



Studying ageing as a two-phase process: the biology of dying



Michaël Rera

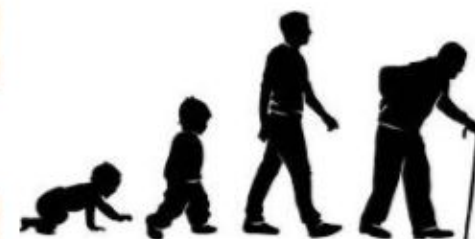
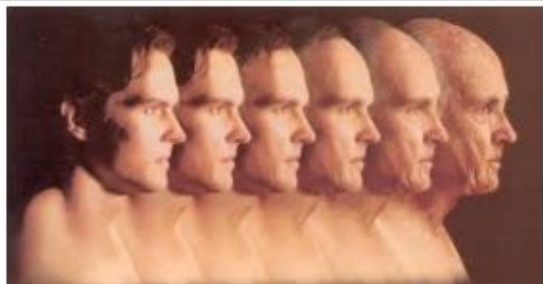
Biologie Fonctionnelle et Adaptative / CNRS



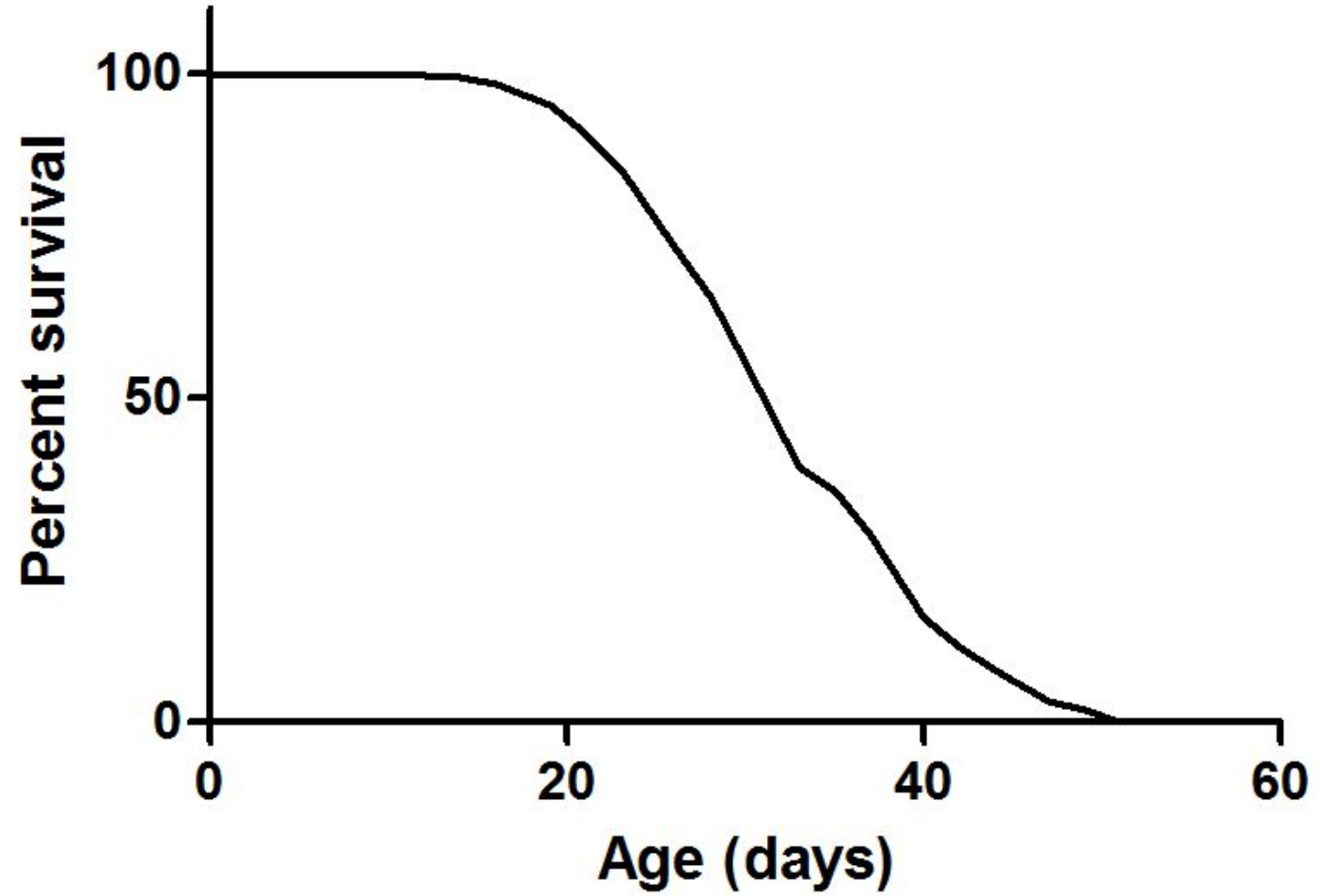
How do we define ageing?



Ageing is a gradual decline



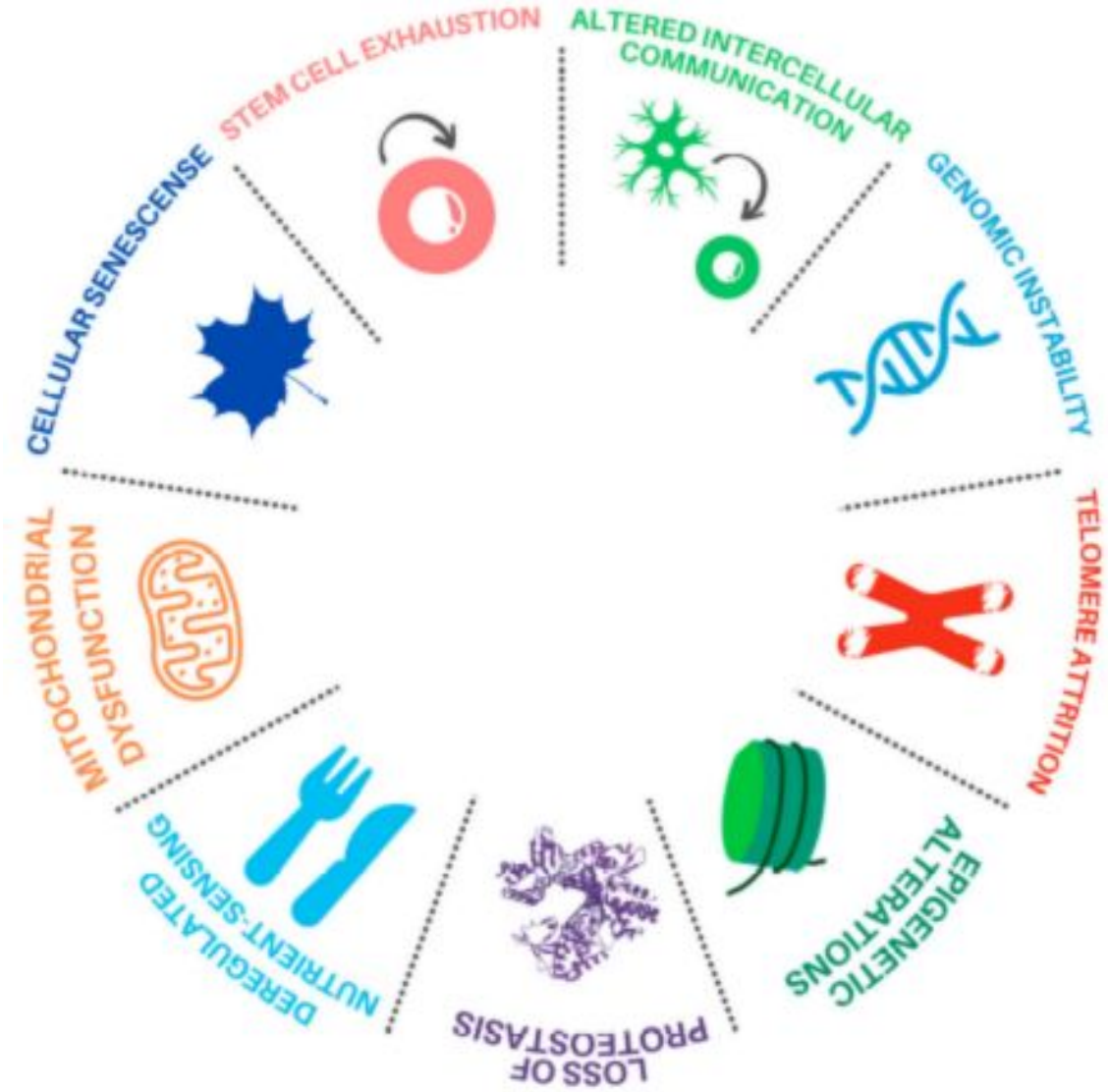
Ageing is defined as time since birth



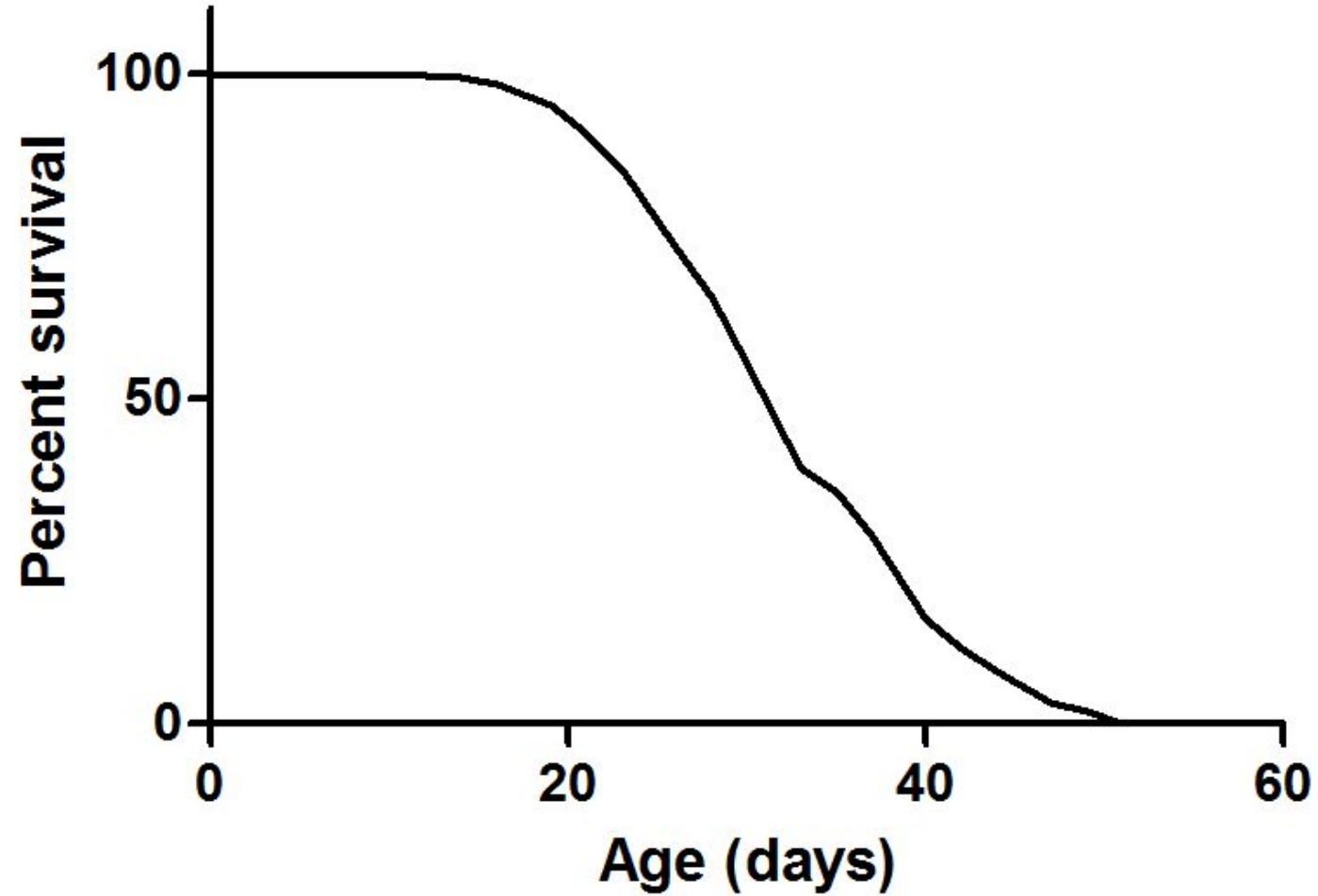
Ageing: a definition

“ ..the time-dependent functional decline that affects most living organisms [...], leading to impaired function and increased vulnerability to death.”

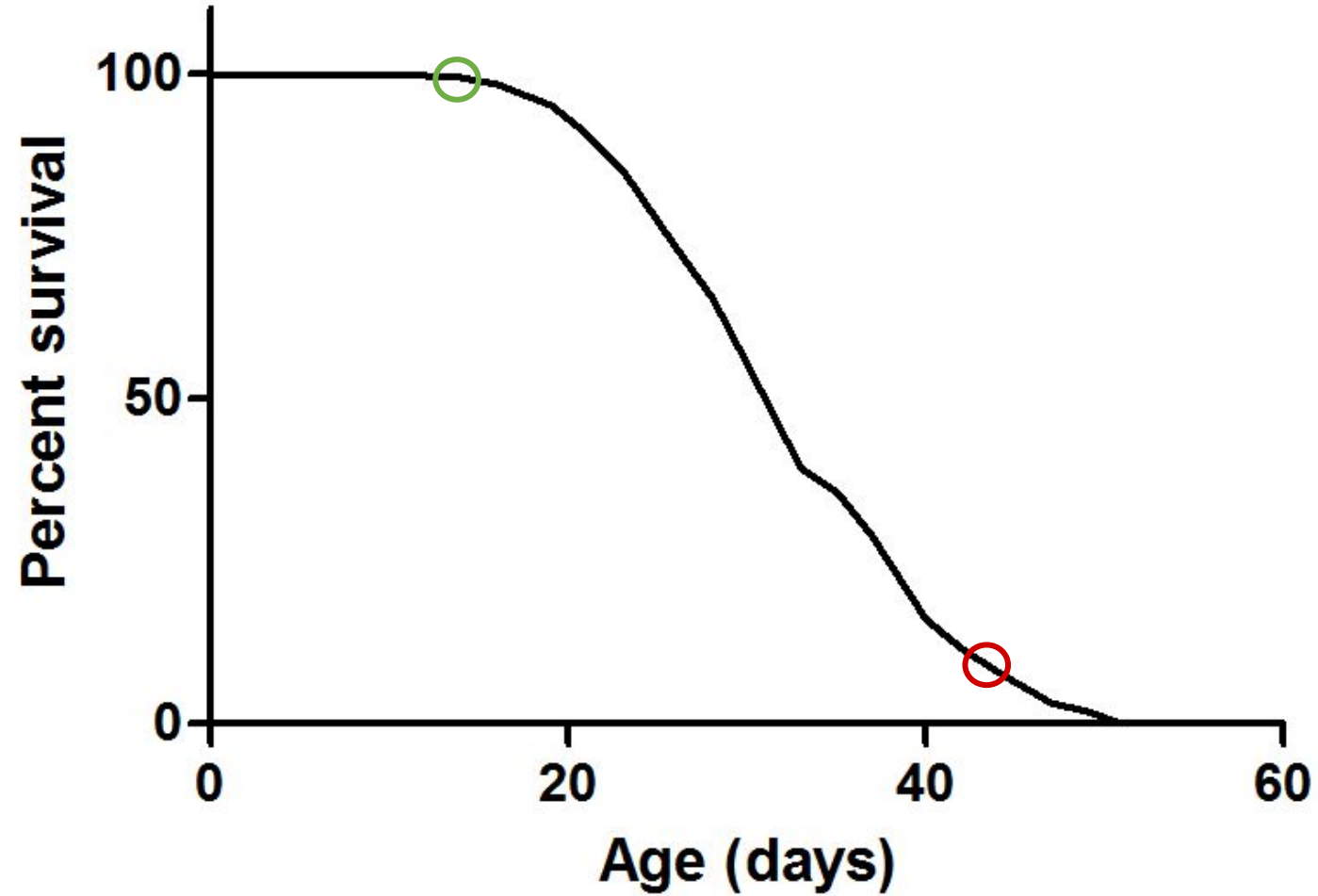
López-Otín et al, 2013



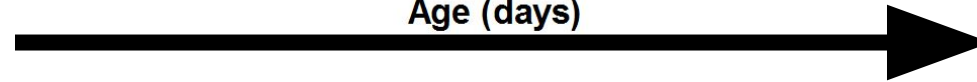
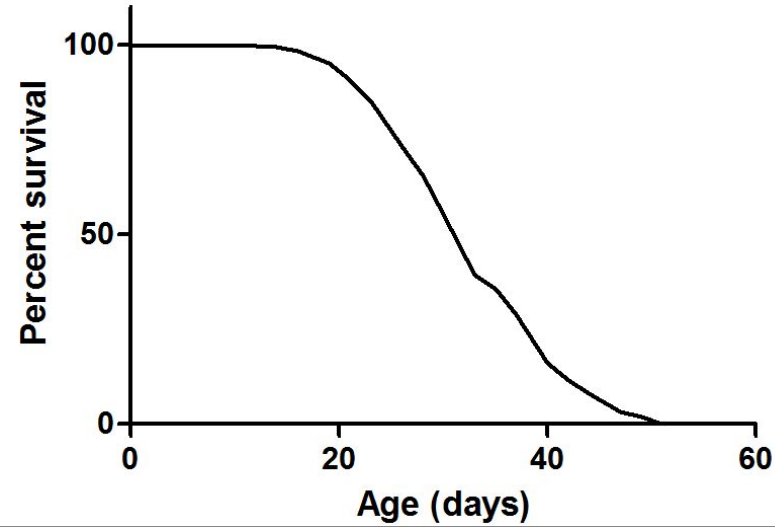
Classical approach for studying ageing



Classical approach for studying ageing

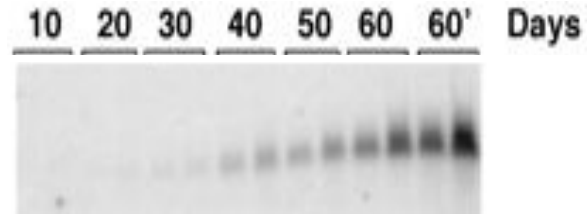


Hallmarks of ageing in a continuous ageing process



Death

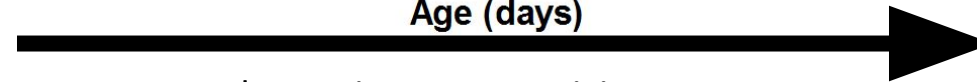
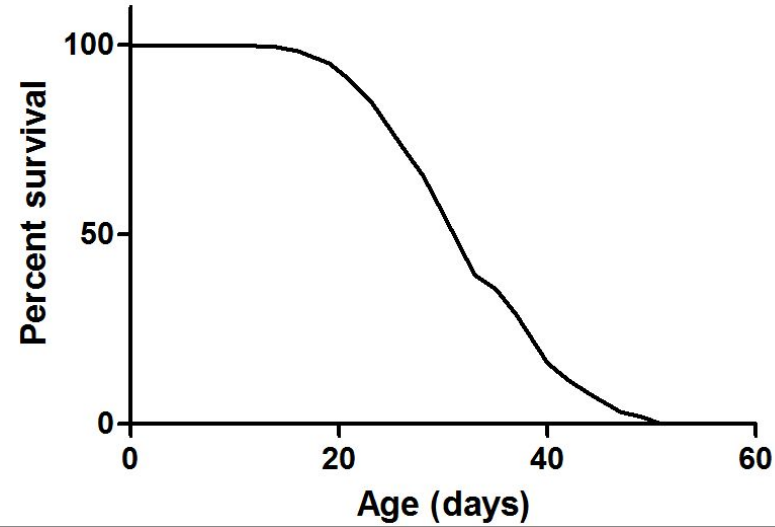
Increasing systemic inflammation



adapted from Landis et al., 2004

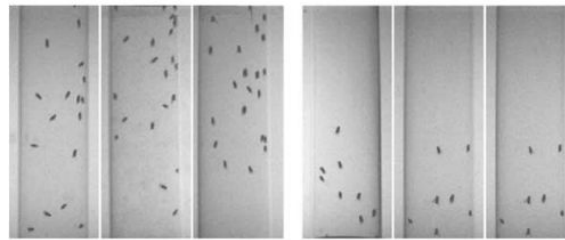
- Continuous changes

Hallmarks of ageing in a continuous ageing process



Death

decreasing motor activity



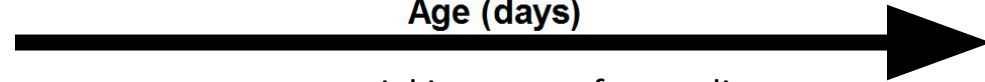
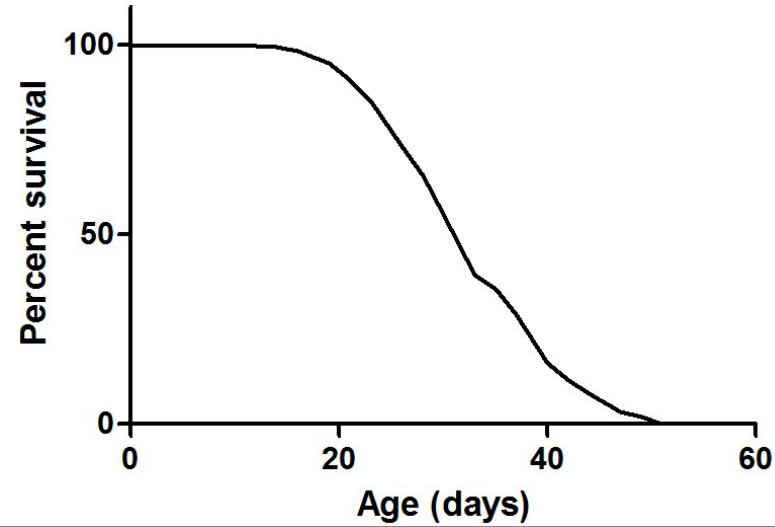
1-week-old males

4-week-old males

(Gargano et al., 2005)

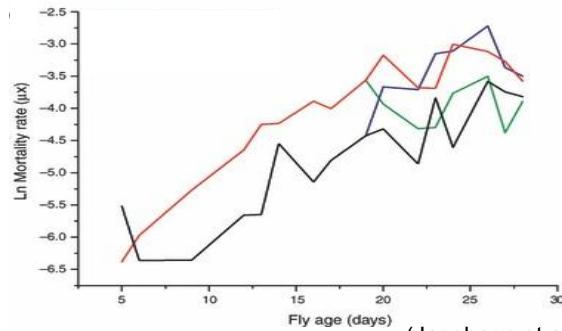
- Continuous changes

Hallmarks of ageing in a continuous ageing process



Death

exponential increase of mortality rates



(Jacobson et al., 2010)

- Continuous changes



Defining ageing as a time to death

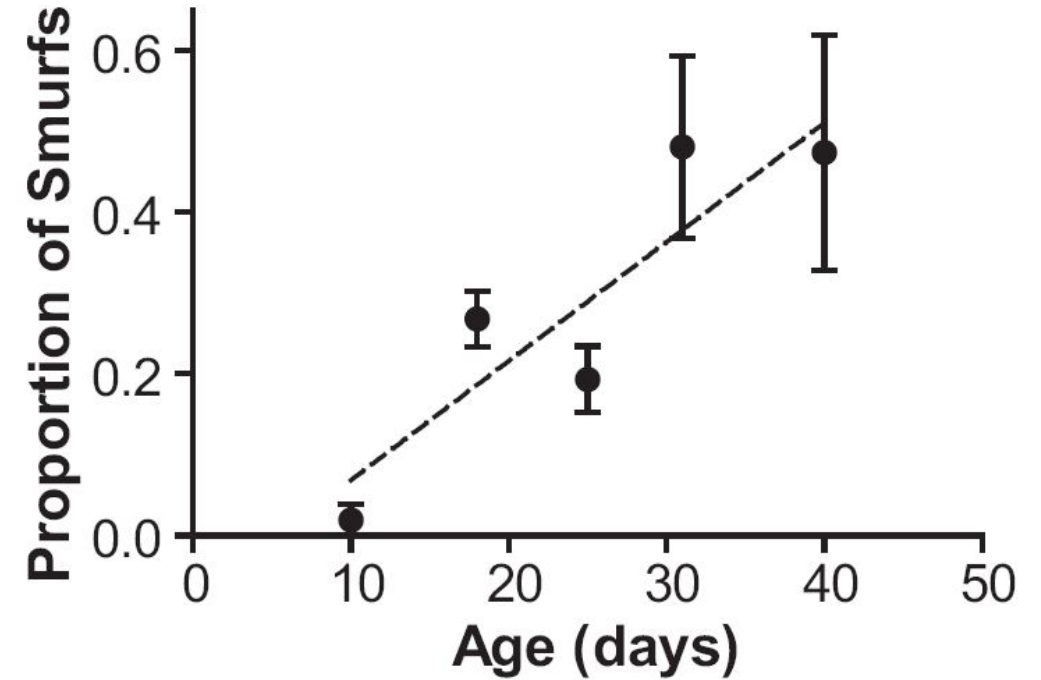
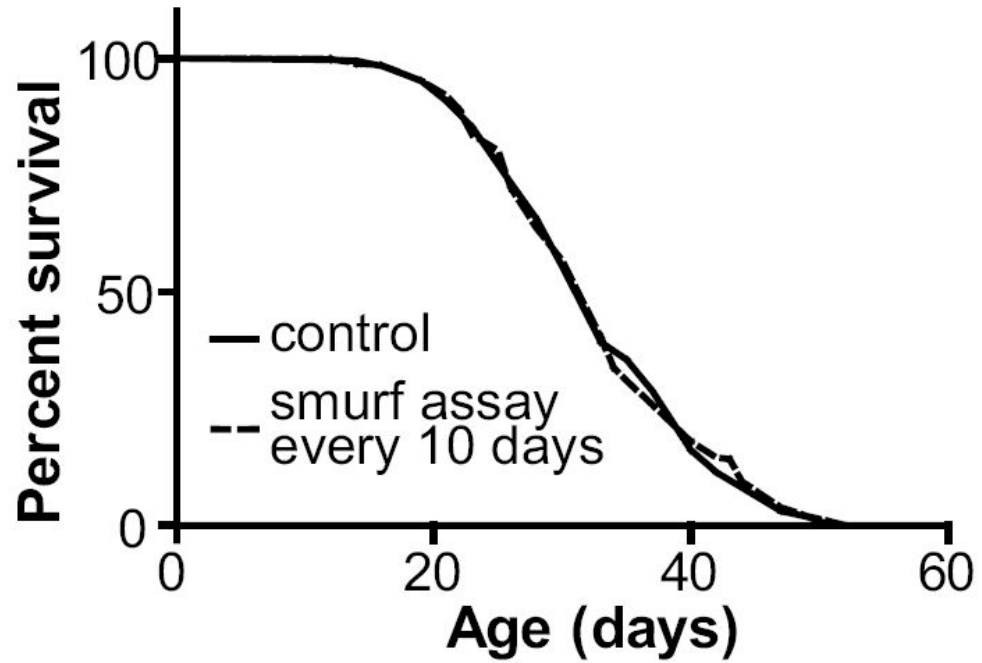


A Simple Assay To Identify Individuals About To Die Of Natural Causes

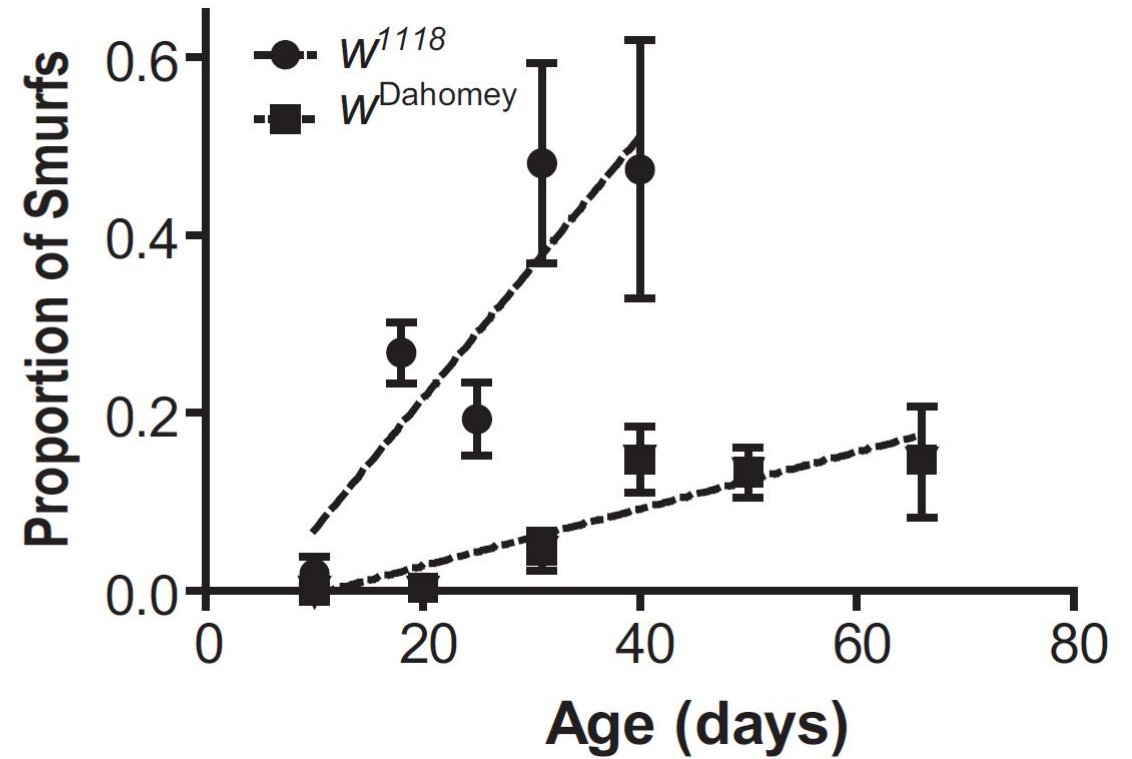
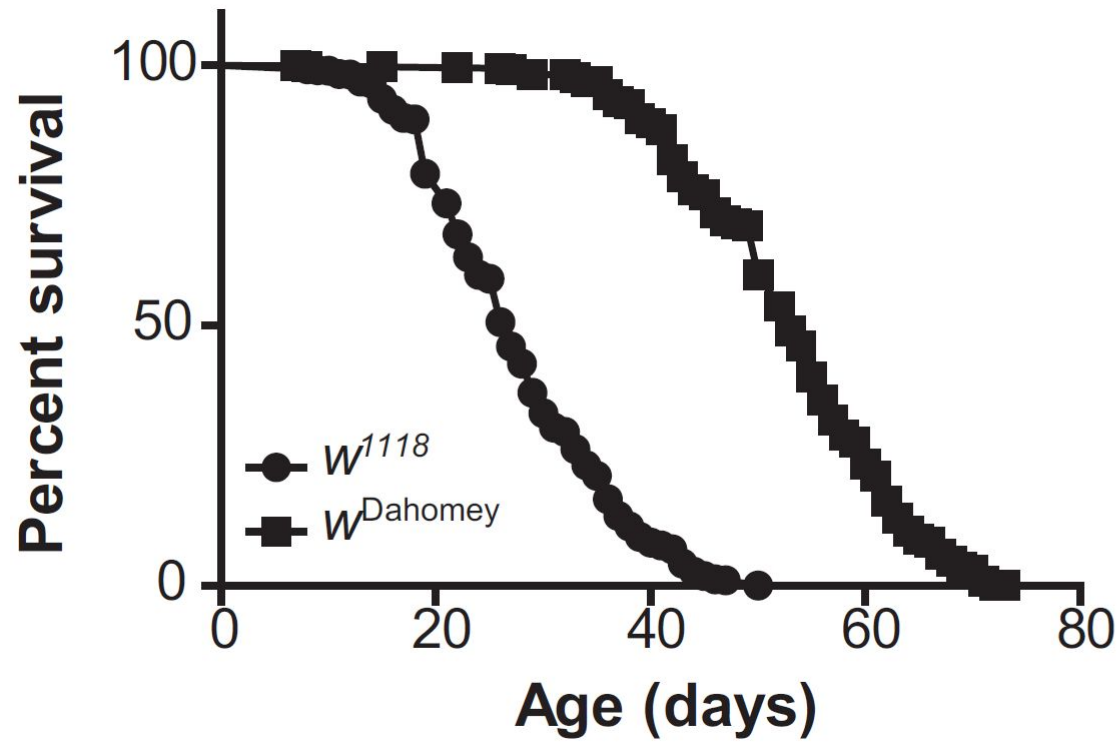


- *in vivo*
- measurement of intestinal permeability
- non-toxic food dye
- non-absorbed food dye
- 'Smurf' phenotype

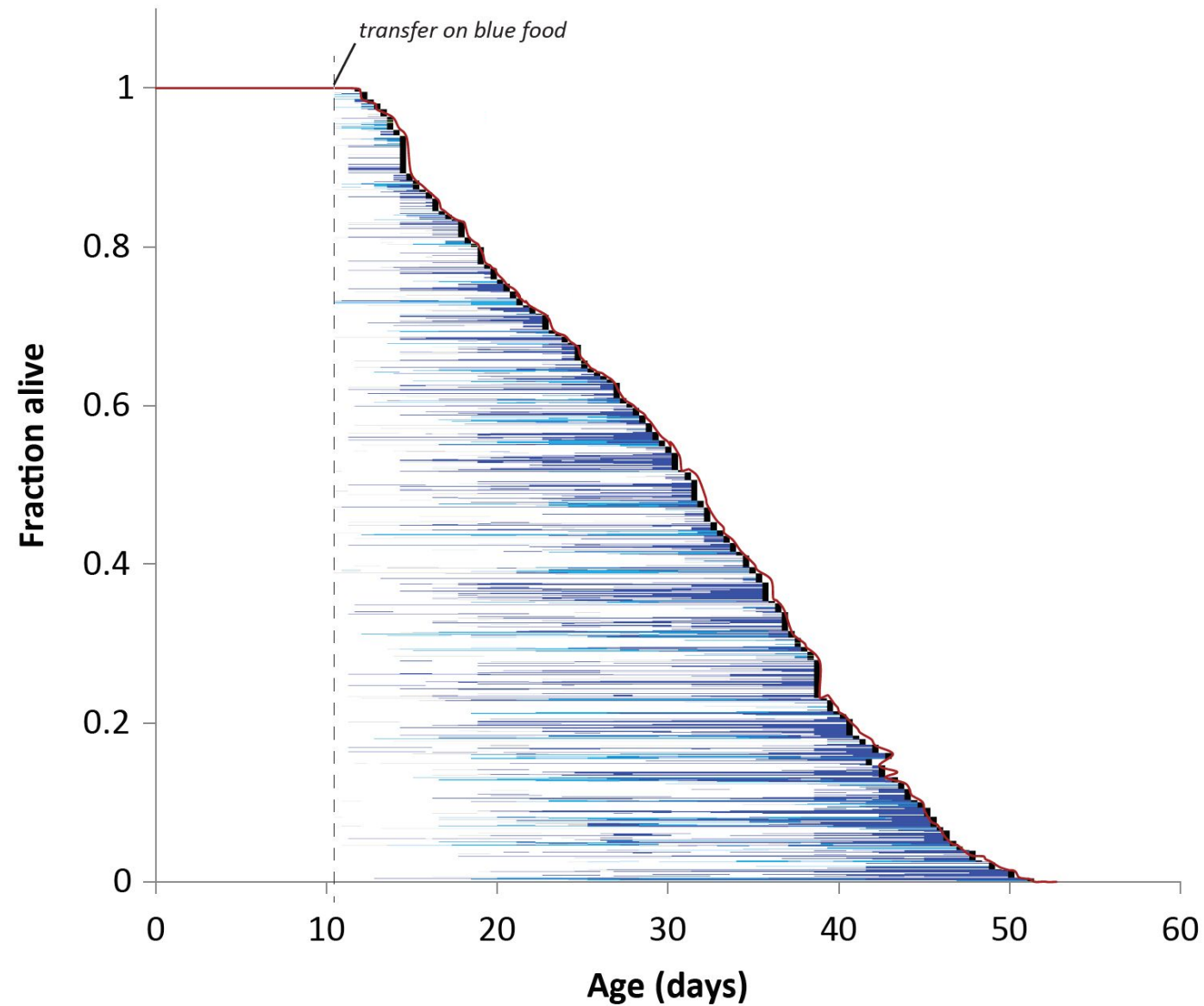
Smurfness is an age-dependent phenotype



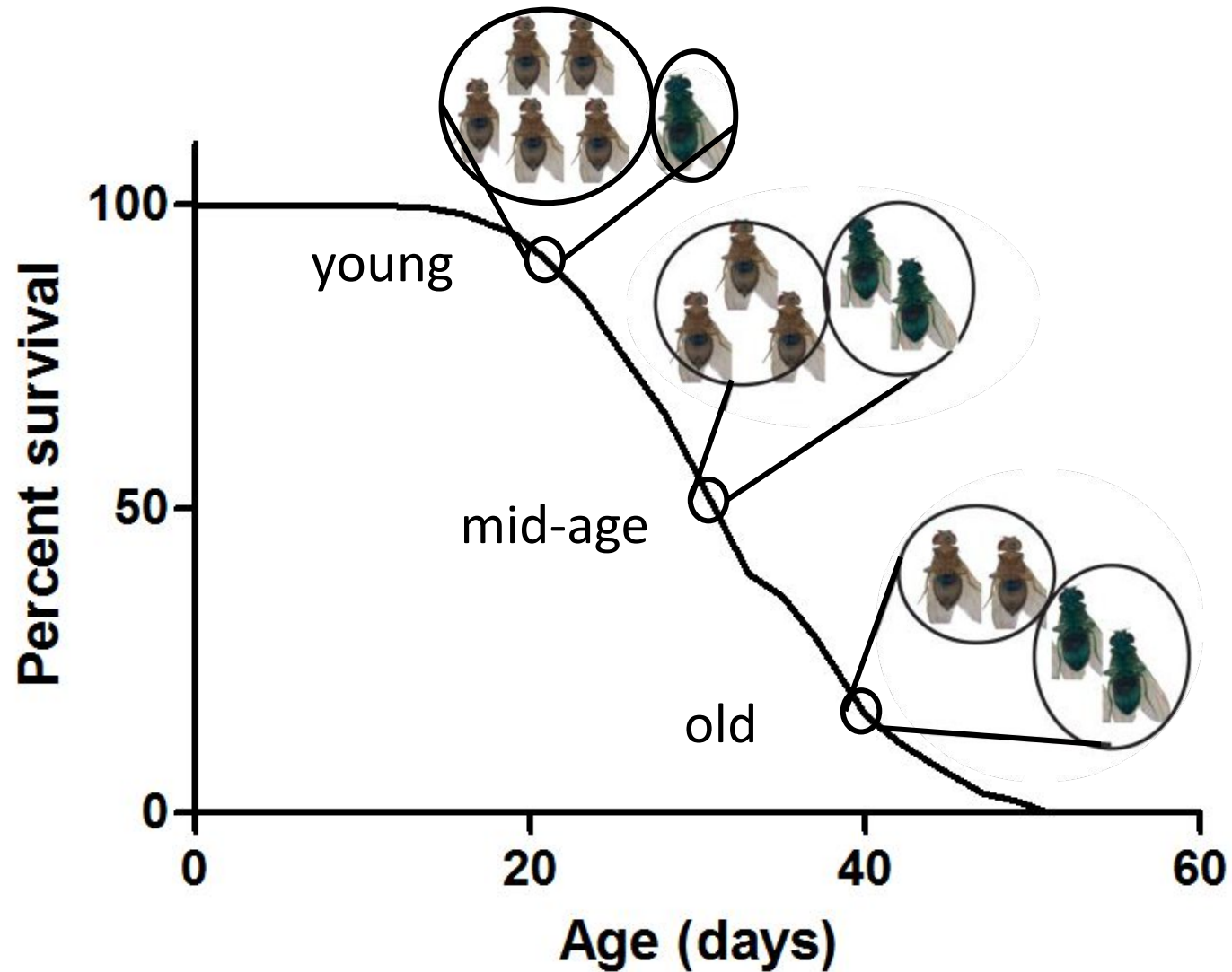
Smurfness is a « physiological age »-dependent phenotype



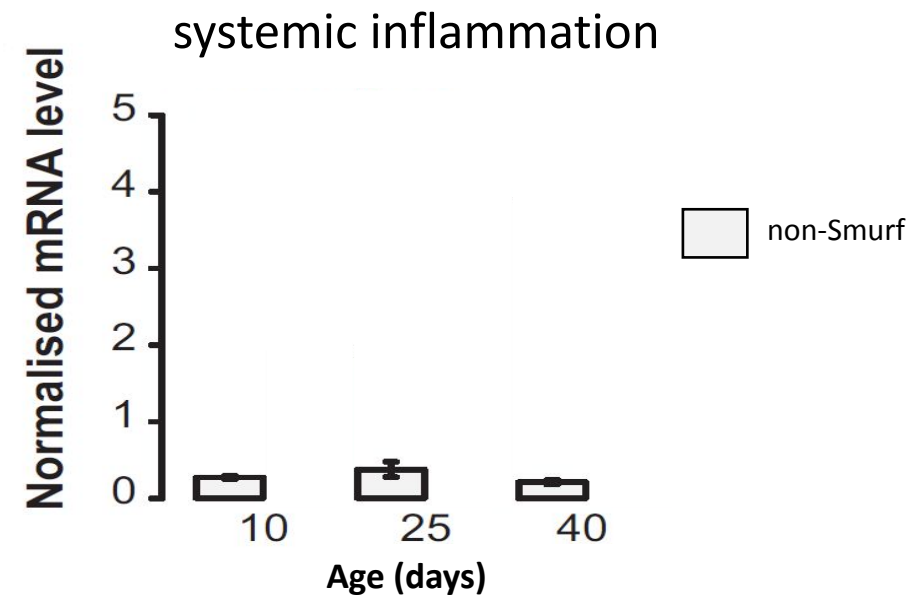
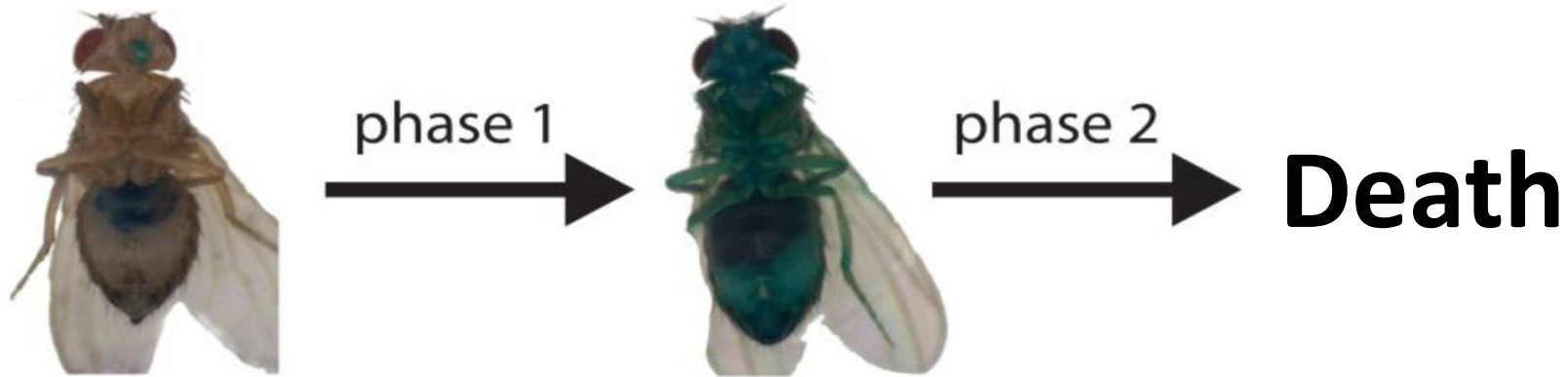
Every individuals turns Smurf prior to death



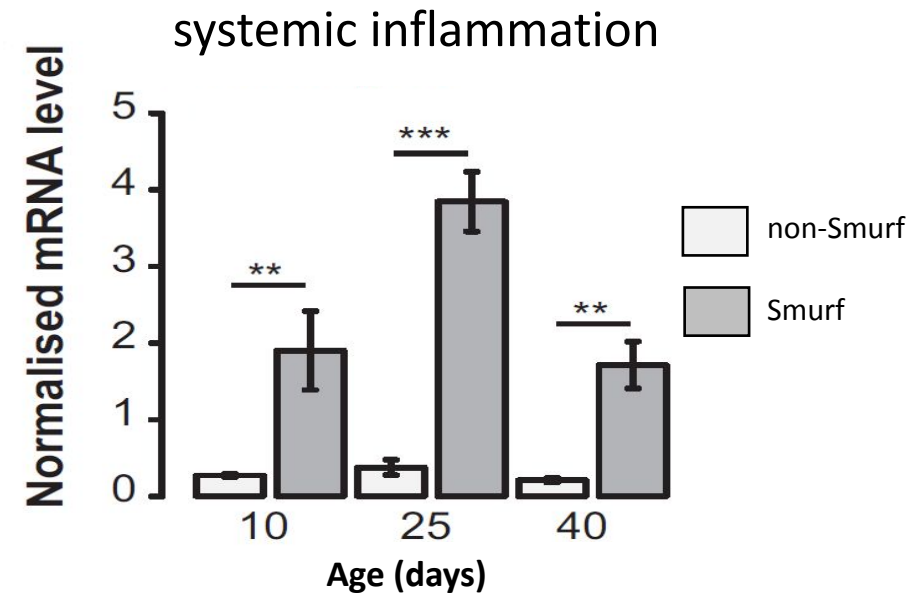
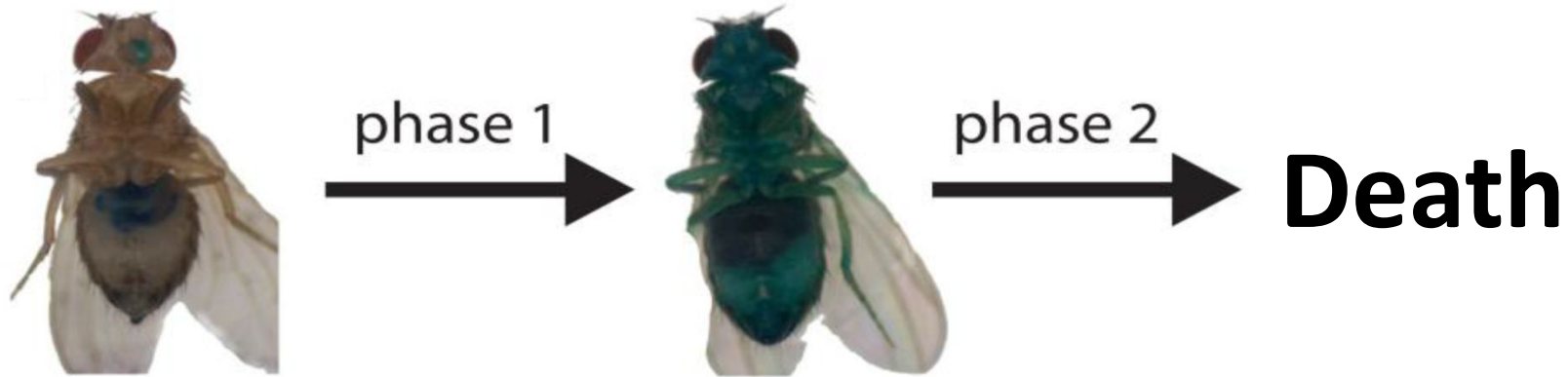
The 2-Phase Model Of Ageing



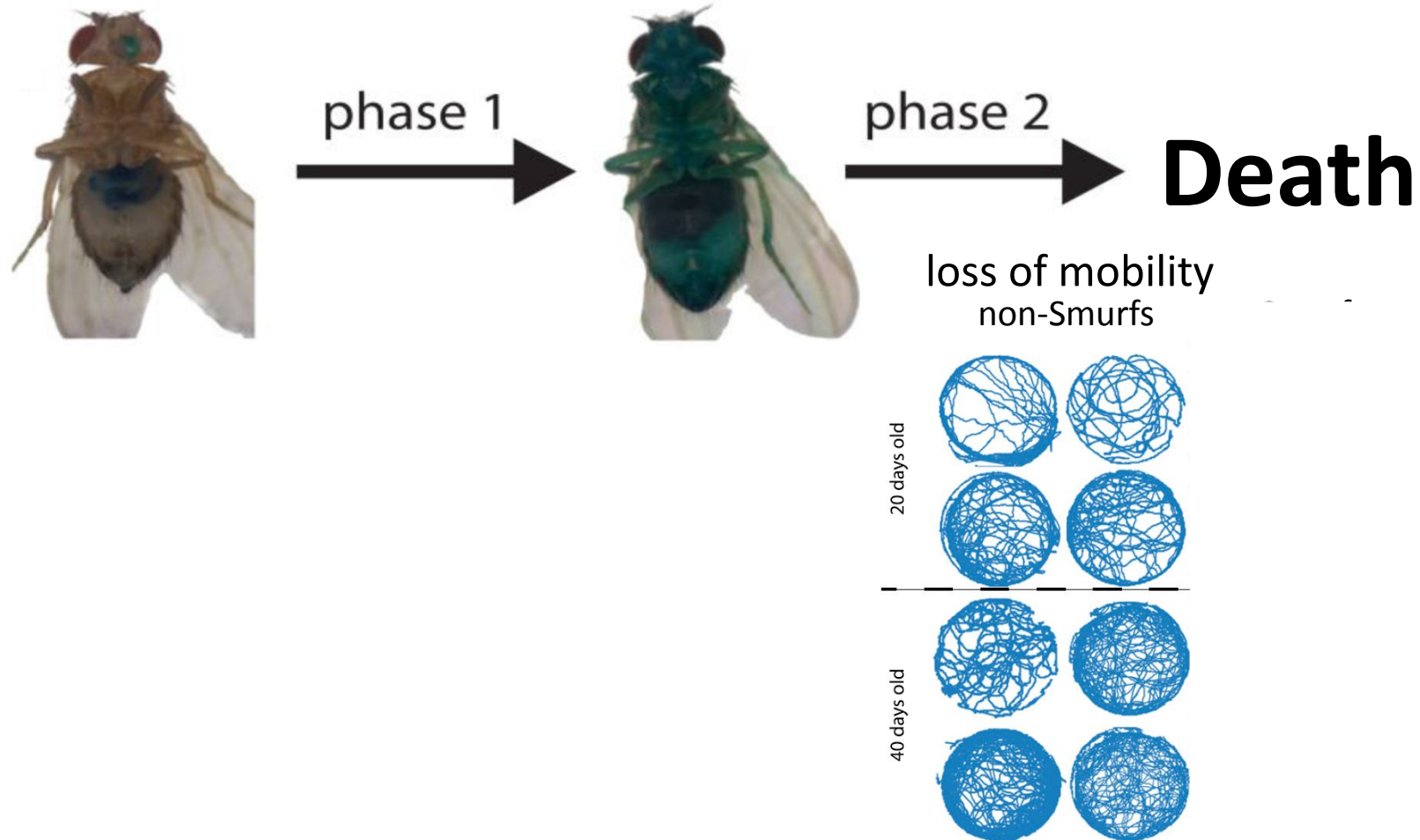
Hallmarks of ageing in the 2-Phase Model



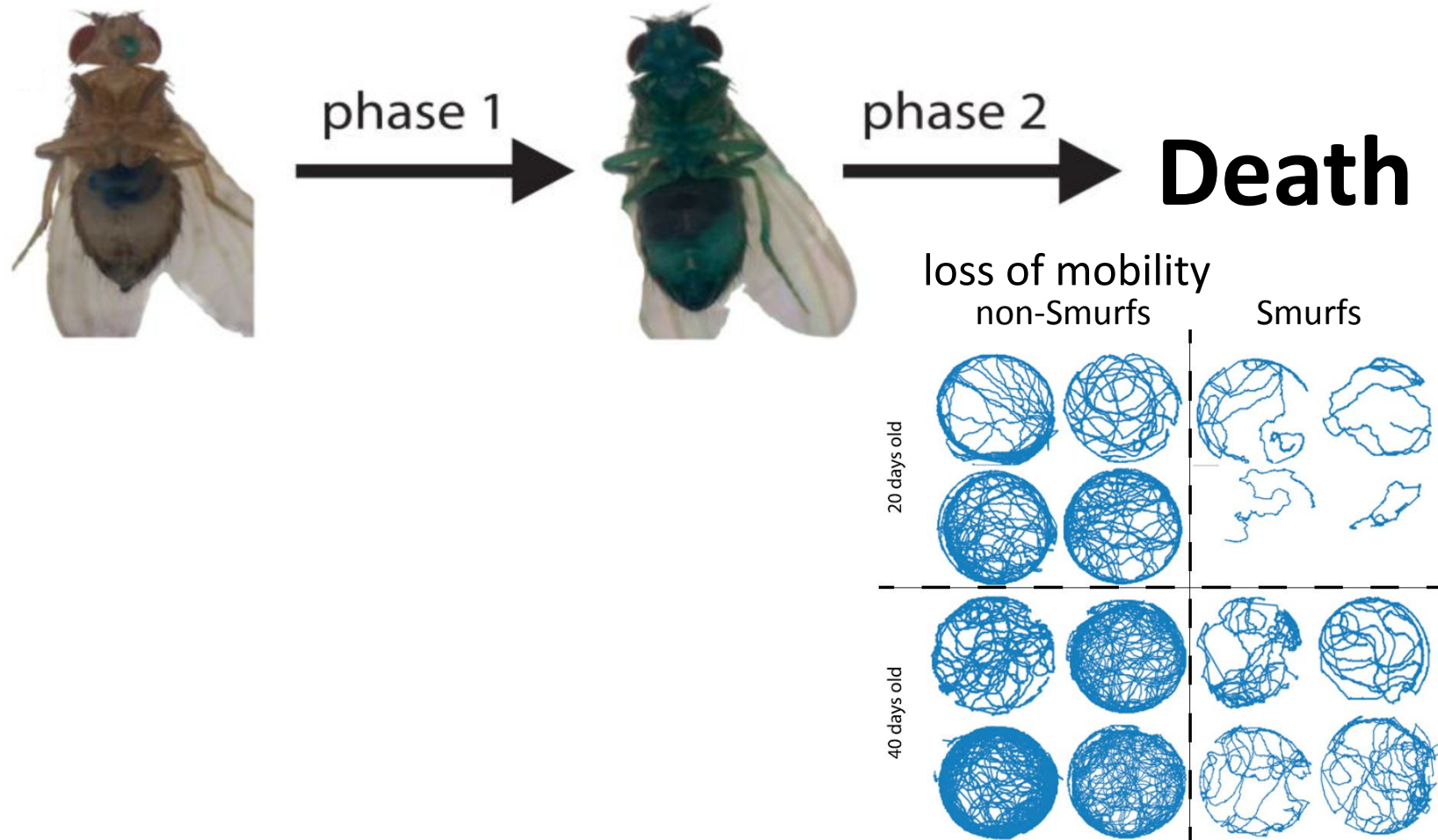
Hallmarks of ageing in the 2-Phase Model



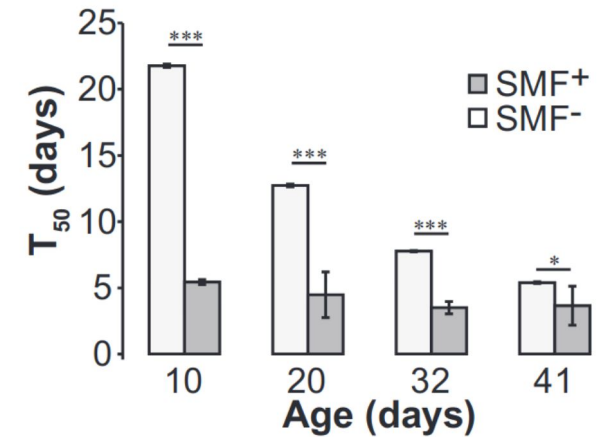
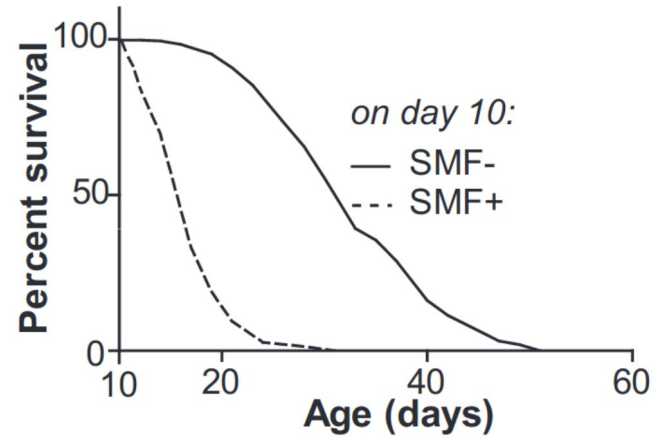
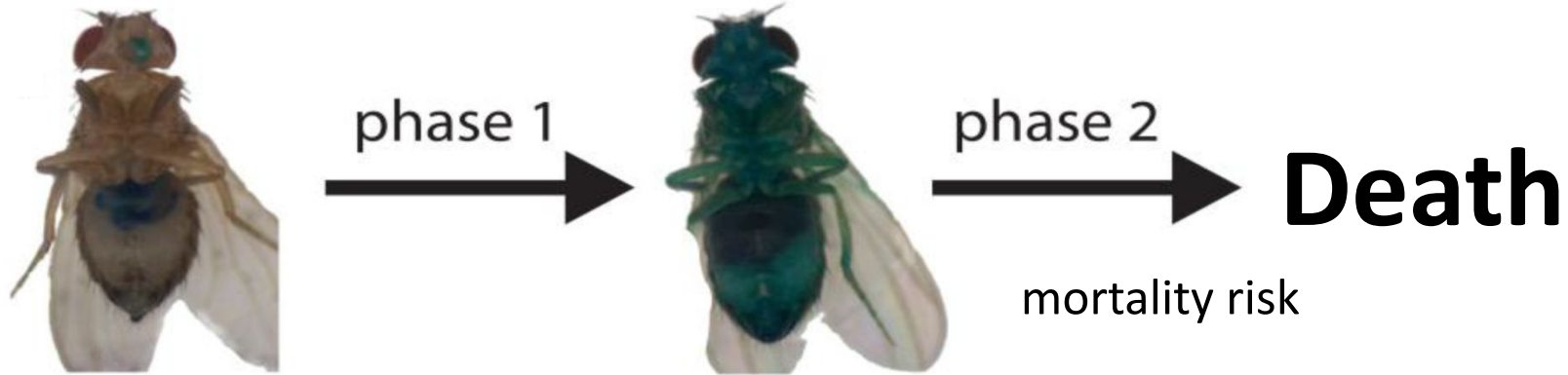
Hallmarks of ageing in the 2-Phase Model



Hallmarks of ageing in the 2-Phase Model



Hallmarks of ageing in the 2-Phase Model



A novel framework for studying ageing



Changing paradigm

Classic framework

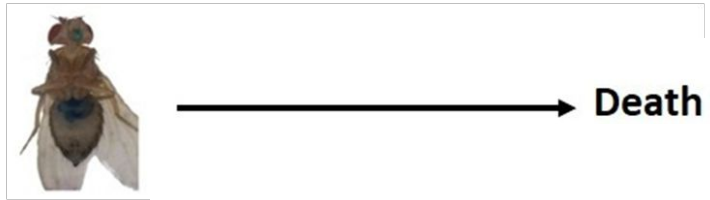


2-phase ageing framework



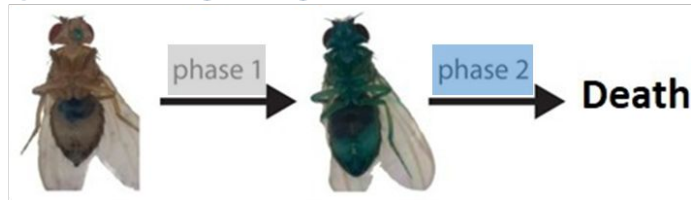
Changing paradigm

Classic framework

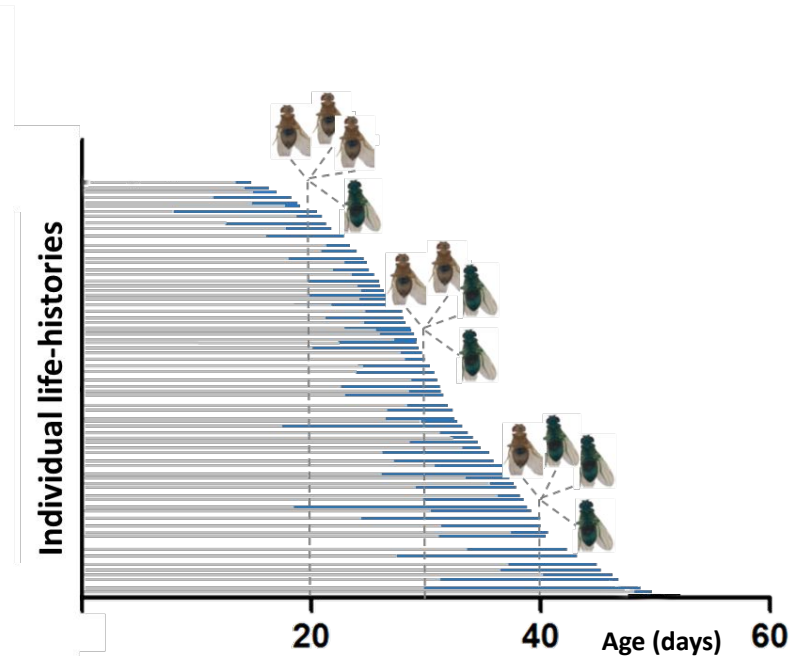
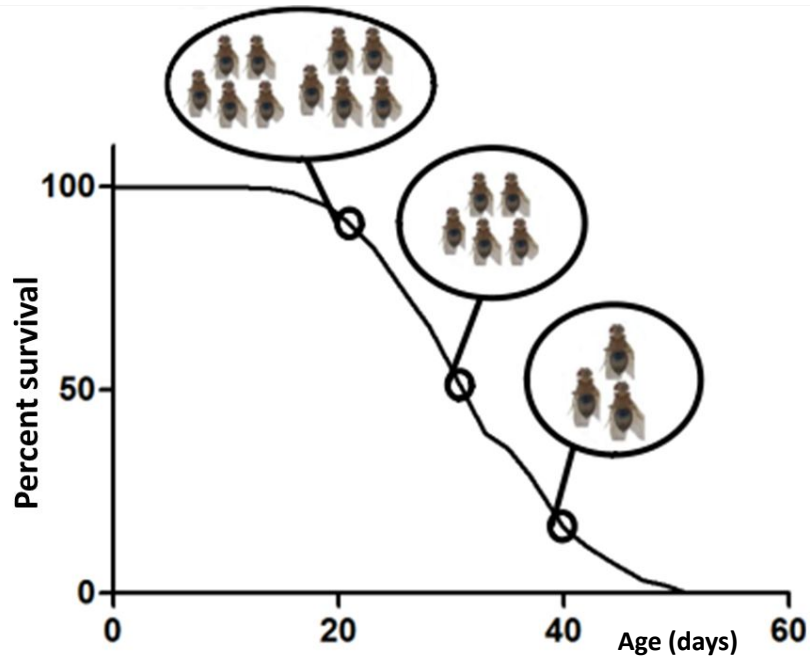


Chronological age

2-phase ageing framework

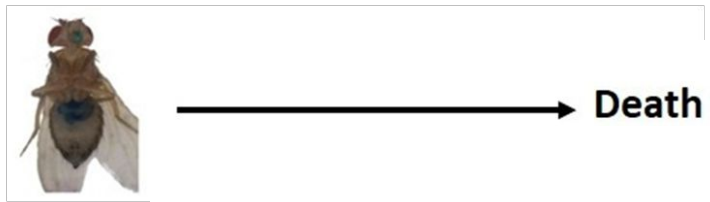


Physiological age



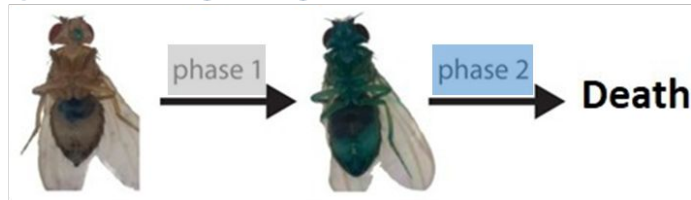
Changing paradigm

Classic framework

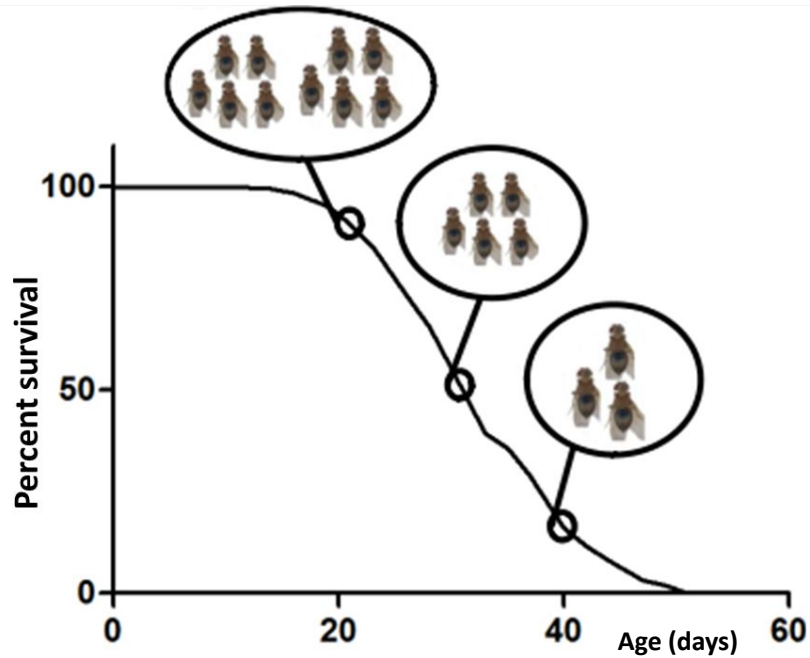


Chronological age

2-phase ageing framework

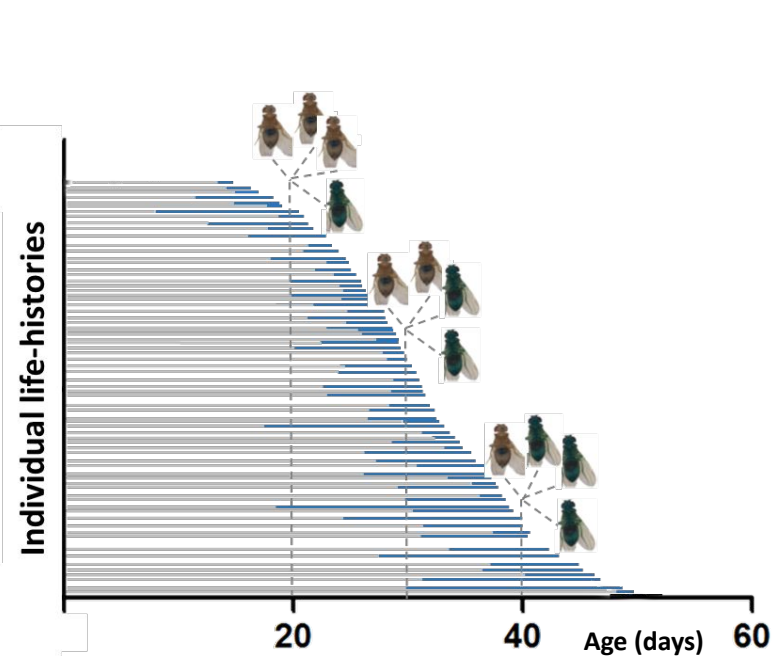
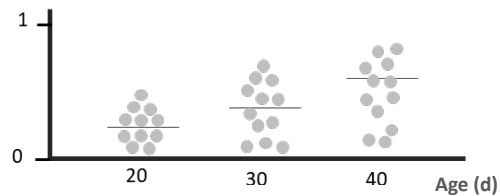


Physiological age

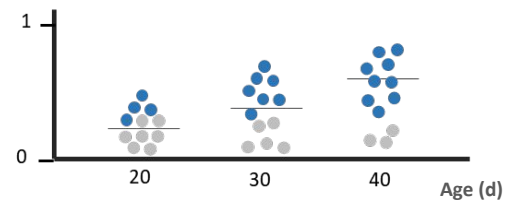


Population-based

Hallmark of ageing



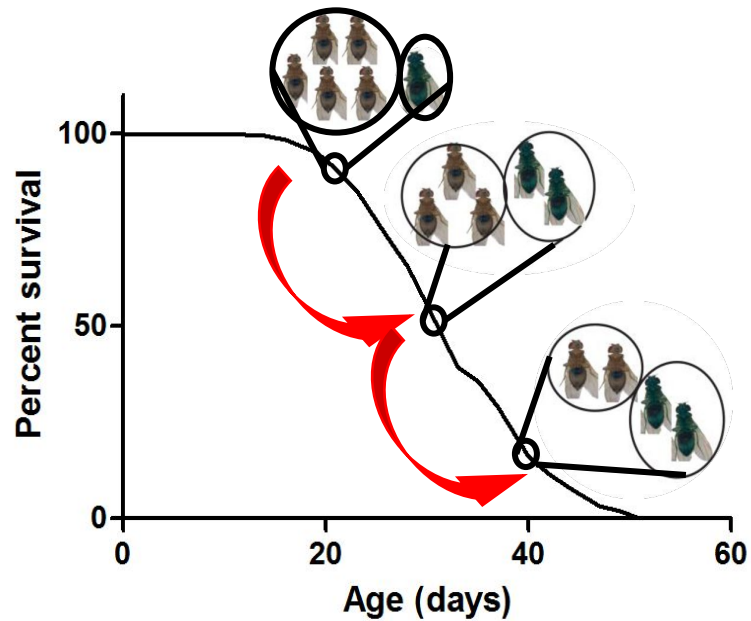
Individual-centered



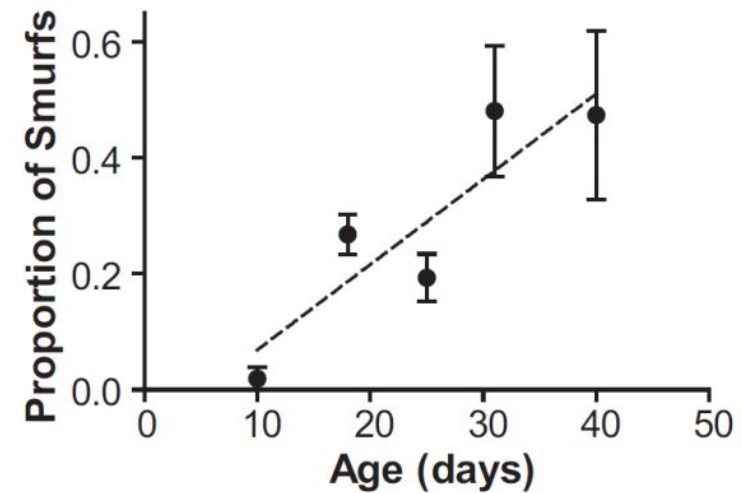
Our approach separates chronology and physiology



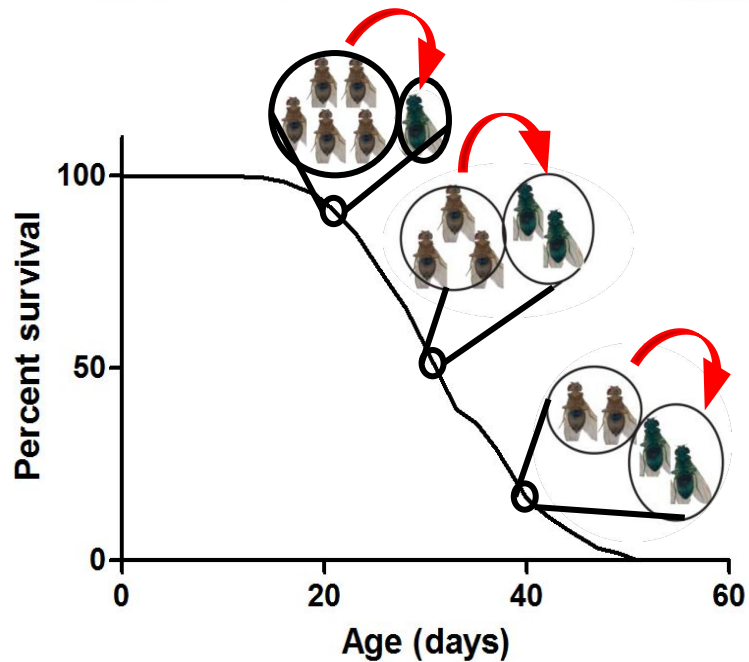
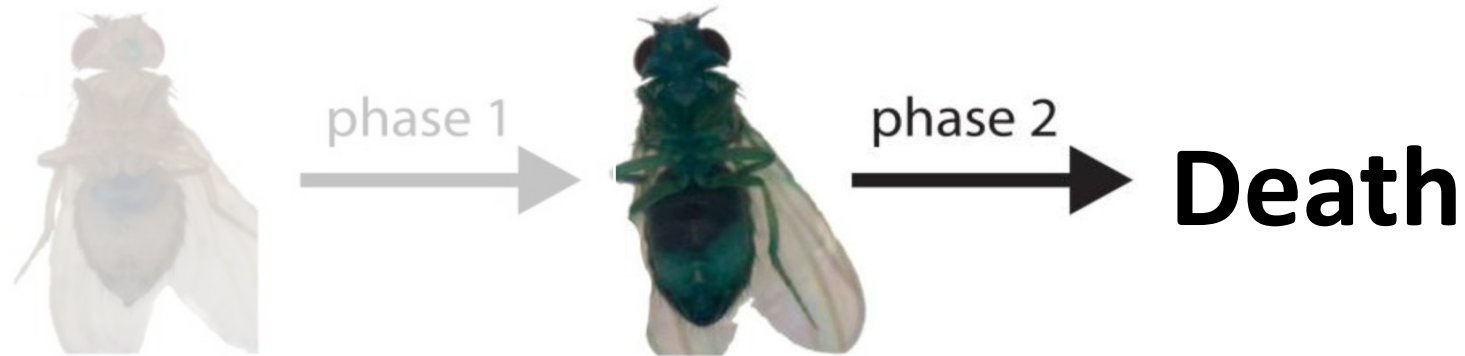
Flaminia Zane
PhD 12/05/22



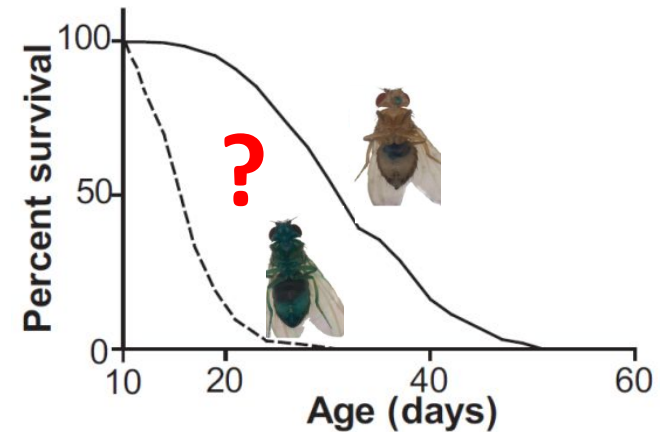
Understanding the increase in age-dependent risks



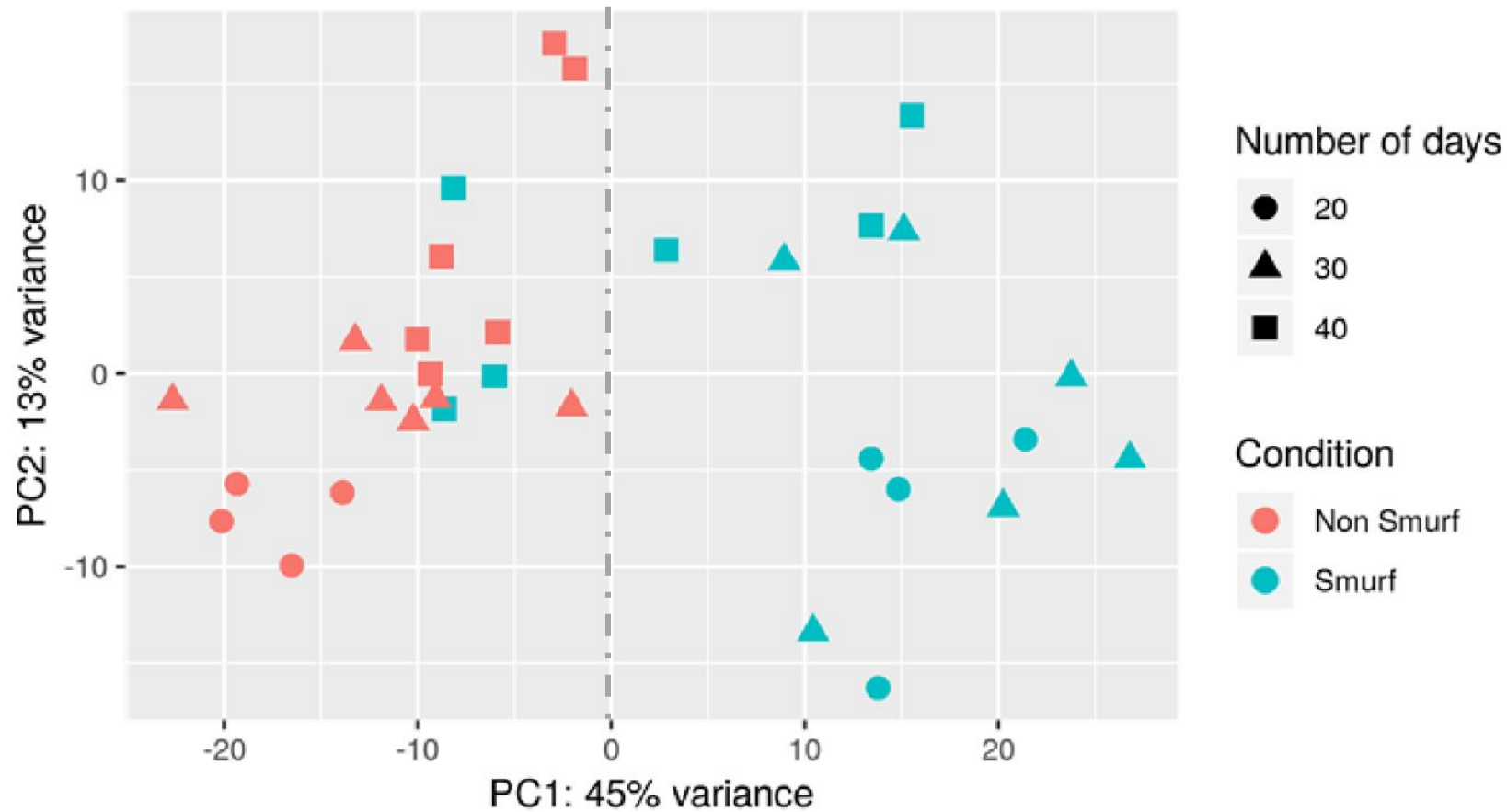
Our approach separates chronology and physiology



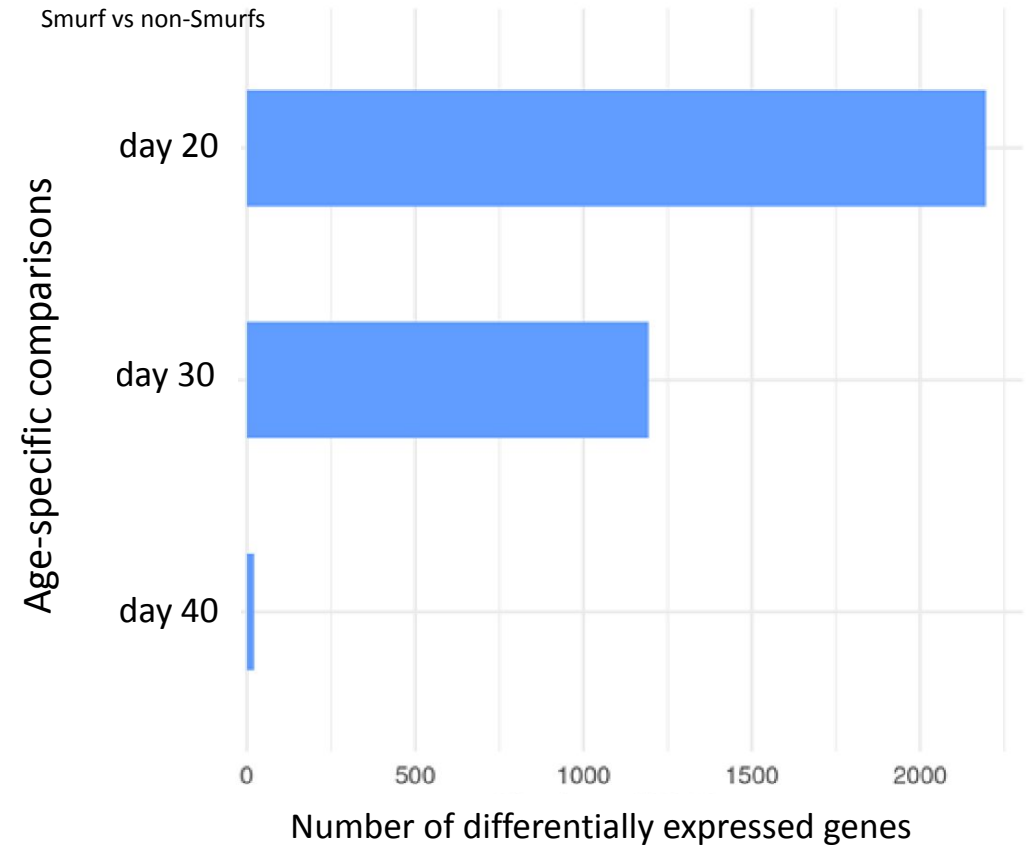
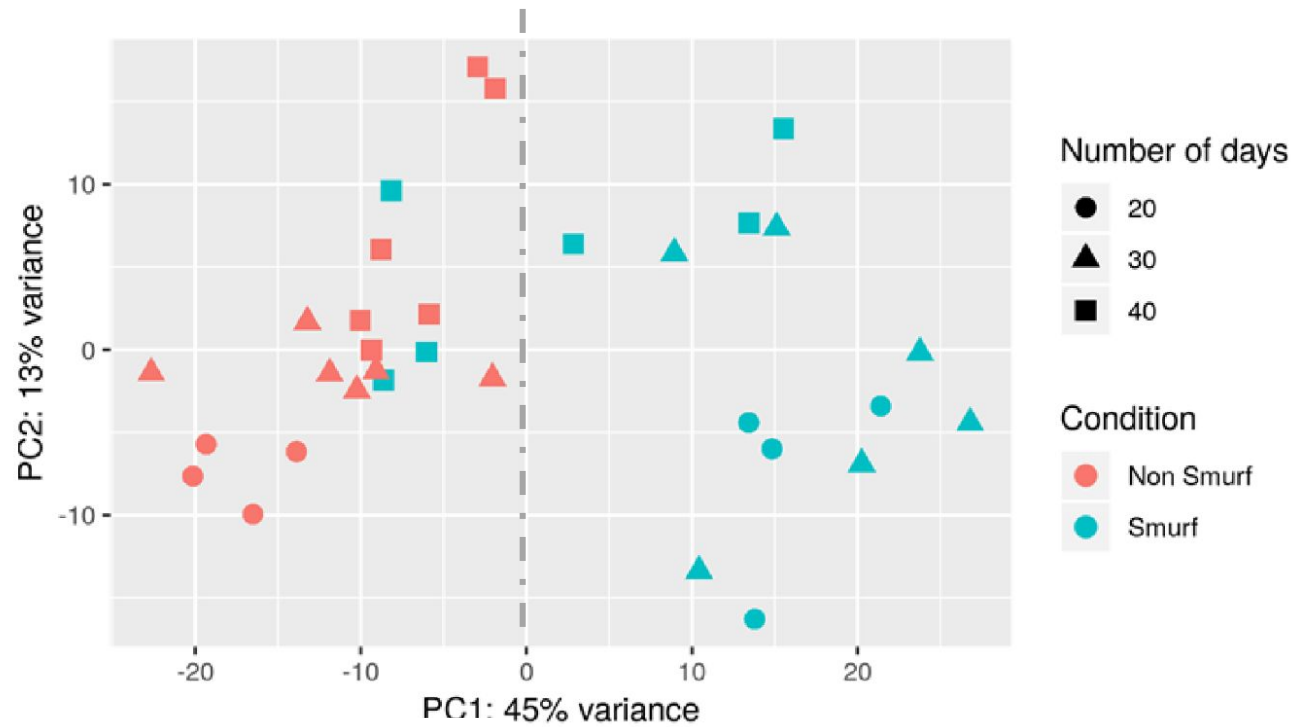
Understanding the high risk of impending death



There is a Smurf-specific signature

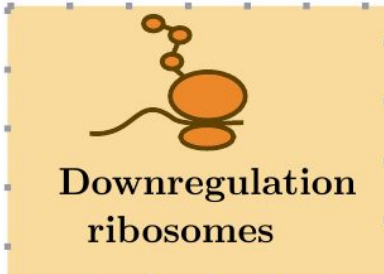
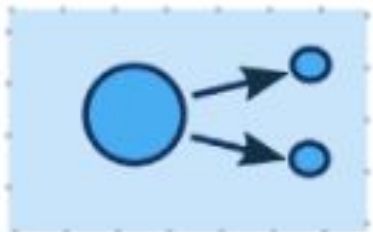
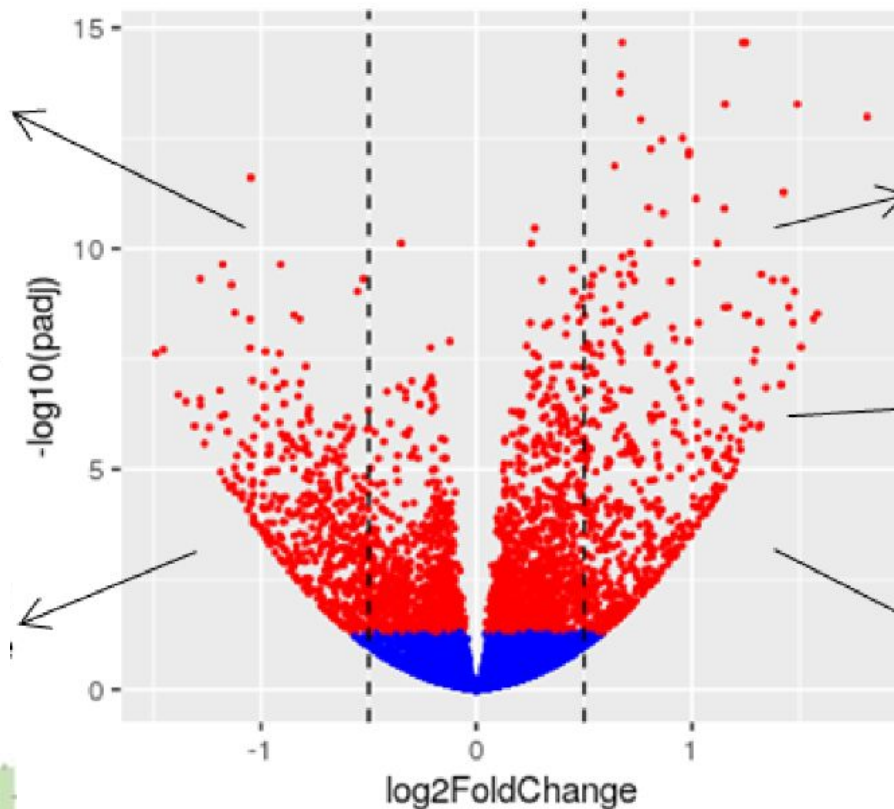


Aged non-Smurfs are close to Smurf

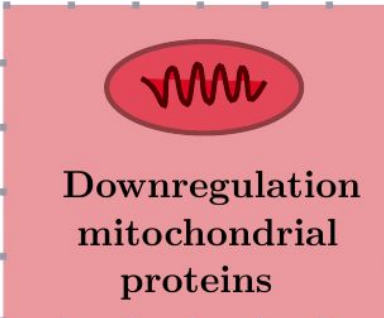


Smurfness recapitulates transcriptional ageing signature

3108 Differentially Expressed Genes (DEGs) / 15364 identified genes



Downregulation
ribosomes



Downregulation
mitochondrial
proteins

Lipid
metabolism

Proteostasis

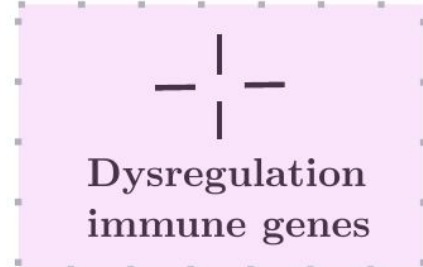
Mitochondrial
respiration



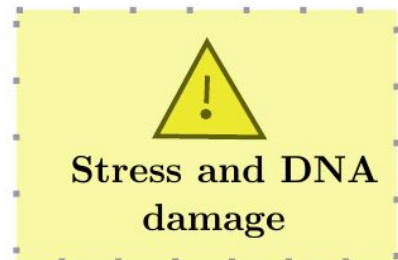
Immune
response

Stress responses
(GSTs, HSPs); UPR^{ER}

Cell
motility



Dysregulation
immune genes



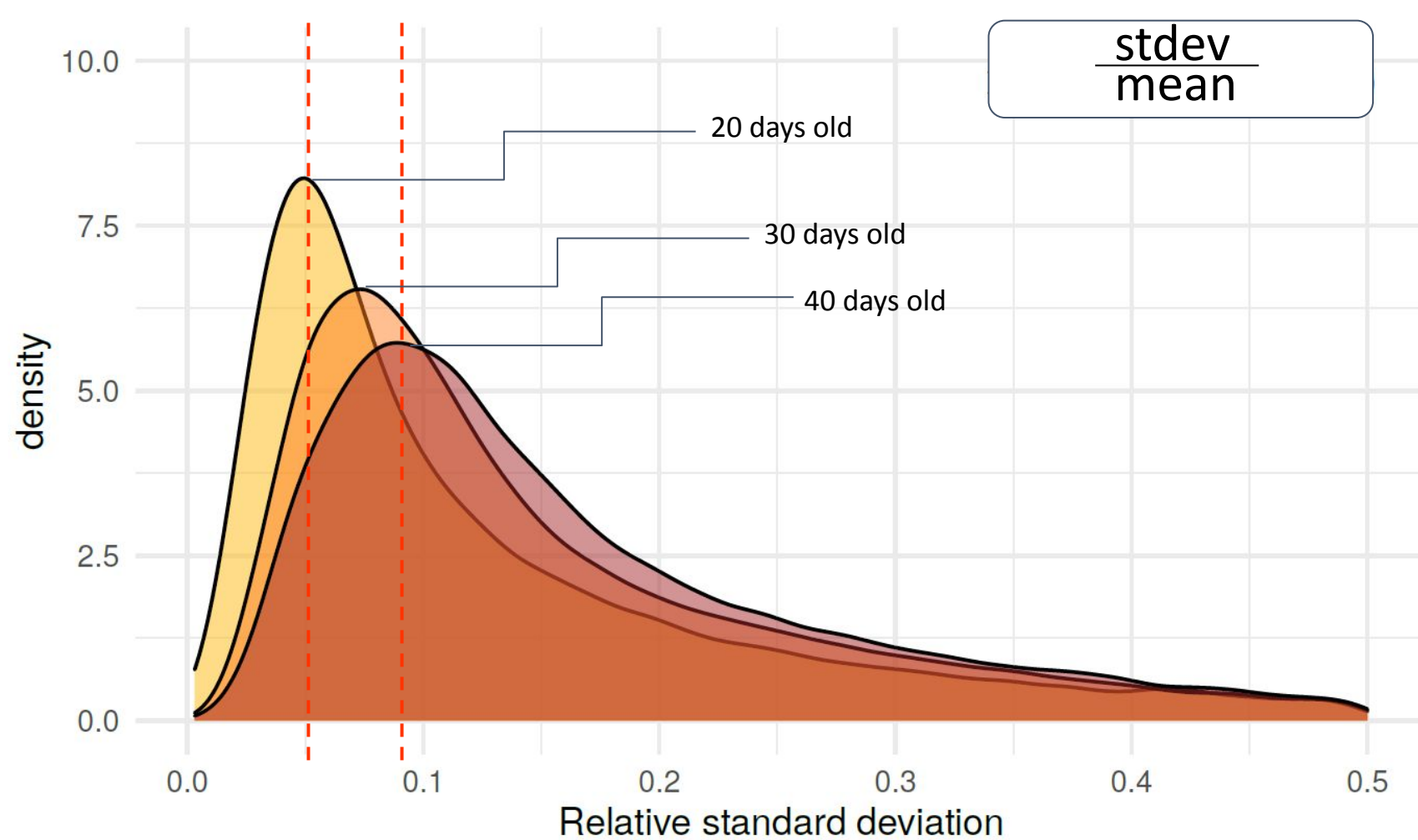
Stress and DNA
damage

Six markers of aged
transcriptome

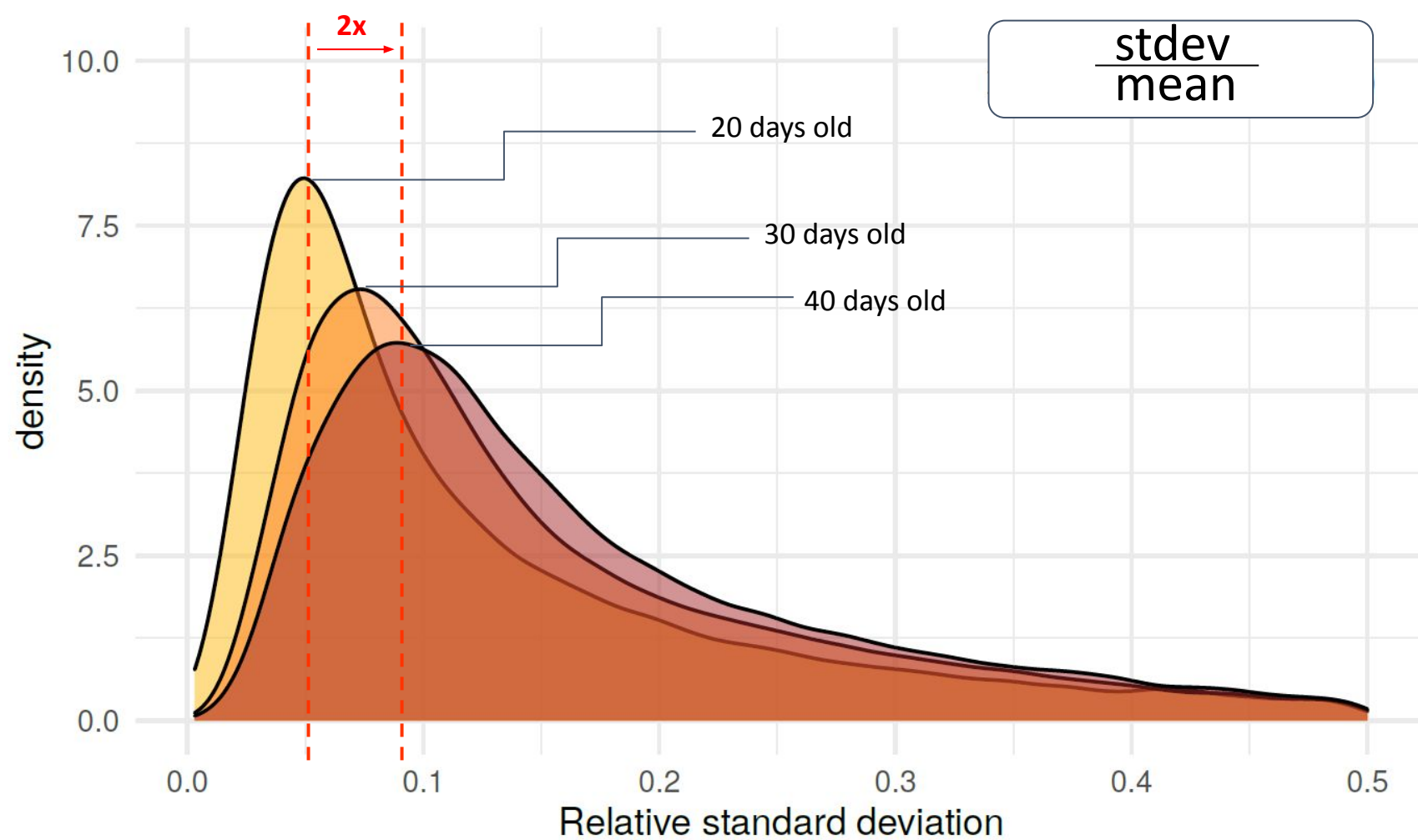
Frenk & Houlsey (2018)

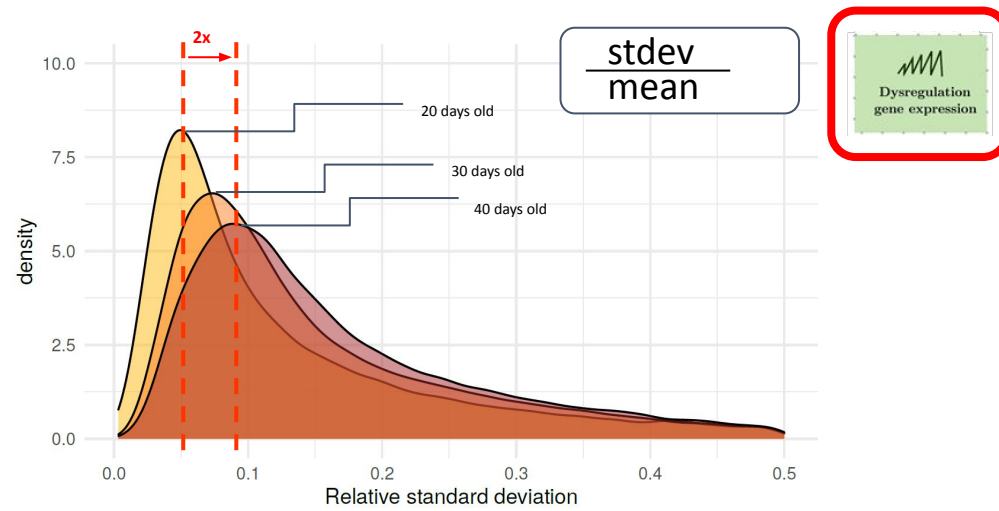
FDR • Non significant • Significant

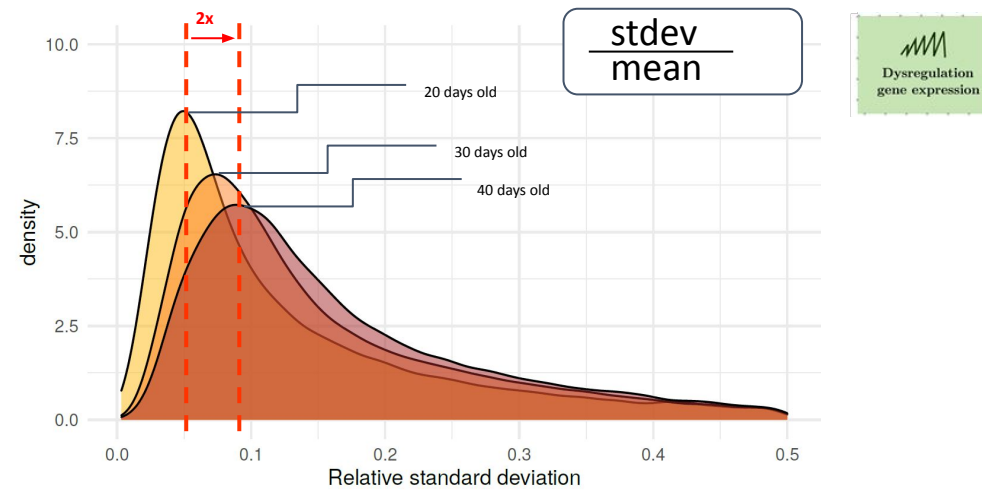
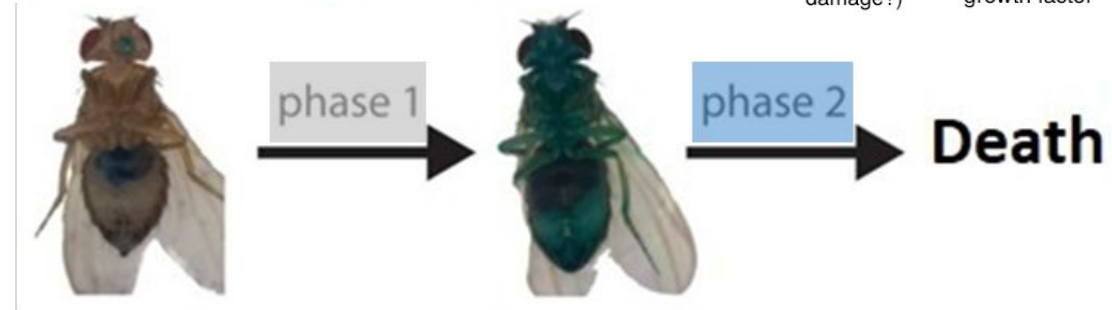
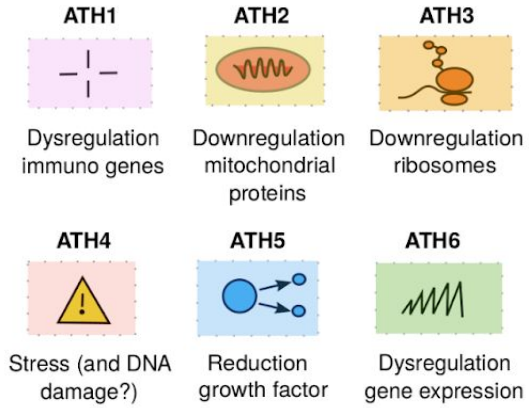
Ageing non-Smurf transcriptome accumulates expression noise



Ageing non-Smurf transcriptome accumulates expression noise





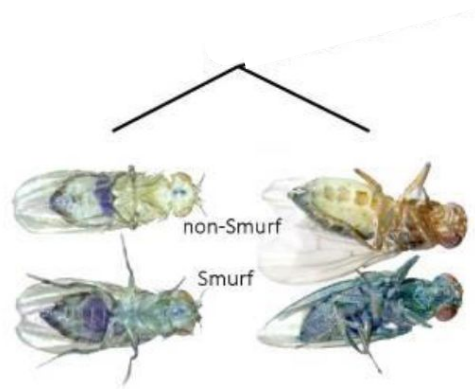


A broadly relevant model of ageing



An evolutionarily conserved End-Of-Life phenotype

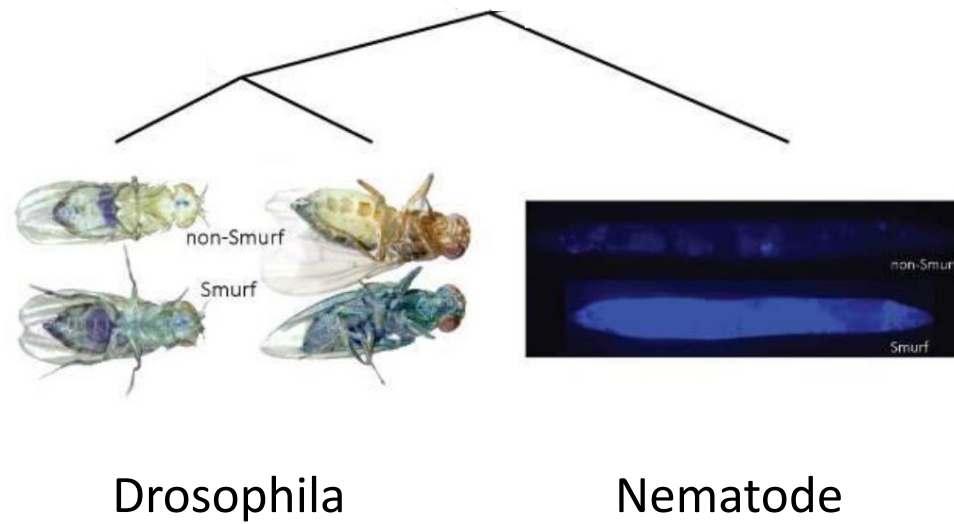
The 2-Phase Model of Ageing is evolutionarily conserved



Drosophila

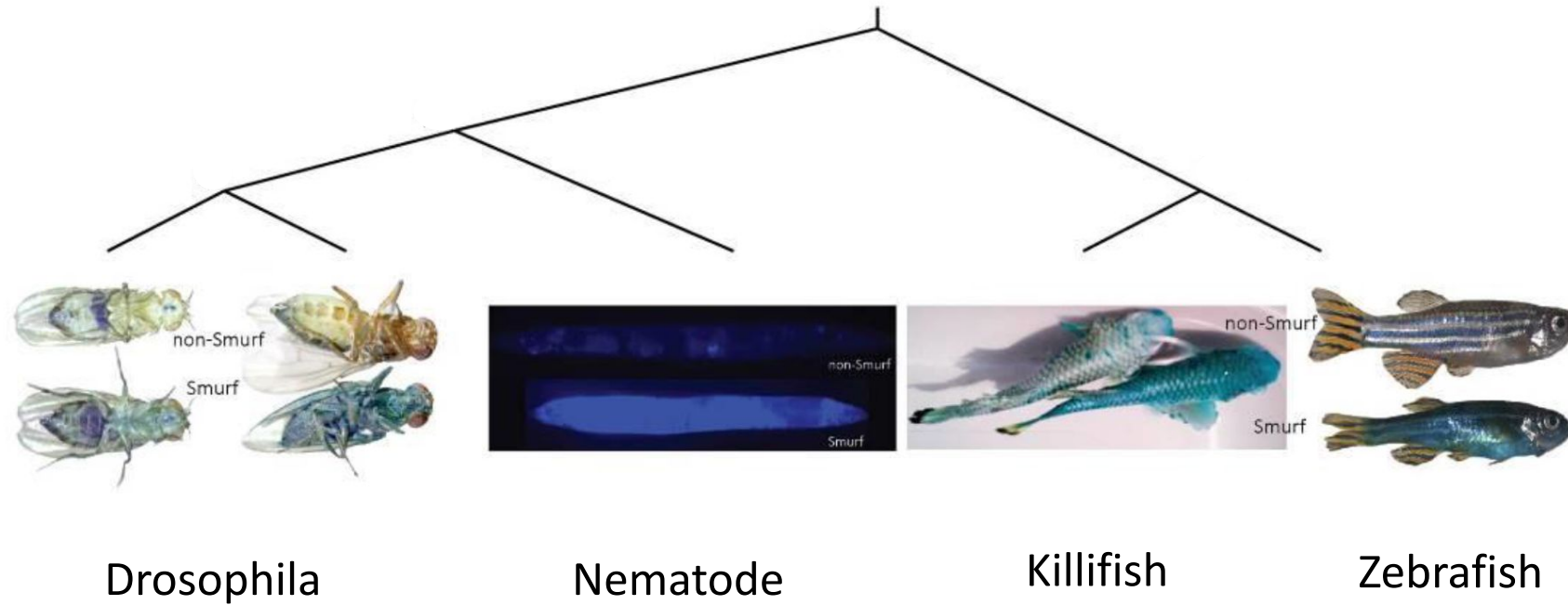
An evolutionarily conserved End-Of-Life phenotype

The 2-Phase Model of Ageing is evolutionarily conserved



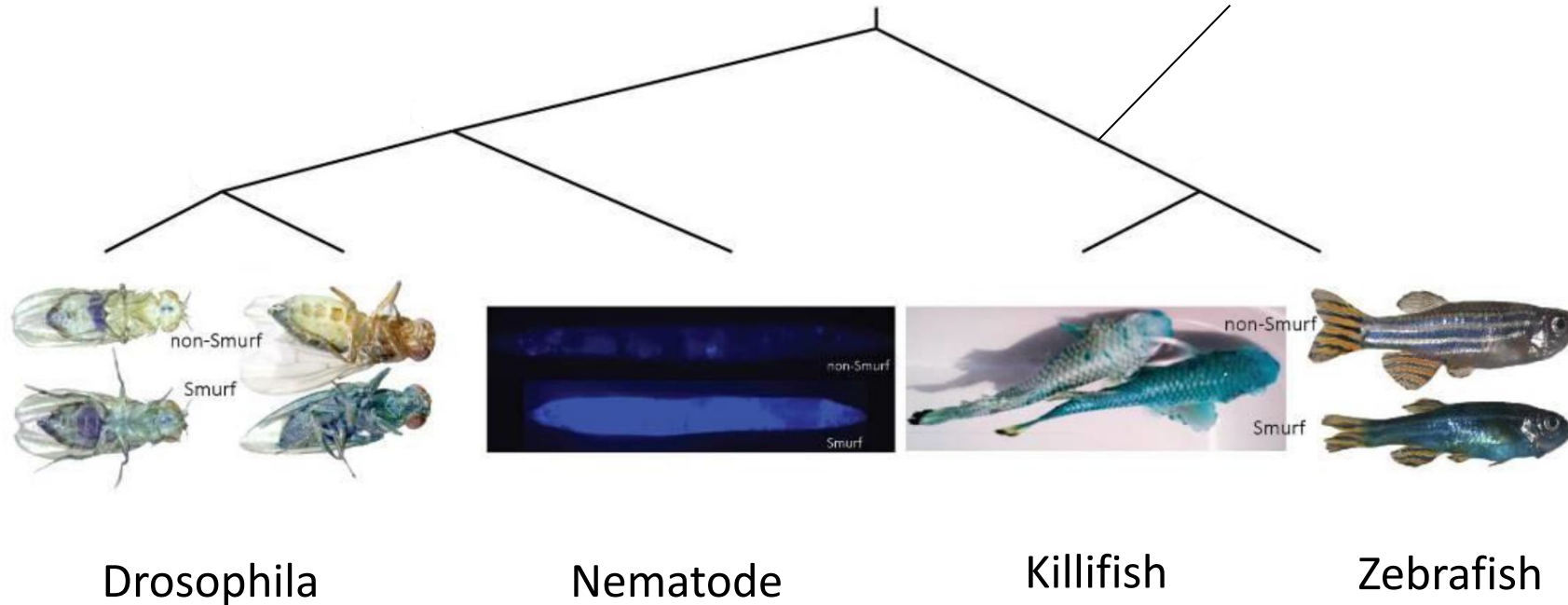
An evolutionarily conserved End-Of-Life phenotype

The 2-Phase Model of Ageing is evolutionarily conserved



An evolutionarily conserved End-Of-Life phenotype

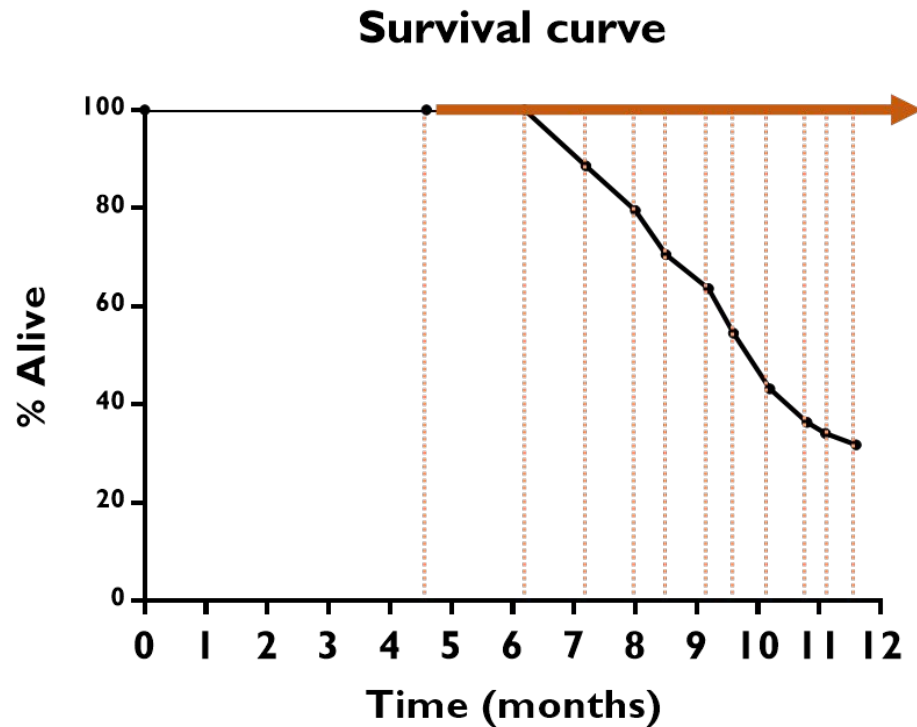
The 2-Phase Model of Ageing is evolutionarily conserved



A “public” path to death: mice



Dr. Céline Cansell



-Intestinal permeability test

- Permeability T1h
- Permeability T3h

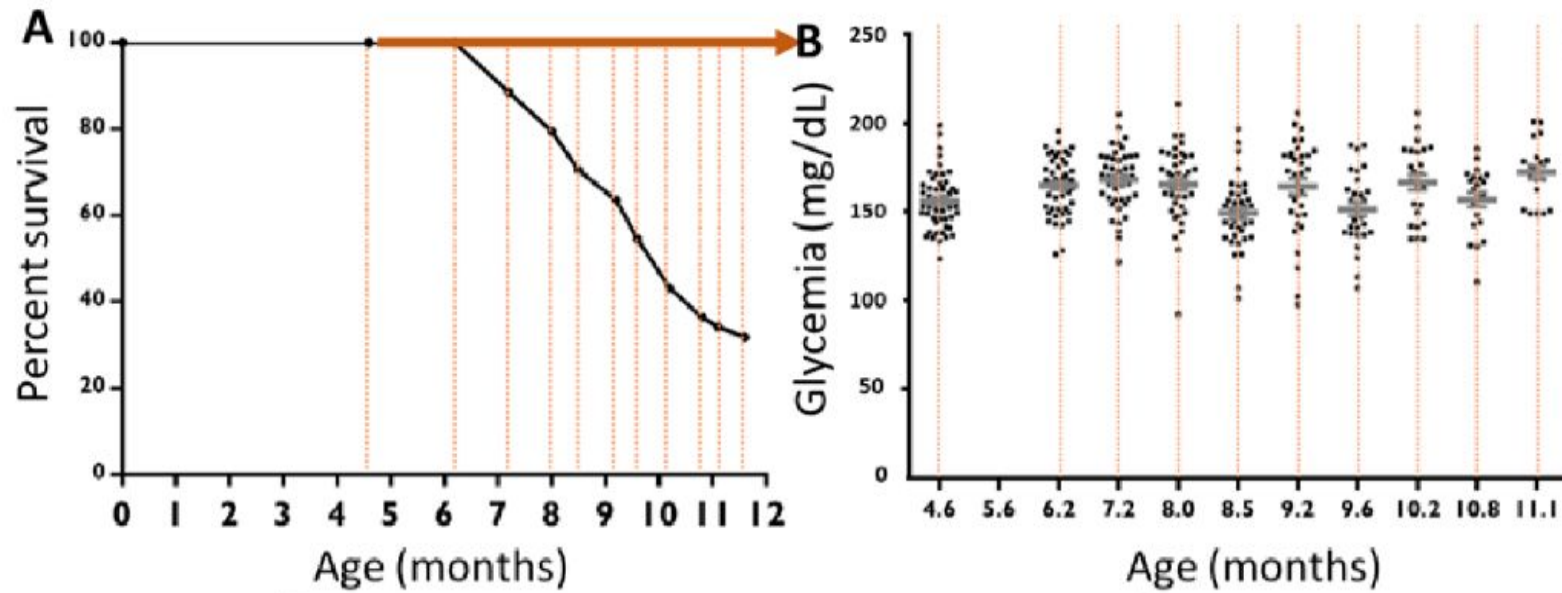
-Measurements :

- Body Weight
- Fat and lean mass
- Body temperature
- Glycemia

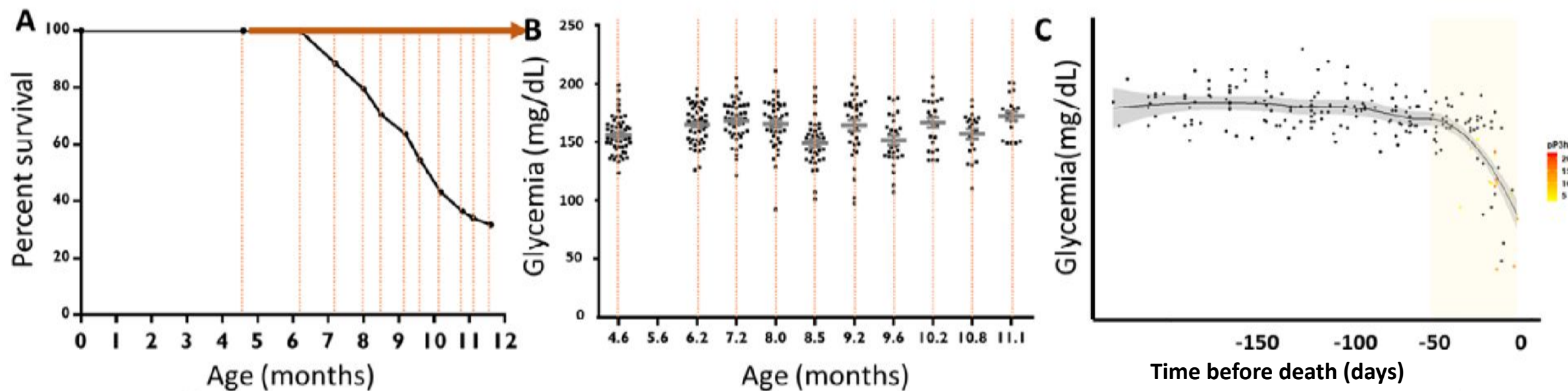
-Metabolic recordings

- Food intake
- Locomotor activity
- Energy expenditure

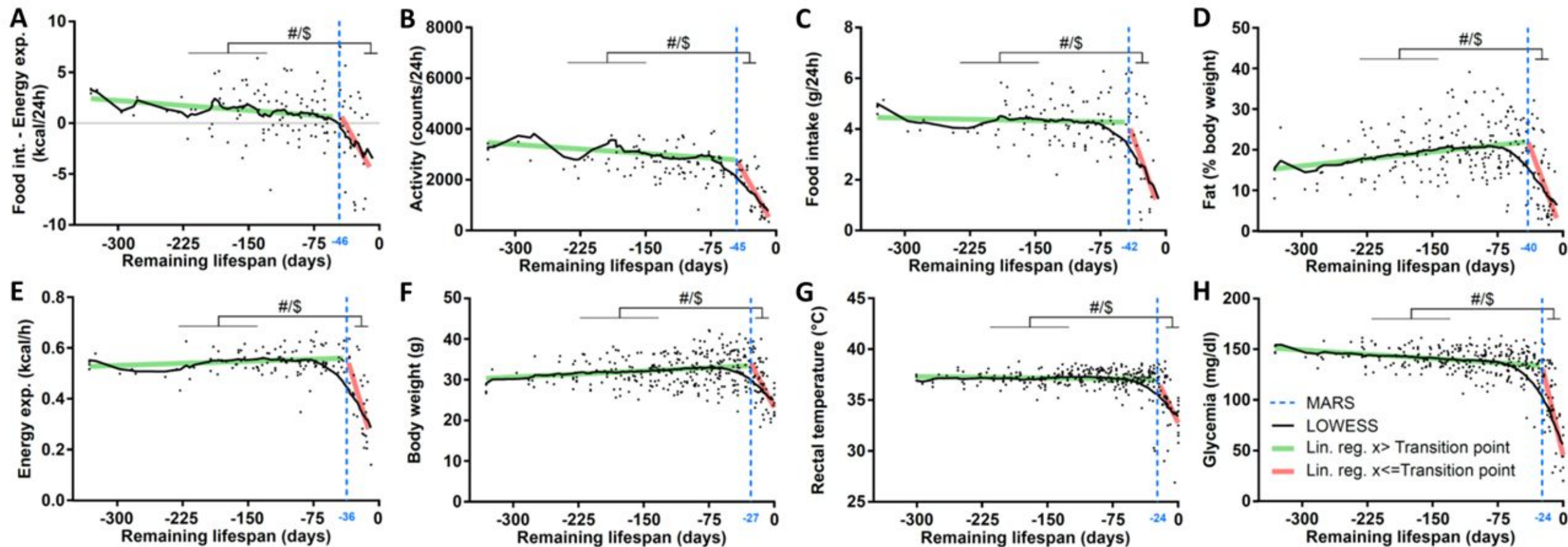
A “public” path to death: mice



A “public” path to death: mice



Smurfness in mice



A “public” path to death: mice



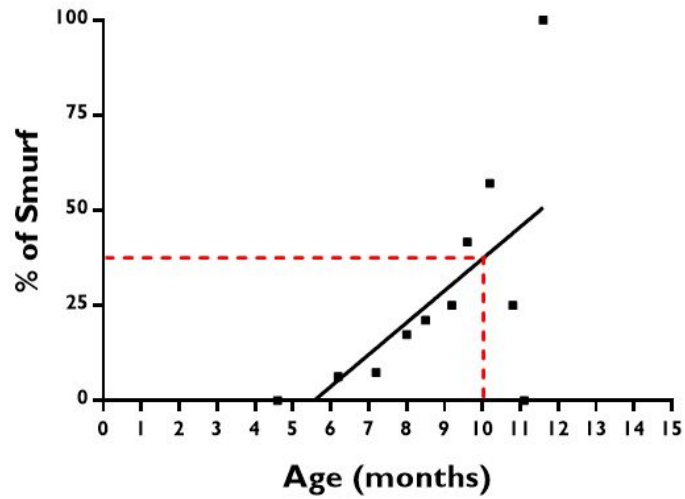
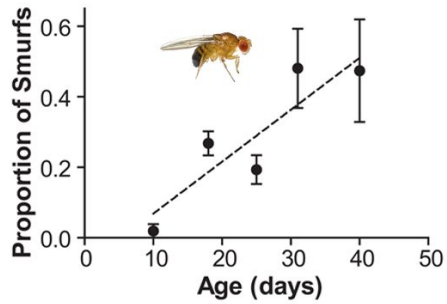
Phase I



Phase 2



Death



A “public” path to death: mice



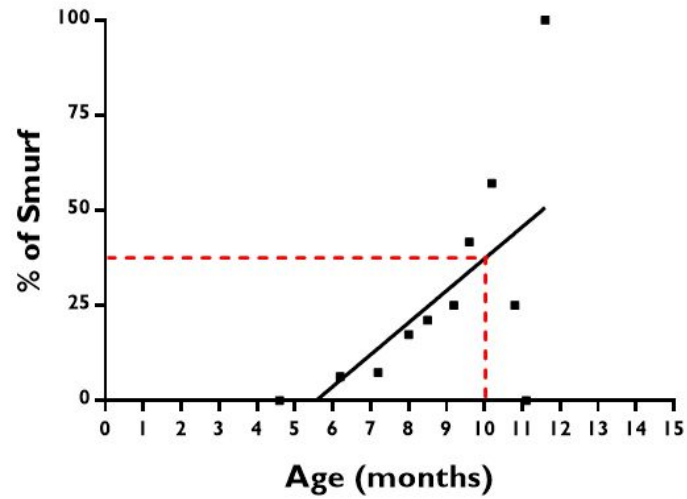
Phase I



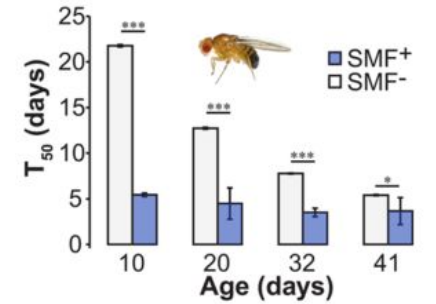
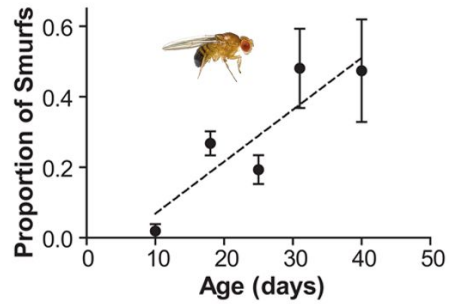
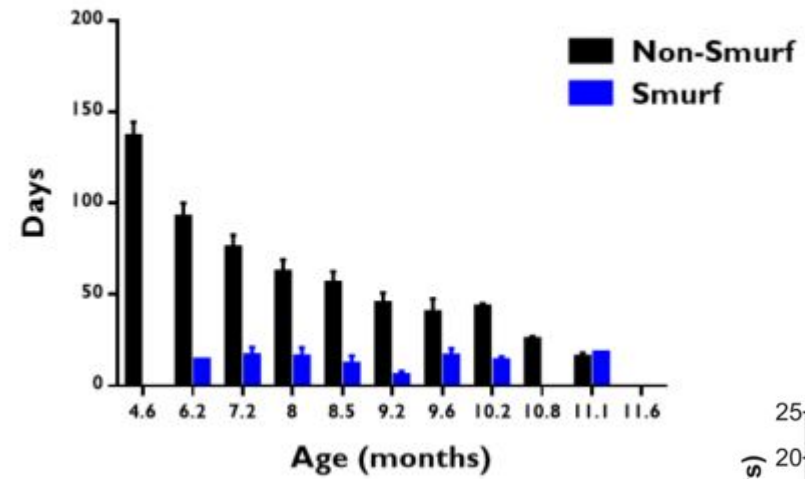
Phase 2



Death



Remaining lifespan

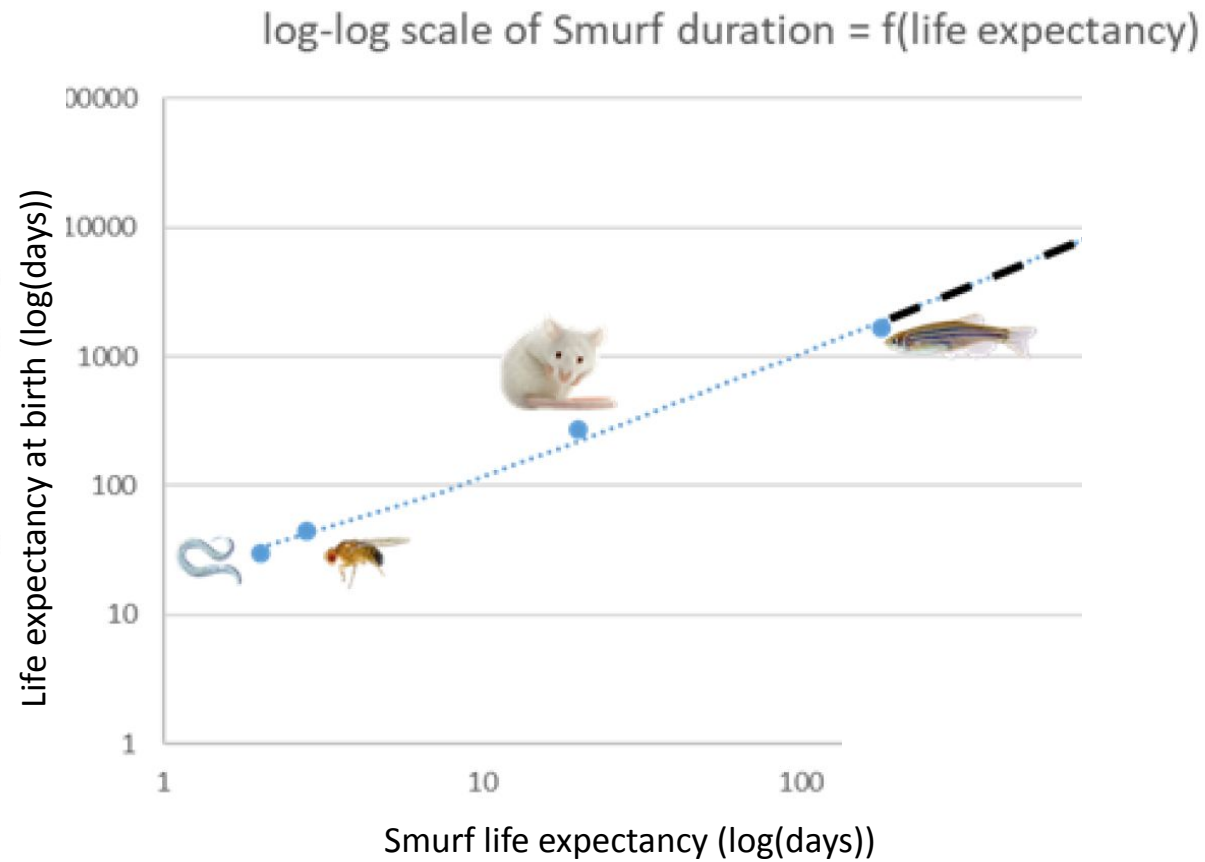




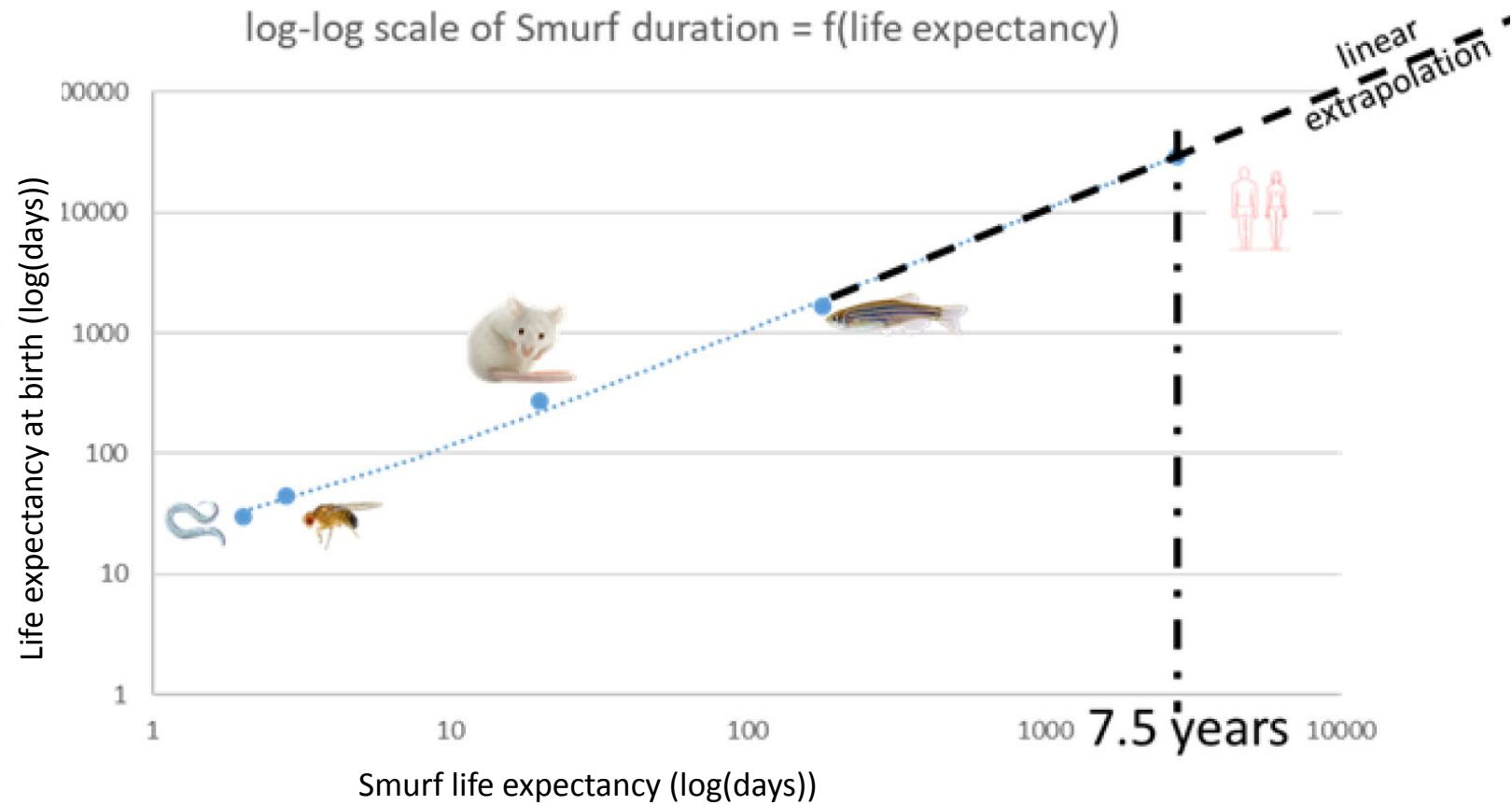
Searching for Smurfs in humans



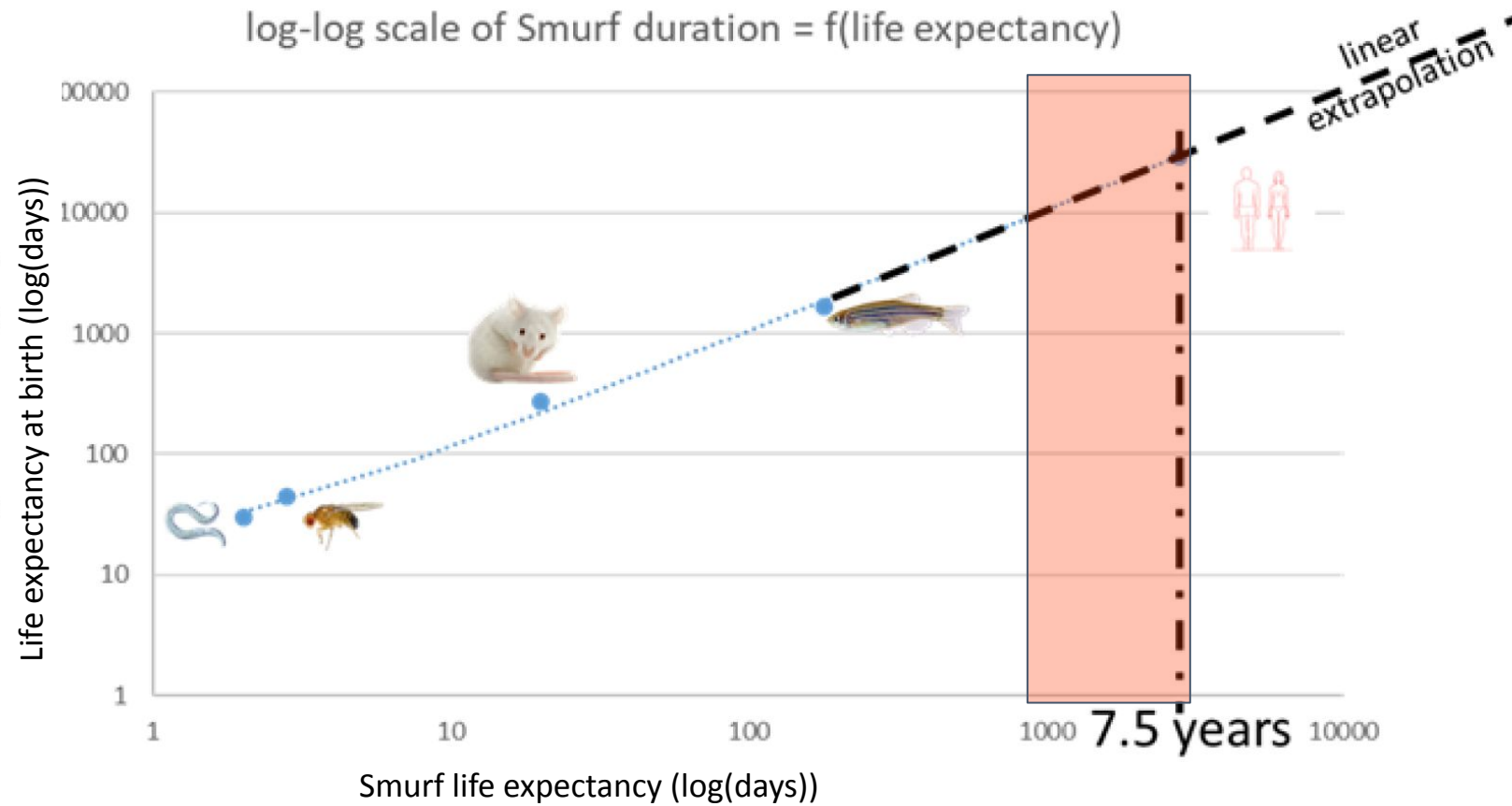
Relevance of the model to the human risk of impending death



Relevance of the model to the human risk of impending death



For how long are we dying?



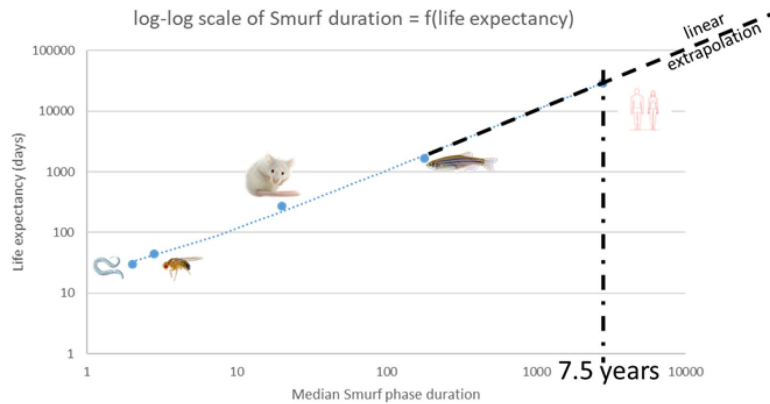
Breuil et al., 2026 bioRxiv

Raz et al., 2026 bioRxiv

Relevance of the model to the human risk of impending death

Grip Strength Predicts Cause-Specific Mortality in Middle-Aged and Elderly Persons

Hideo Sasaki, MD, PhD,^{a,b} Fumiyo Kasagi, PhD,^c Michiko Yamada, MD, PhD,^a Shoichiro Fujita, PhD^d



Biomarker Profiling by Nuclear Magnetic Resonance Spectroscopy for the Prediction of All-Cause Mortality: An Observational Study of 17,345 Persons

Krista Fischer  , Johannes Kettunen , Peter Würtz  , Toomas Haller, Aki S. Havulinna, Antti J. Kangas, Pasi Soininen, Tõnu Esko, Mari-Liis Tammesoo, Reedik Mägi, Steven Smit, Aarno Palotie, Samuli Ripatti, [...],

Andres Metspalu 

[view all]

Published: February 25, 2014 • DOI: 10.1371/journal.pmed.1001606

Expression of specific inflammasome gene modules stratifies older individuals into two extreme clinical and immunological states

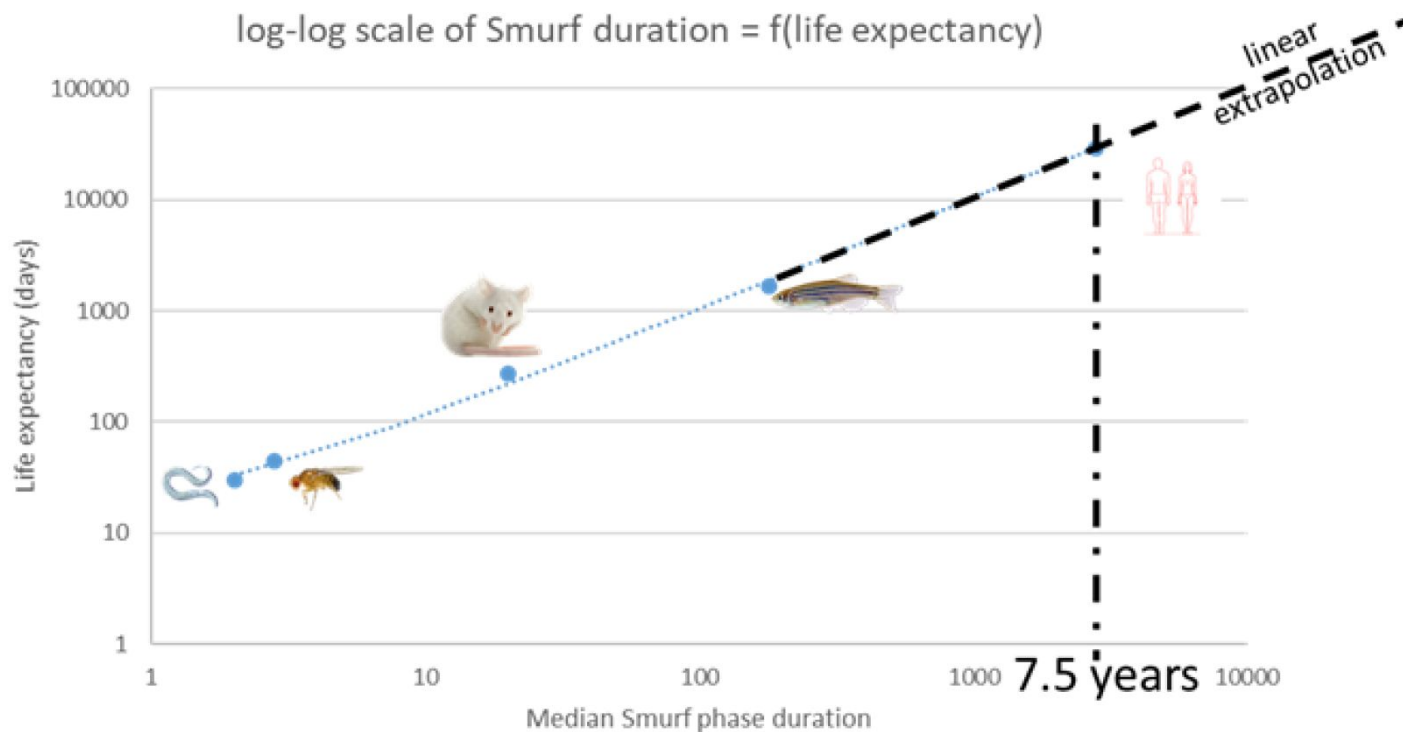
David Furman^{1,2}, Junlei Chang³, Lydia Lartigue⁴, Christopher R Bolen^{5,11}, François Haddad⁶, Brice Gaudilliere⁵, Edward A Ganio⁵, Gabriela K Fragiadakis⁵, Matthew H Spitzer⁵, Isabelle Douchet⁷, Sophie Daburon⁷, Jean-François Moreau⁷, Garry P Nolan⁵, Patrick Blanco⁷, Julie Déchanet-Merville⁷, Cornelia L Dekker⁸, Vladimir Jojic⁹, Calvin J Kuo³, Mark M Davis^{1,10} & Benjamin Faustin⁷

Assessing intestinal permeability in human natural death



Clément Dubost
Réa Bégin

- ICU patients, Smurfness and ICU scores



Scientific council IHA Bégin ✓
Research division SSA ✓
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Extending the Smurf assay to public health issues



risks of age-related pathologies?

predicting treatment failure?

helping the curative/palliative transition?

Extending the Smurf assay to public health issues



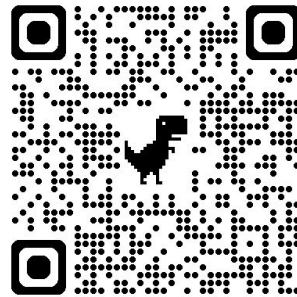
Research article | [Open access](#) | Published: 27 July 2020

Ethical and social implications of approaching death prediction in humans - when the biology of ageing meets existential issues

[Marie Gaille](#) , [Marco Araneda](#), [Clément Dubost](#), [Clémence Guillermain](#), [Sarah Kaakaj](#), [Elise Ricadat](#), [Nicolas Todd](#) & [Michael Rera](#)

BMC Medical Ethics 21, Article number: 64 (2020) | [Cite this article](#)

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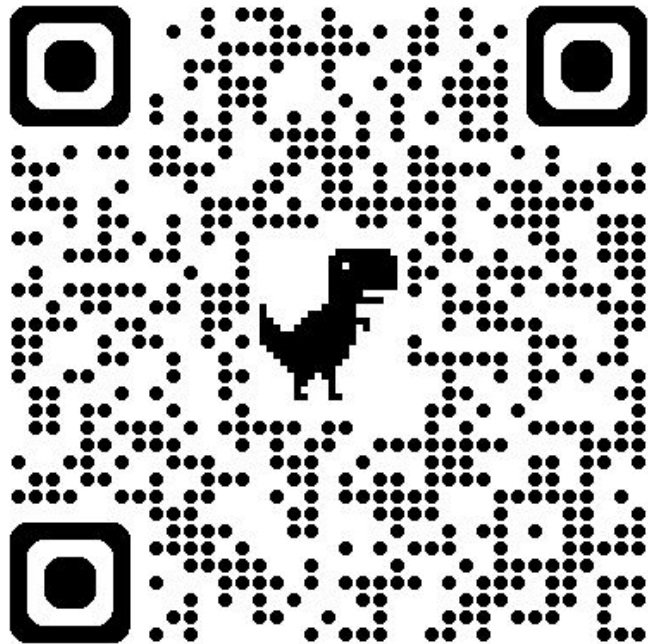
risks of age-related pathologies?

predicting treatment failure?

helping the curative/palliative transition?

Gaille et al., 2020 BMC Medical Ethics

Research Platform on the End of Life



PLATEFORME NATIONALE
POUR LA RECHERCHE
SUR LA FIN DE VIE

SUPPORT RESEARCH

National Directory RESEARCHERS

Directory of RESEARCH PROJECTS

WHO ARE WE ? - RESEARCH OBSERVATORY - SCIENTIFIC MEETINGS - PRI END OF LIFE - OPPORTUNITIES

Current scientific and human challenges in pain research

Professor Nathan Moreau's webinar is now available as a video.

READ MORE

Current scientific and human challenges in pain research

Launch of the interdisciplinary research program on end of life

Presentation of the Horizon 2026 call for projects "Earlier and more precise palliative care"

The complexity of suffering in palliative and end-of-life care

PLATFORM EVENTS

| Platform Event | Workshop

Friday, April 24, 2026, from 12:30 PM to 1:15 PM

Online

Journal club

Regular meetings for reading and analyzing scientific articles concerning palliative care and end of life.

LEARN MORE

Webinar | Platform Event

Thursday, April 30, 2026, from 12:30 PM to 1:30 PM

Online

Ageing and end of life: from the fly to the human being

This webinar will present a re-conceptualization of ageing and end of life developed from animal models.

CALLS FOR PROJECTS

Letters of intent must be submitted by April 10, 2026.

Call for projects Emergence 2026 - J'InvEst-I

GIRCI East - Interregional Group for Clinical Research and Innovation East

Submission guidelines: <https://girci-est.fr/jinvest-i-campagne-en-cours/>

Letters of intent must be submitted by April 10, 2026.

Call for projects Emergence 2026 - APPARA

GIRCI East - Interregional Group for Clinical Research and Innovation East

Collaborators:

Sylvie Méléard



Clément Dubost



SCIENCES
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Savandara Besse (postdoc)



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Funding:



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