Age-Diminished

-Energy production

-Ca^{+2} homoeostasis

-Metabolism

--ROS production

-Cell Death

Clean up *within* the neuron:

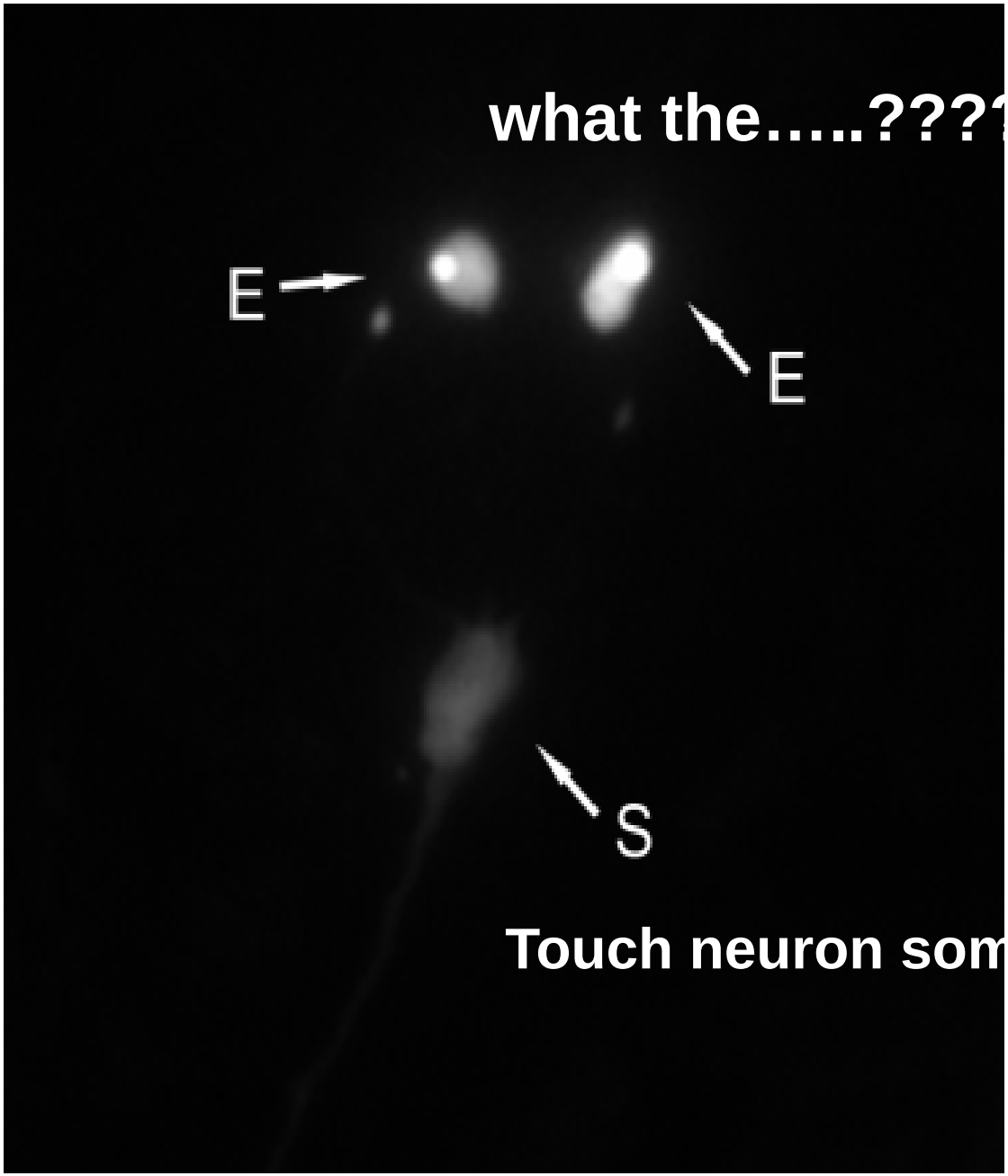
Chaperones fold

Proteasome degrades

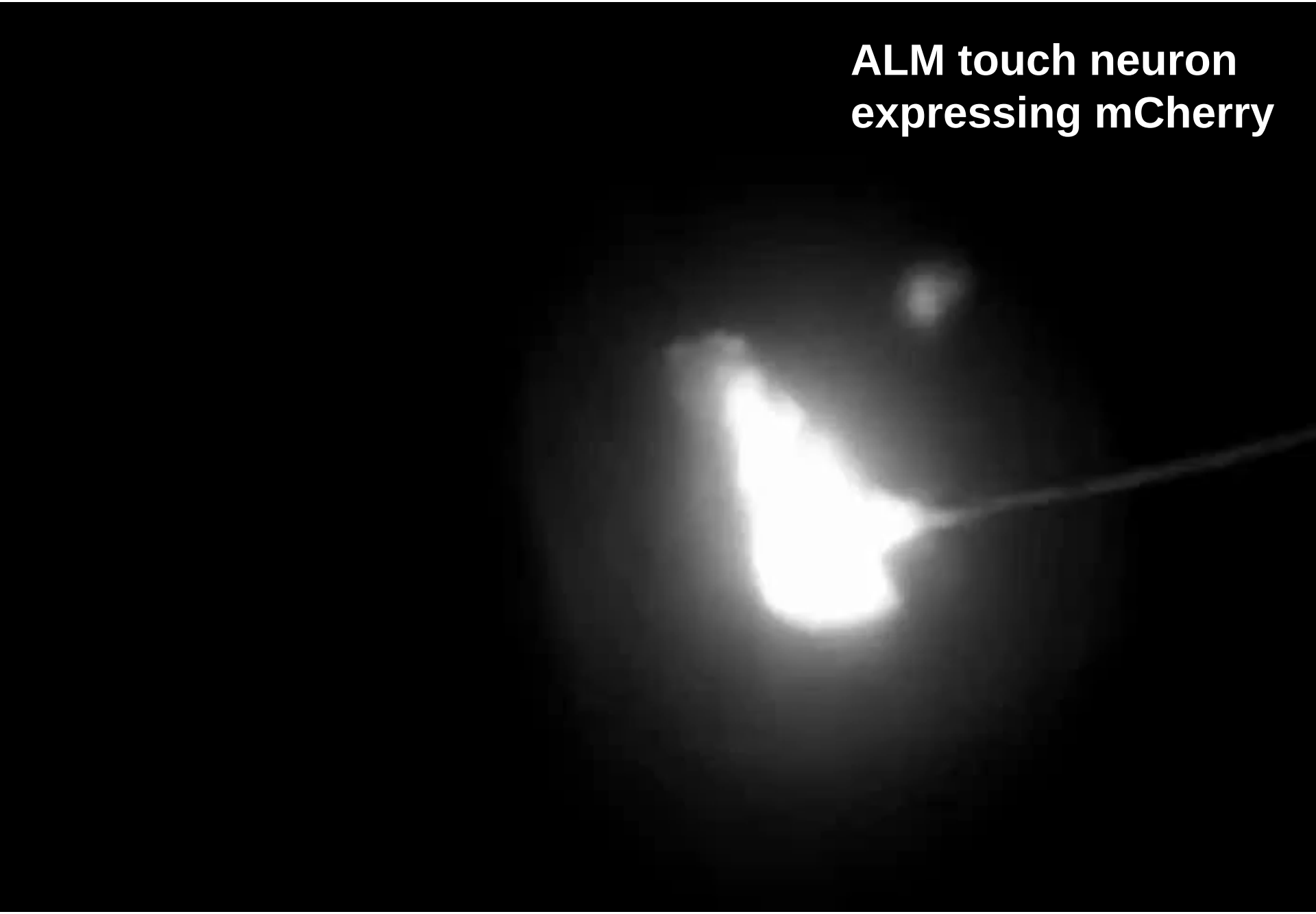
Autophagy/lysosome degrades

bizarre fluorescence appears **outside** the touch neuron

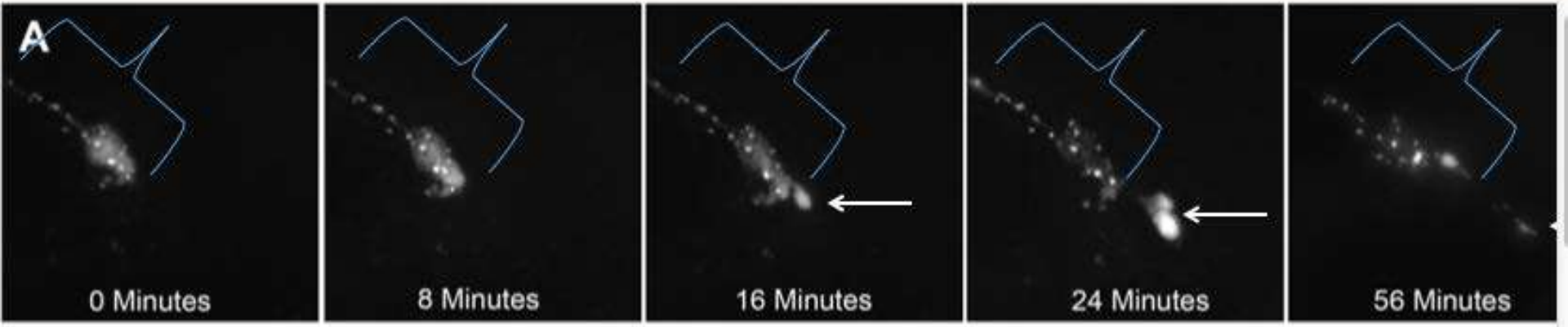
Ilija Melentijevic



$P_{mec\text{-}4}$mCherry


ALM touch neuron
expressing mCherry

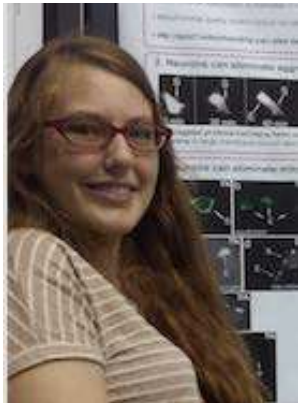
An exopher is born…..



A near-soma-sized packet is jettisoned from the cell body

Ilija Melentijevic

Meghan Arnold



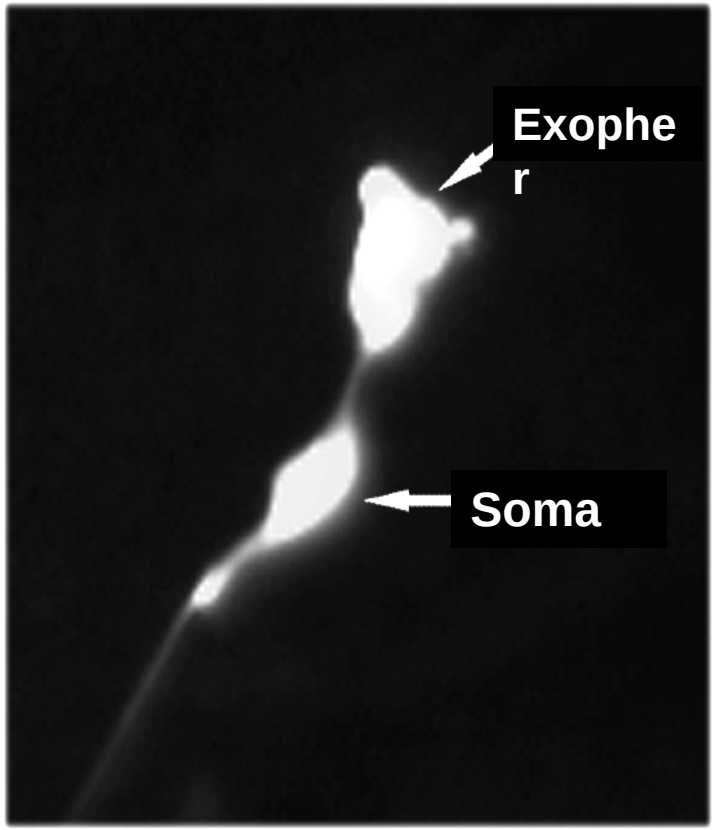
Joelle Smart

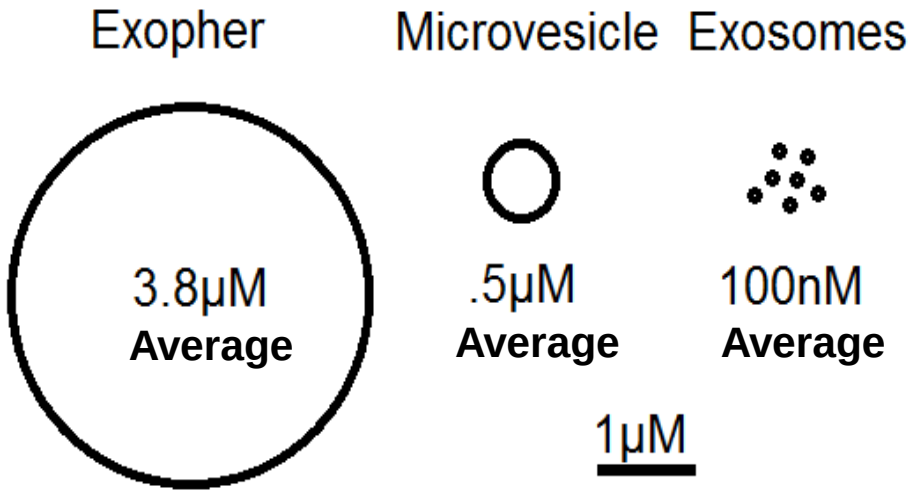
Ryan Guasp

Girish Harinath

Marton Toth

C. elegans can extrude large vesicles, or “exophers”

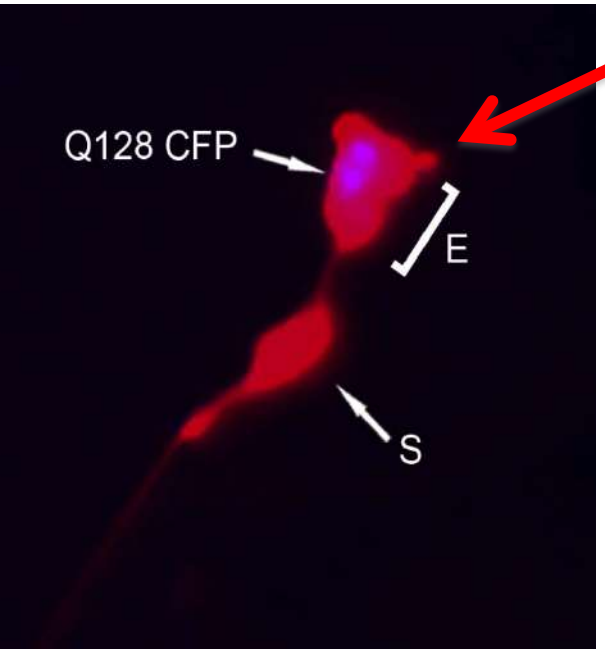


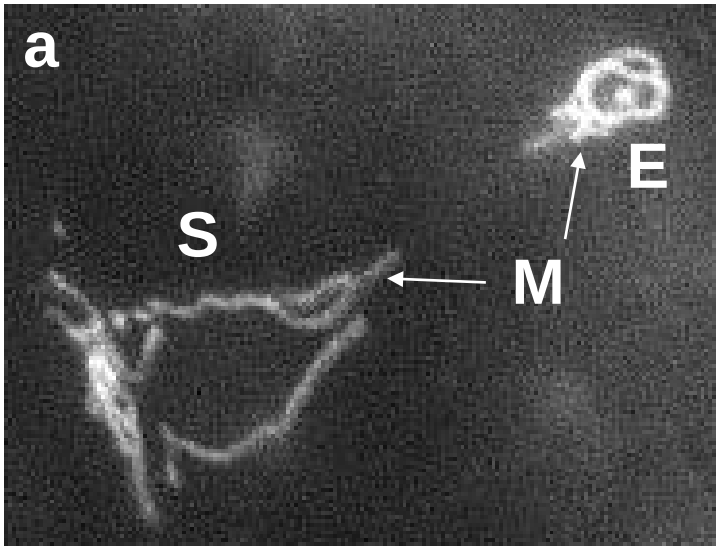


(not an exosome!!!!)

Extrusions can contain mitochondria or disease protein aggregates…

PolyQ-CFP

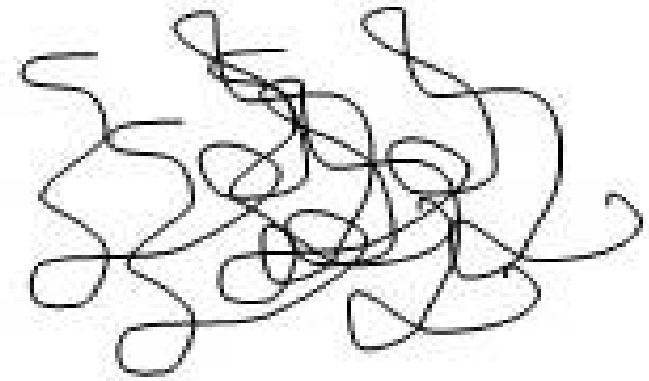




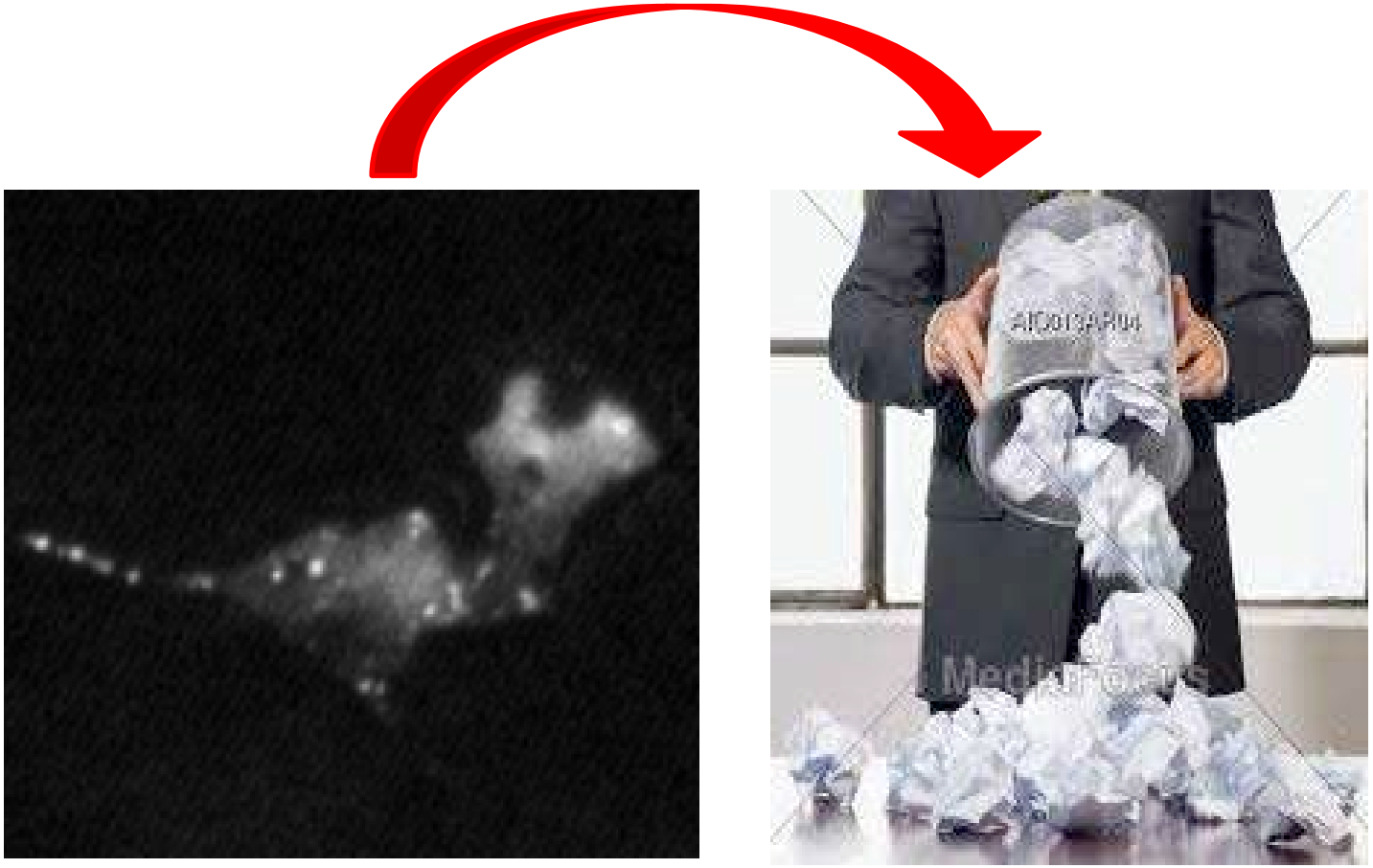
Mito-GFP

Exophers: a mechansim for dumping the trash?

Exopher production increases under Proteo-stress

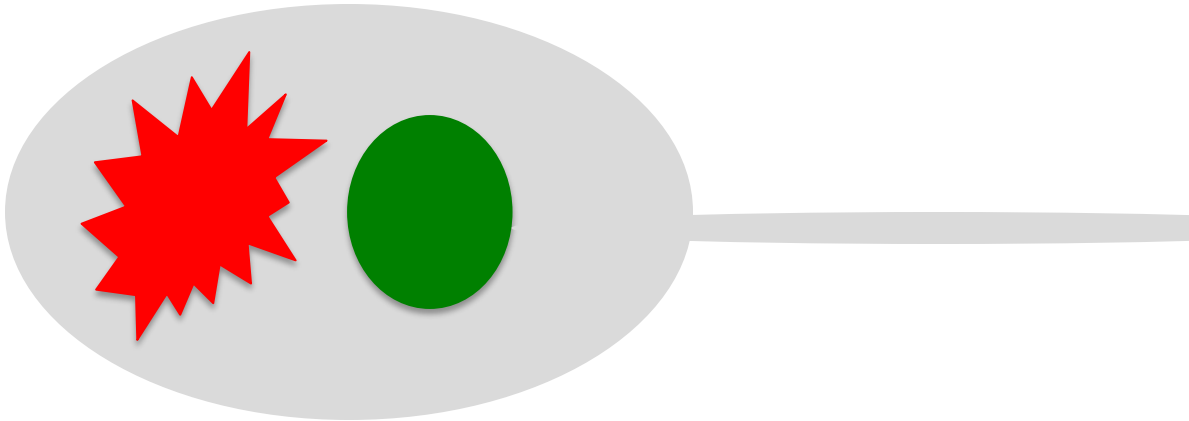


Neurons can eliminate protein aggregates and mitochondria by a dramatic extrusion mechanism



Compromising proteostasis components increases exophers

Is the mechanism selective for compromised proteins?

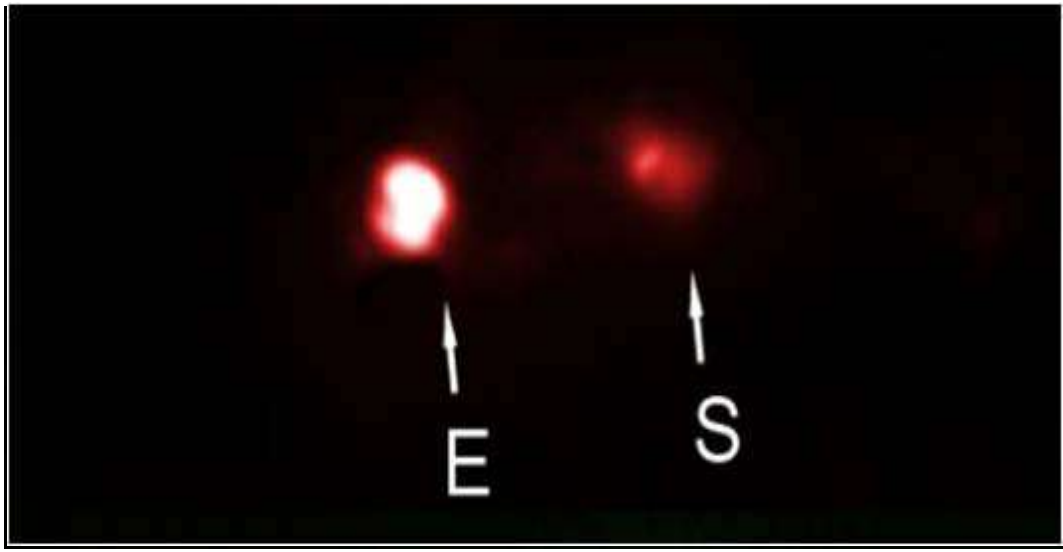


Exophers selectively include aggregates

Double label strain

mCherry (aggregating)

GFP (non-aggregating)

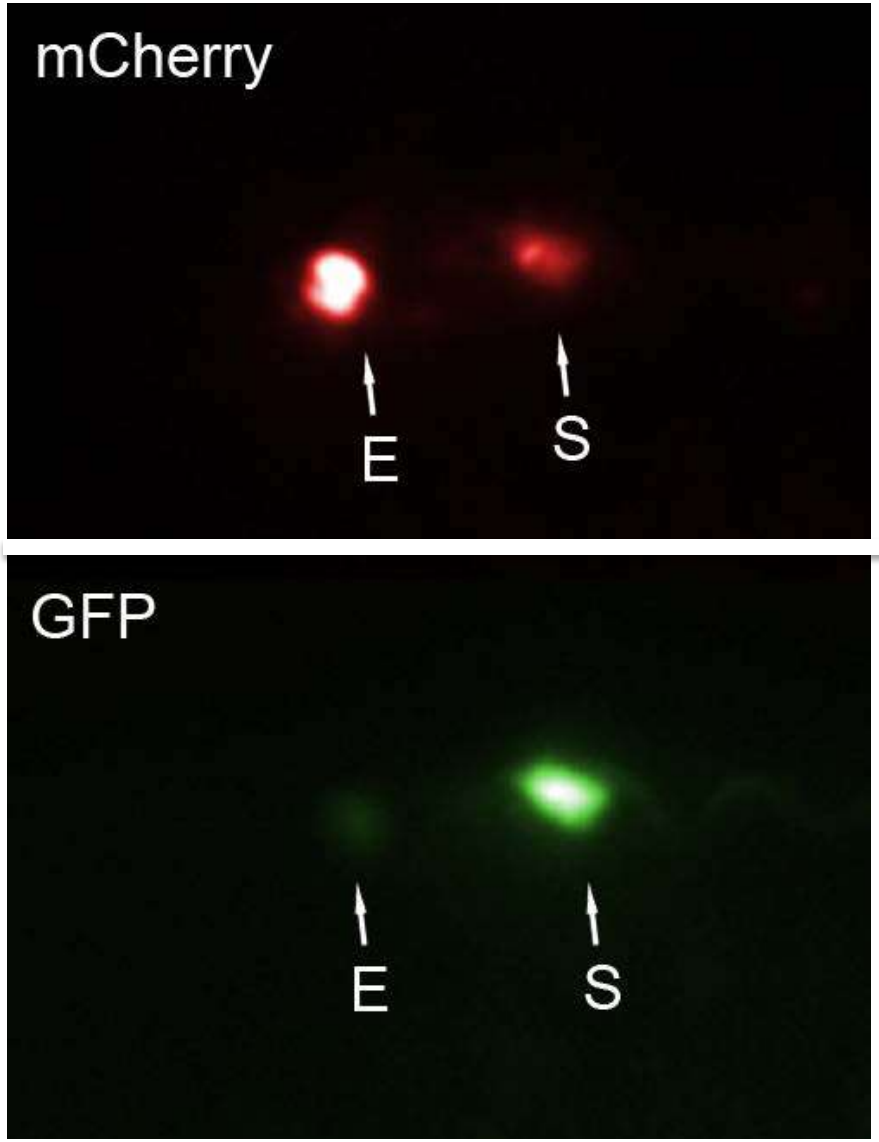


Exophers *preferentially* include aggregates

Double label strain

mCherry (aggregating)

GFP (non-aggregating)

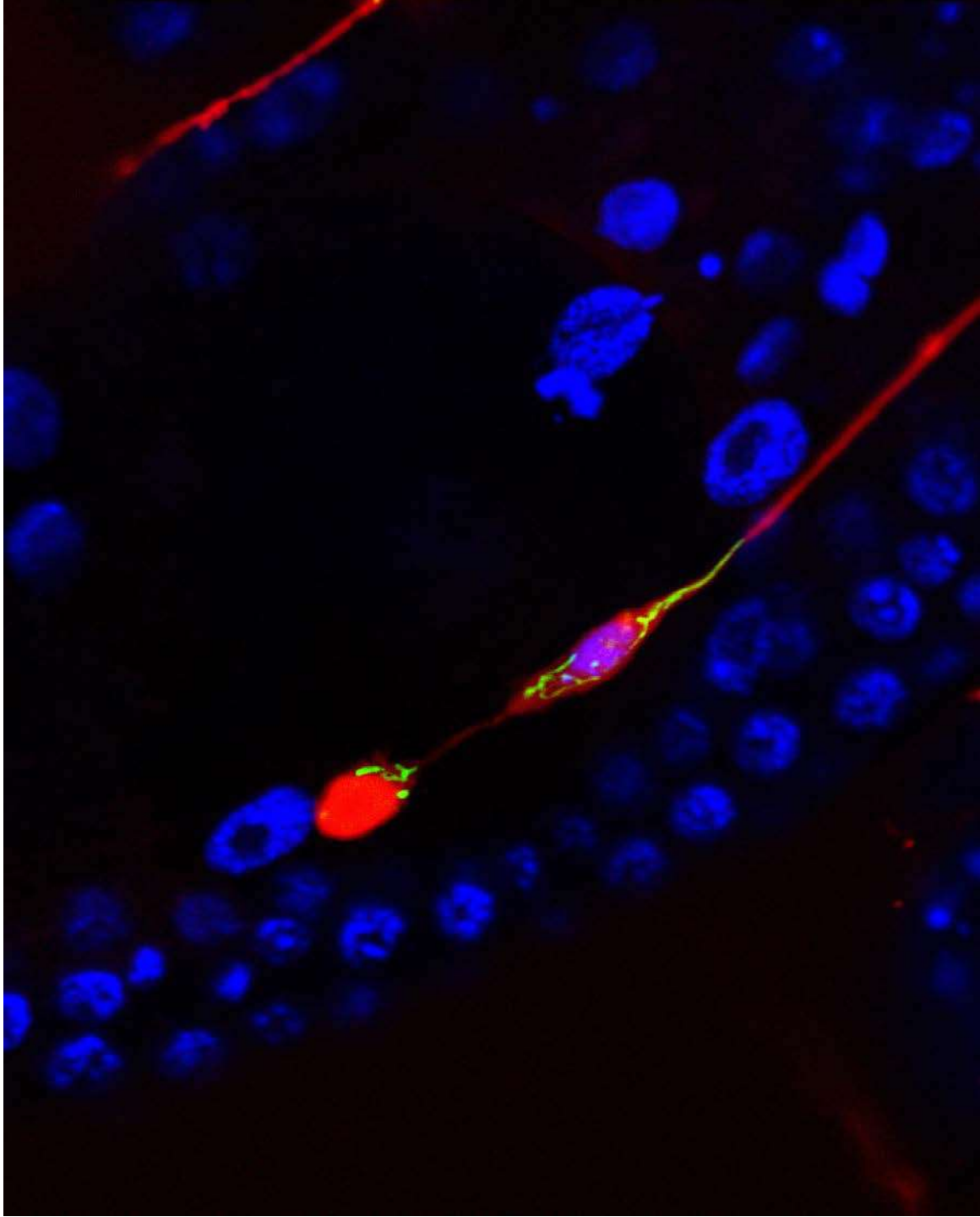


Trash is sorted away from good functional proteins and orga

Multiple types of garbage go into the same trash bag

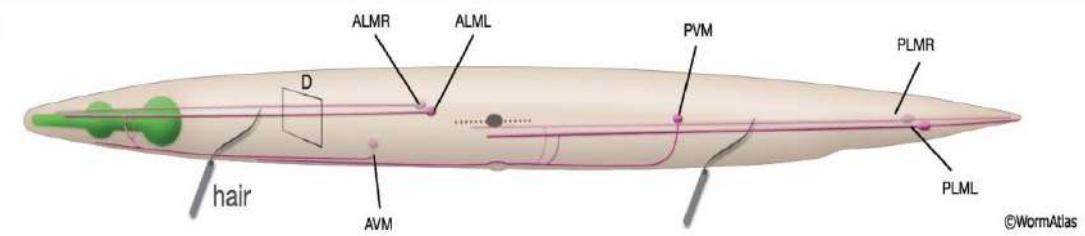
mitochondria

mCherry

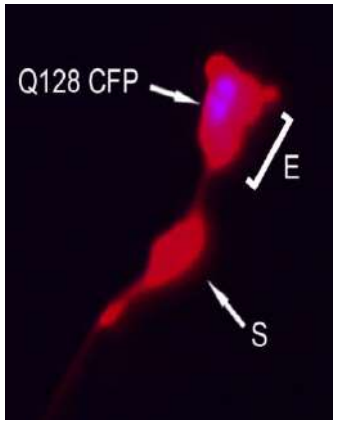


Not clearing out trash can impair functionality

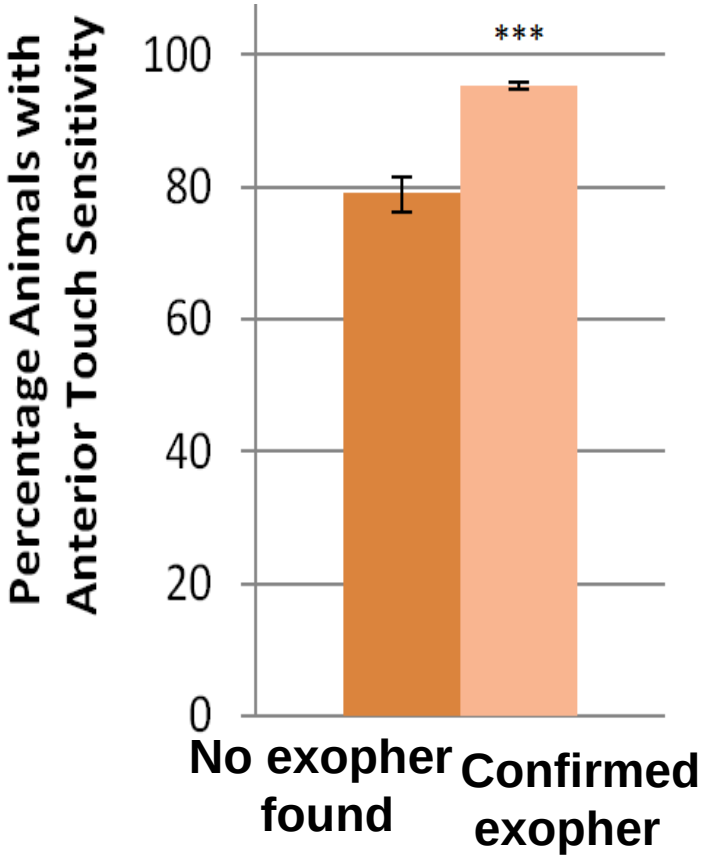
Exophers appear to be neuroprotective to neurons expressing Q128



VS

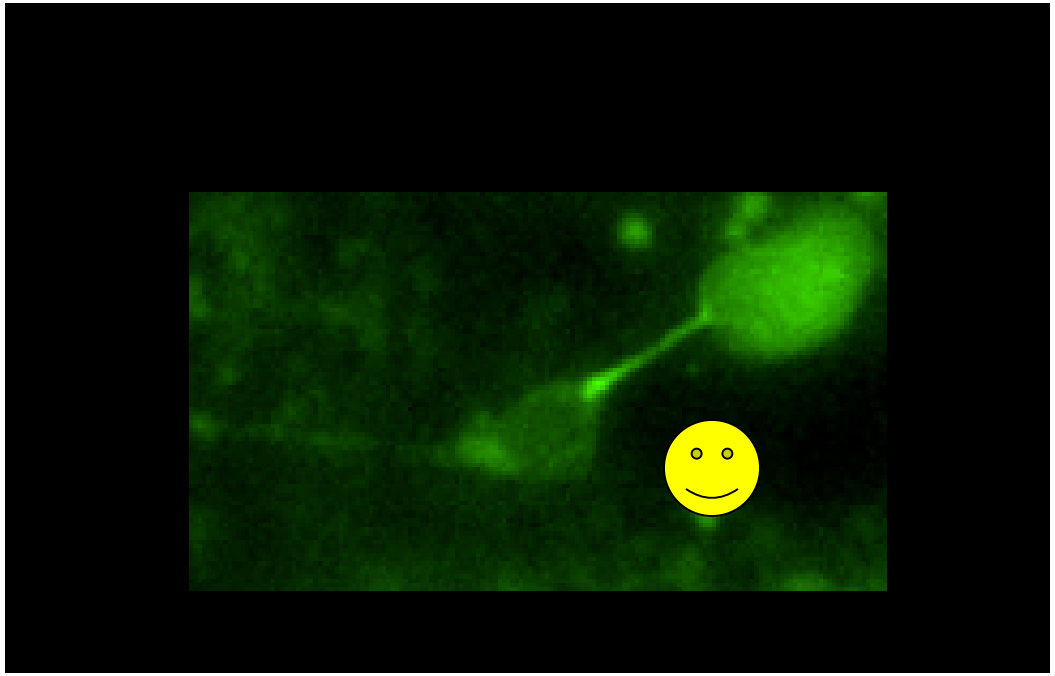


Q128 animals with an early exopher had better maintained touch sensitivity

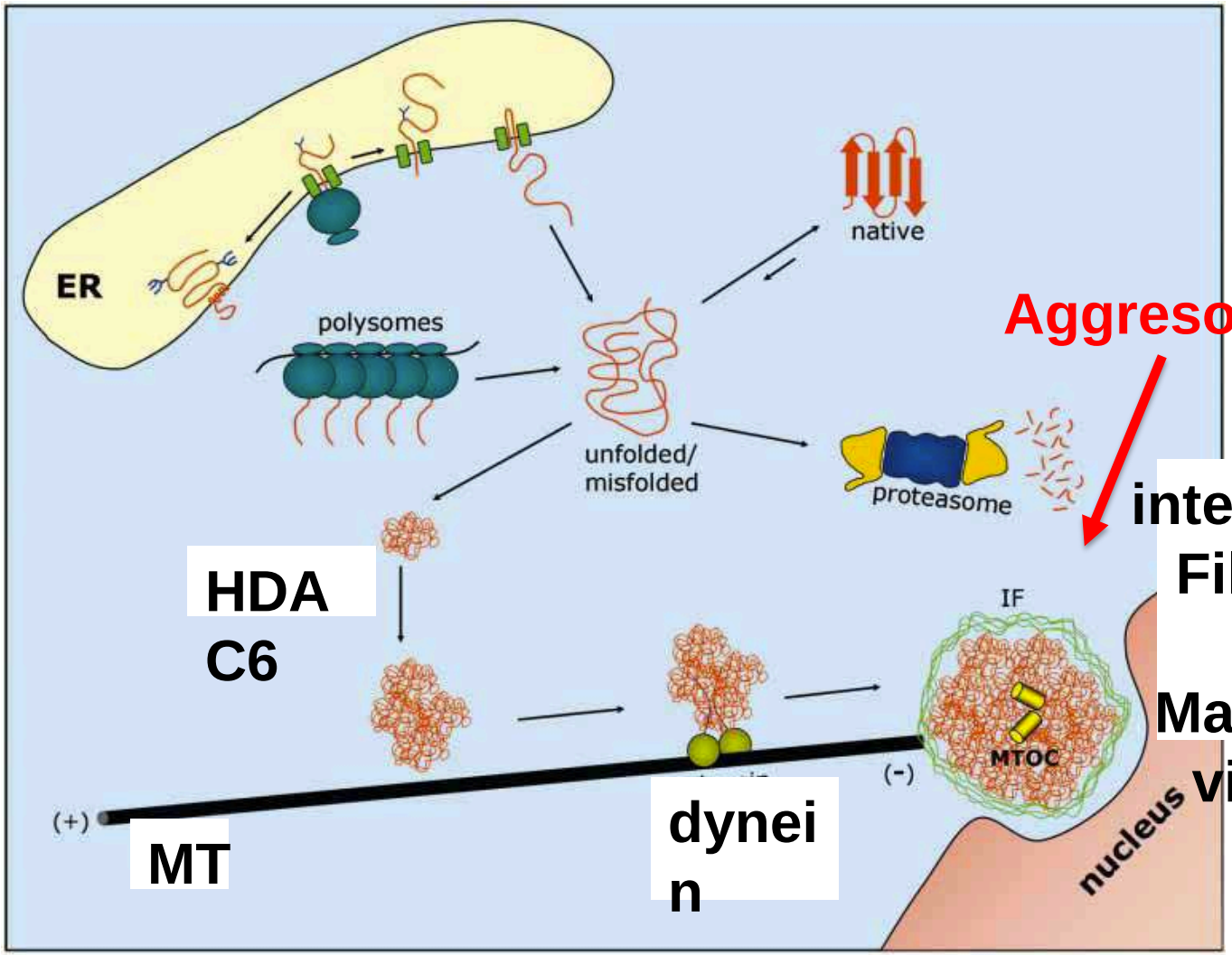


N=100

Exopher production is good for neuronal function



An aggresome-related mechanism may help organize exopher trash



Garcia-Mata, Traffic 2002 3:338

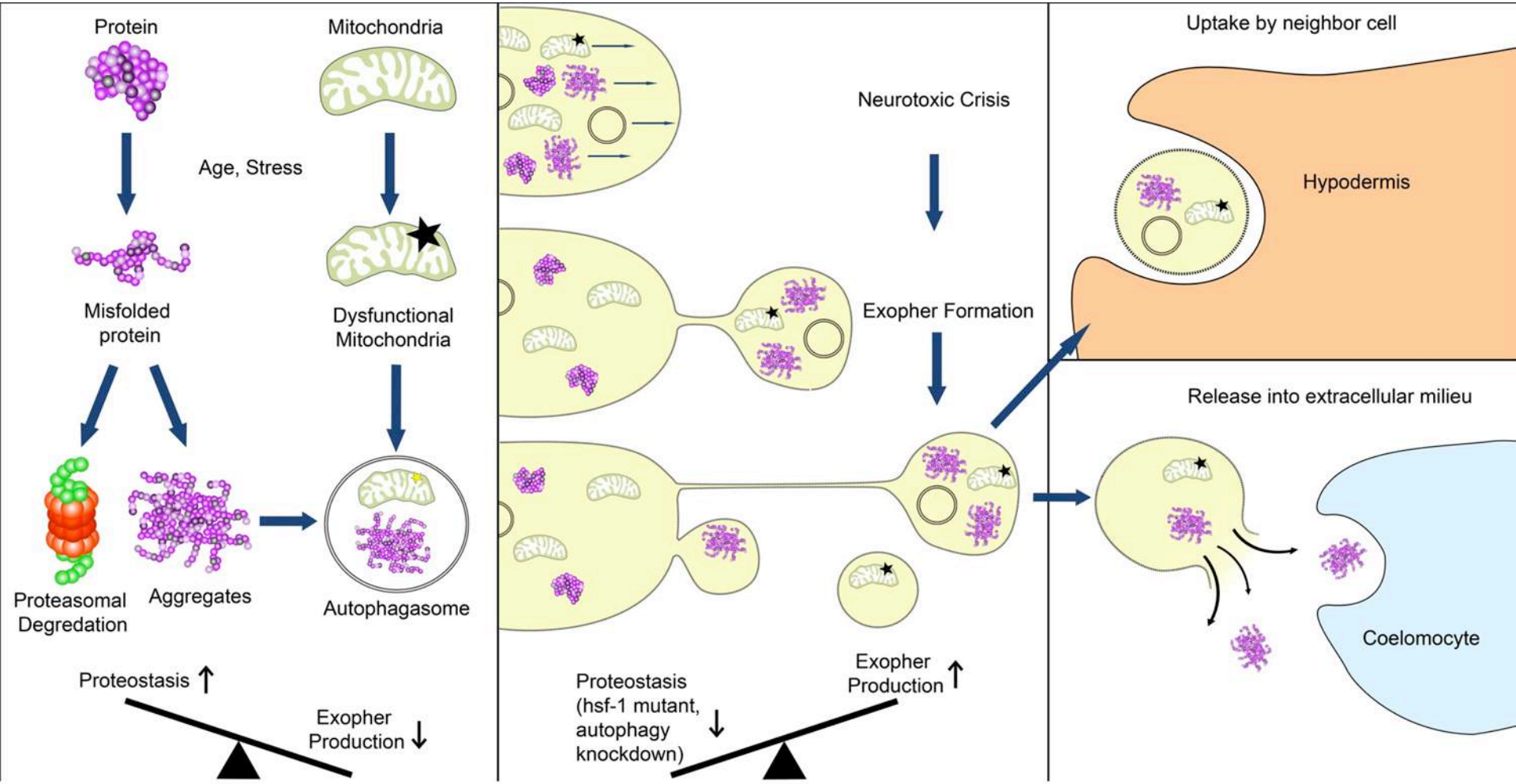
External garbage removal

Neuron

surrounding hypodermis
glia-like

coelomocytes

A C. elegans neuronal extrusion mechanism



proteostasis is critical for neuronal health

inside

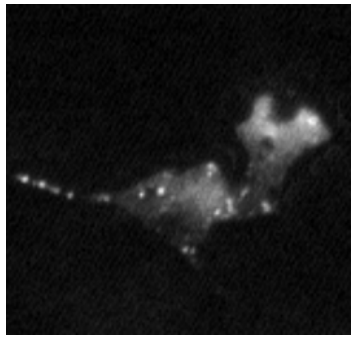
chaperones and folding quality control

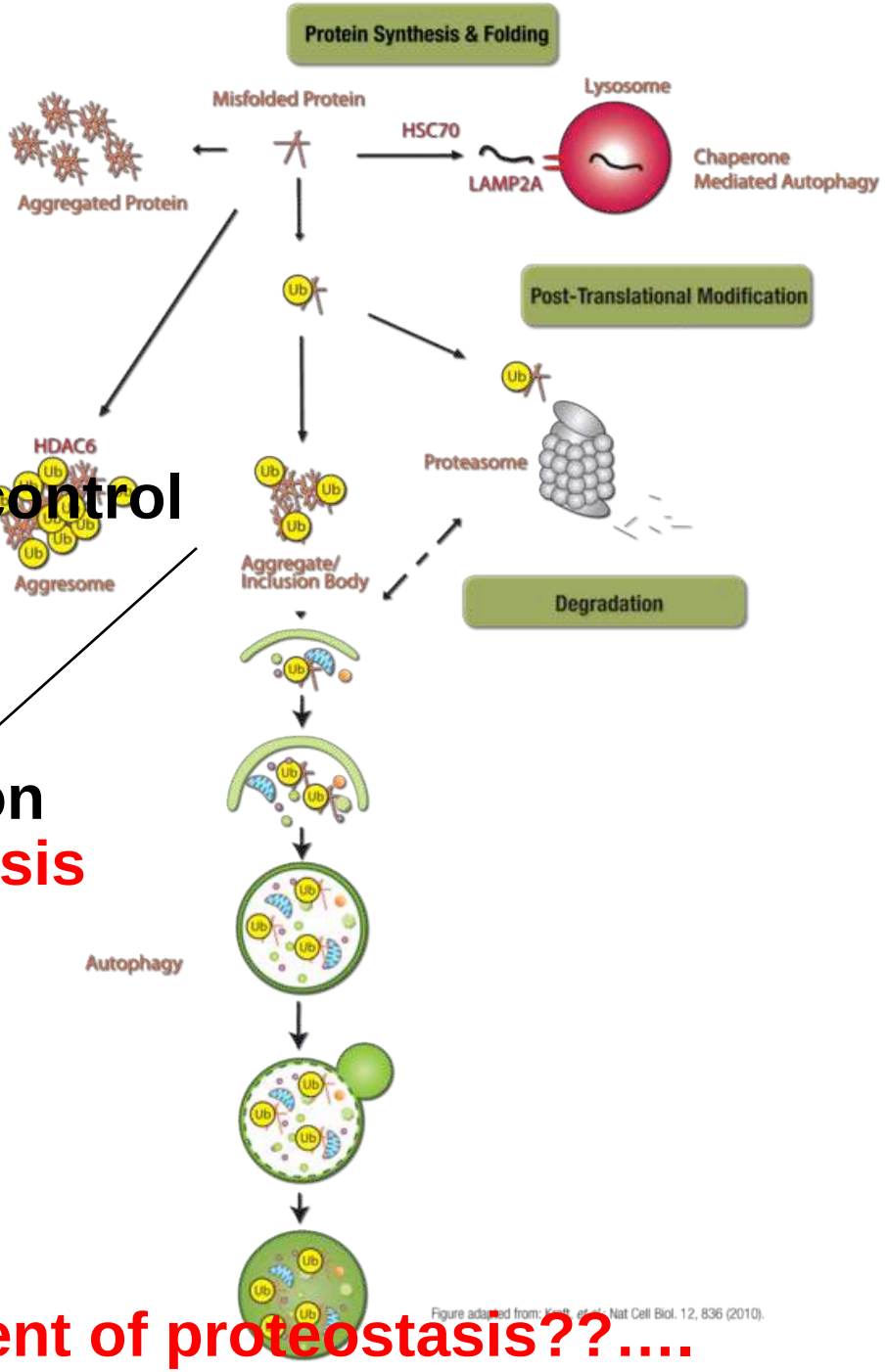
proteasome degradation

autophagy/lysosomal degradation

outside

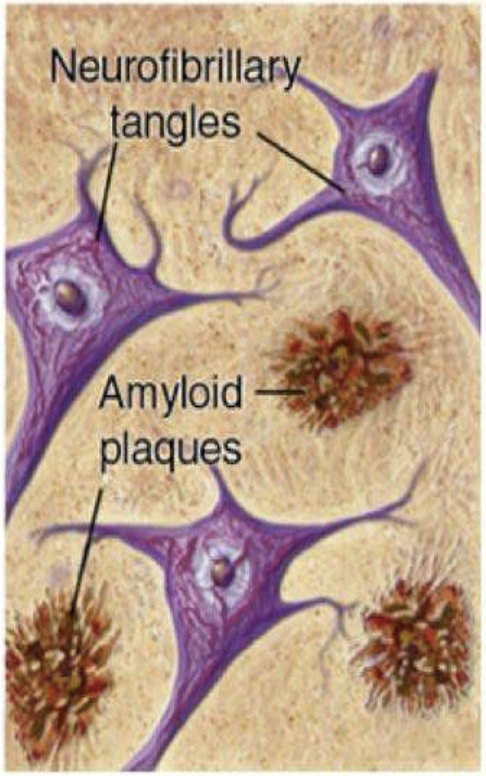
Exopher-genesis



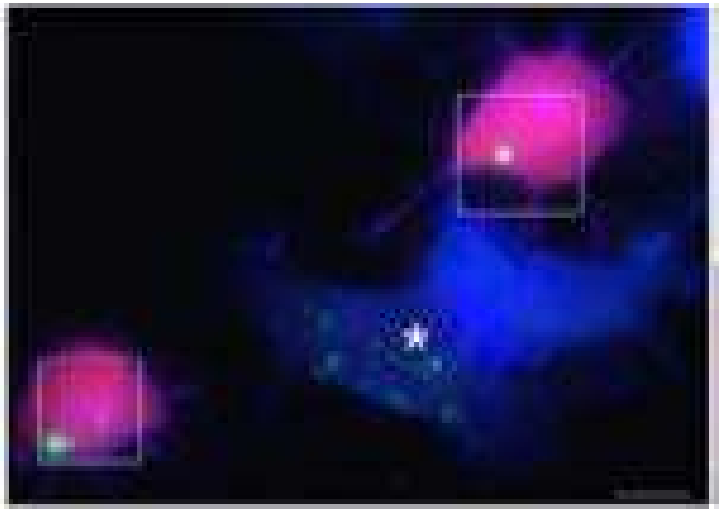


a novel but conserved component of proteostasis??….

Human neurodegenerative disease protein aggregates can be transferred between cells



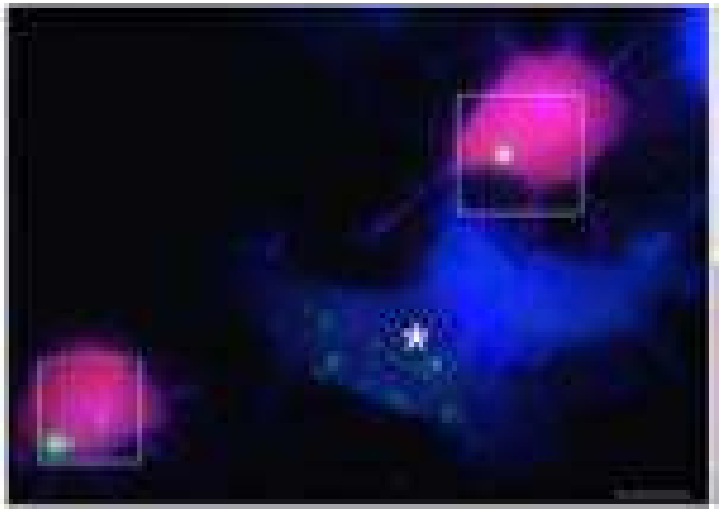
- Alzheimer's
- Parkinson's
- Huntington's
- ALS
- Prion disease

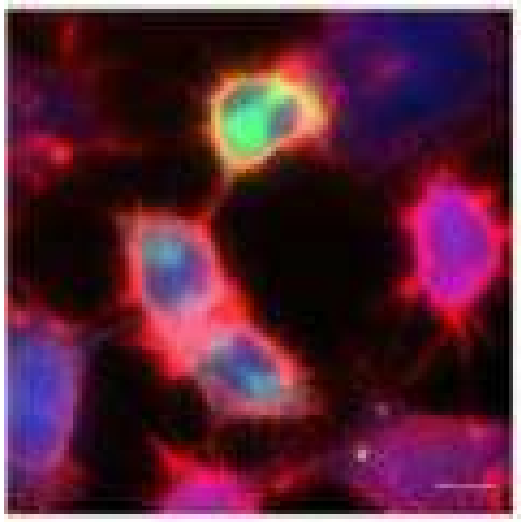


Costansa et al., J Cell Sci. 2013 126:3678-85.

Novel ideas about disease pathogenesis, new target for therapy, from the worm…

A hot topic in neurodegenerative disease is the spread of disease proteins/aggregates between neurons via some extrusion mechanism,





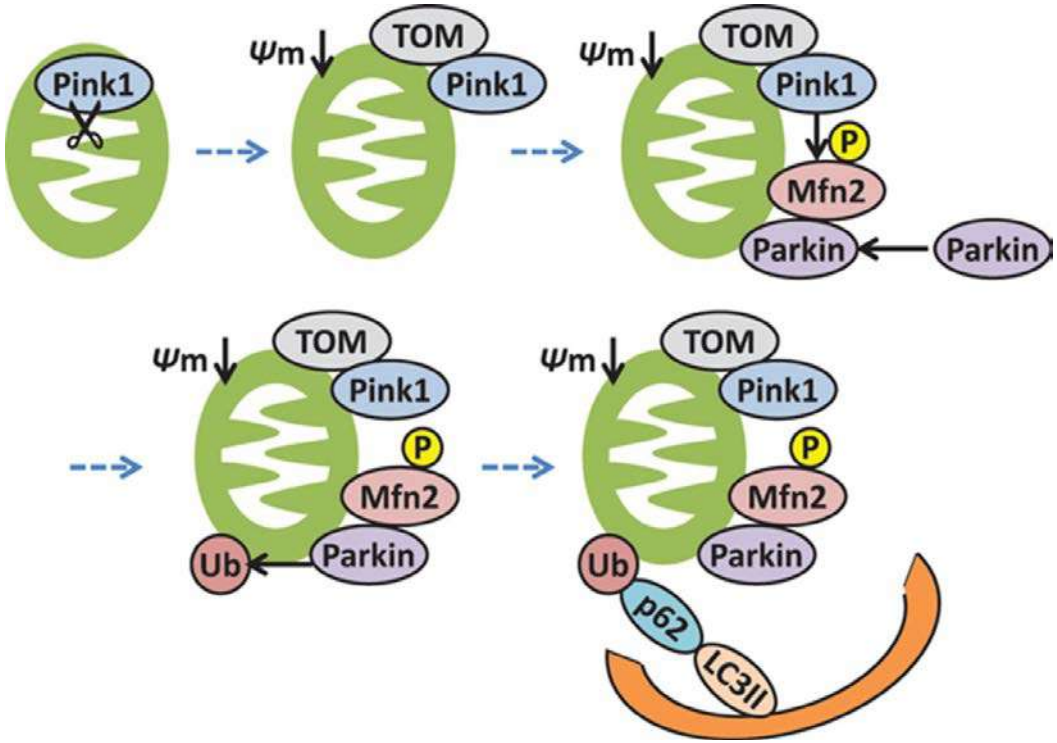
Costansa et al., J Cell Sci. 2013 126:3678-85.

postulated to contribute to disease progression and spread

Does exopher biology represent the homologous process/mechanism?

mitophagy is critical for neuronal health

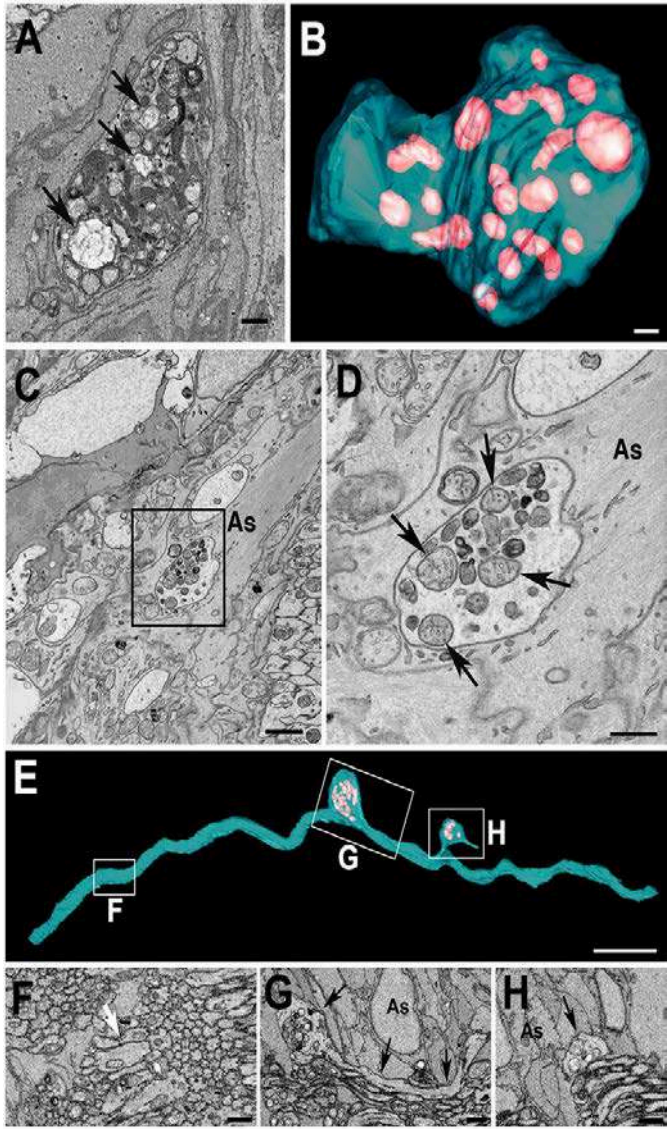
inside



outside

We postulate a novel but conserved component of mito-stasis

Mouse neurons can transfer mitochondria



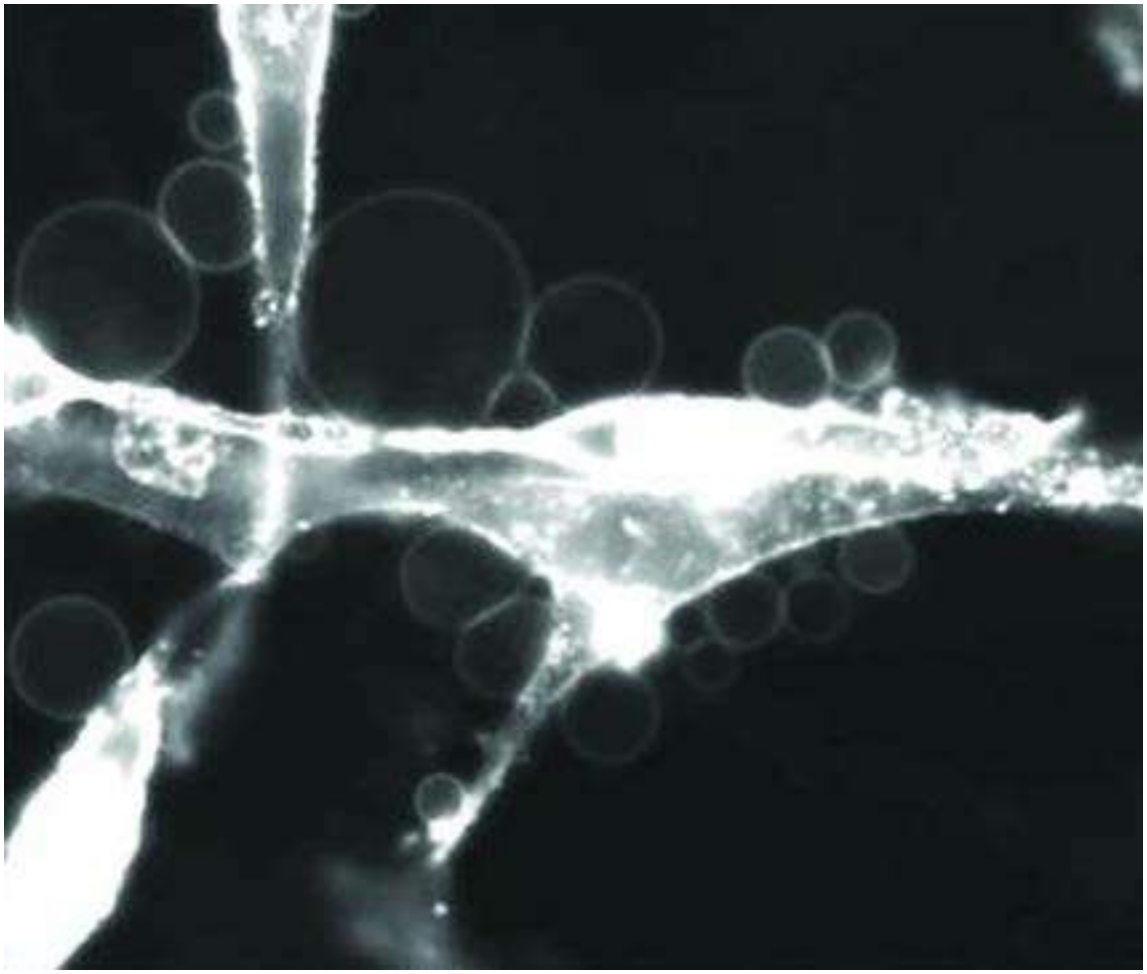
-retinal ganglion cell mitos to astrocyte neighbors

-also in superficial layers of the cerebral cortex

Davis, C.H., et al. Transcellular degra
axonal mitochondria. (Marsh-Armstr
Proc Natl Acad Sci U S A 111, 9633-9

are exopher-like processes involved?

Oncosomes: large vesicles from cultured tumor cells

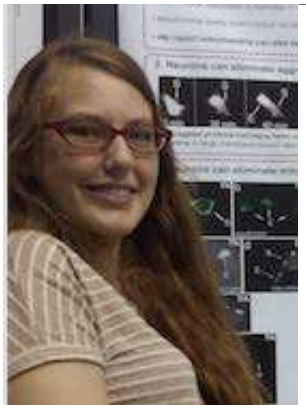


Transfer of materials….but maybe detox mechanism..

Thanks to the exopher team

Ilija Melentijevic

Meghan Arnold



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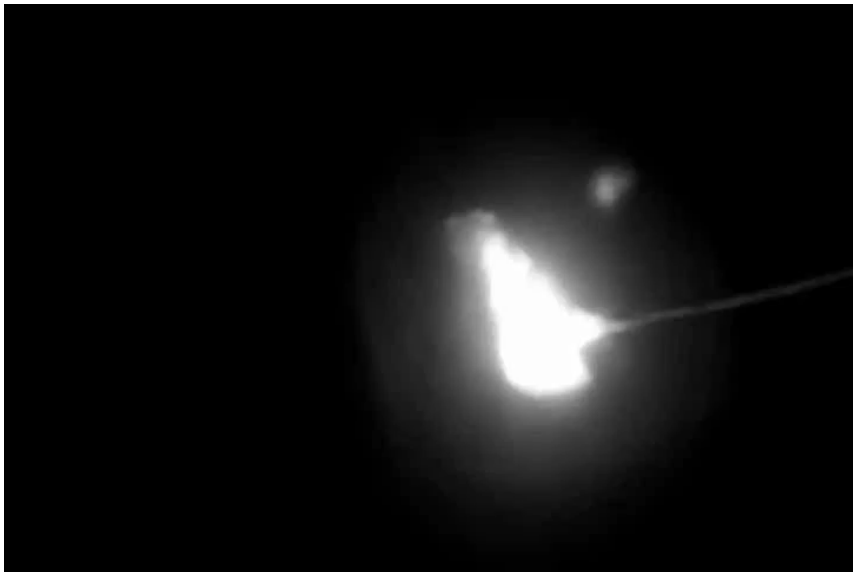
Barth Grant

Funding

National Institute of Neurological Disorders and Stroke

NIH National Institute on Aging



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