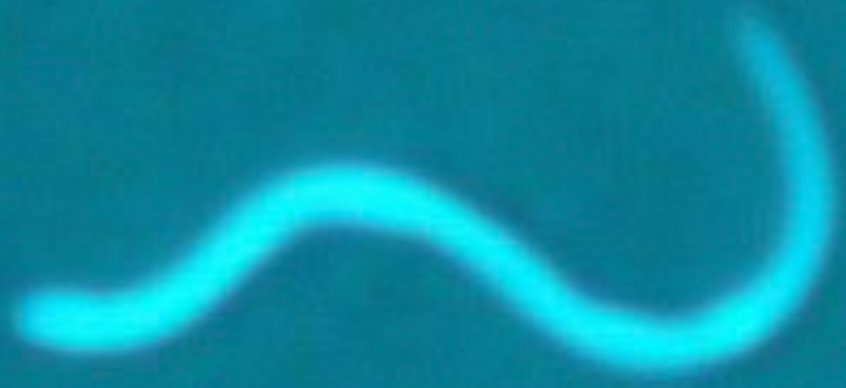
Cross-species genetic mapping of targets in mitochondria and aging



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https://auwerx-lab.epfl.ch/

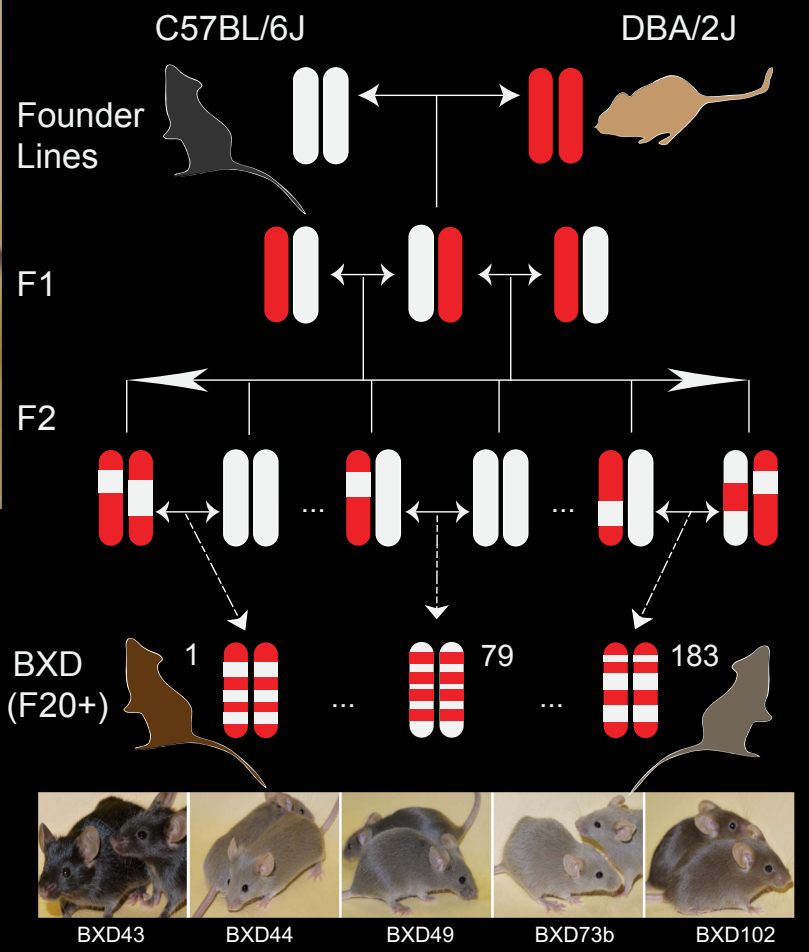
Genetic reference populations

the BXDs

- Metabolic phenotypes in male & female BXDs
- Intensive metabolic phenotypes for chow and high fat-fed BXDs
- Lifespan in BXDs
- Lifespan in ITP controls
- NASH and CKD in the CC founders and F2 cross
- Healthspan and mito stress in the HDPs

Mouse Genetic Reference Populations (GRPs)

GRPs - a holistic approach to map genes



- 5 million sequence variants, similar to human populations
- 4'700 genes with protein coding variants
- 2'000 with predicted high-impact variants
- >6'000 clinical phenotypes
- multi-omics molecular phenotypes in >35 tissues

www.genenetwork.org
www.system-genetics.org

Andreux et al, *Cell*, 2012, 150, 1287-1299
Wu et al, *Cell*, 2014, 158, 1415-1430
Williams & Auwerx, *Cell*, 2015, 162, 23-32
Williams et al, *Science*, 2016, 352, aad0189
Li et al, *Cell Systems*, 2018, 6, 90-102
Li et al, *Genome Res.*, 2019, 29, 2034-2045
Jha et al, *Cell Systems*, 2018, 6, 709-21
Jha et al, *Cell Systems*, 2018, 6, 722-33
Li et al, *Cell Metab.*, 2022, 34, 1594-1610

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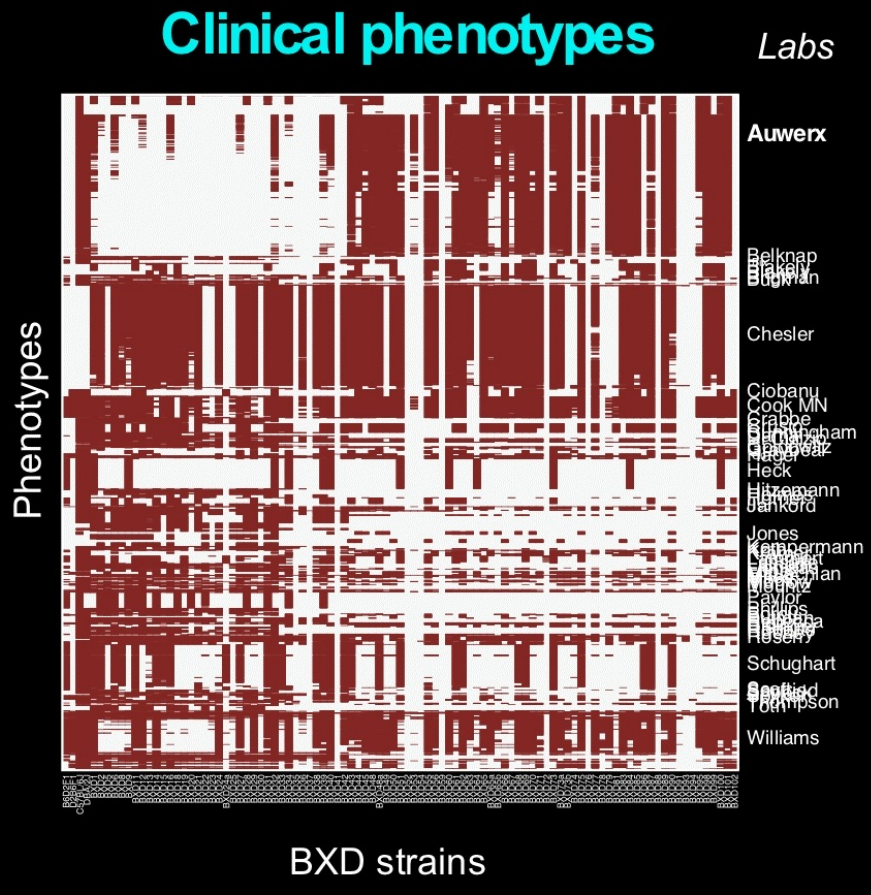
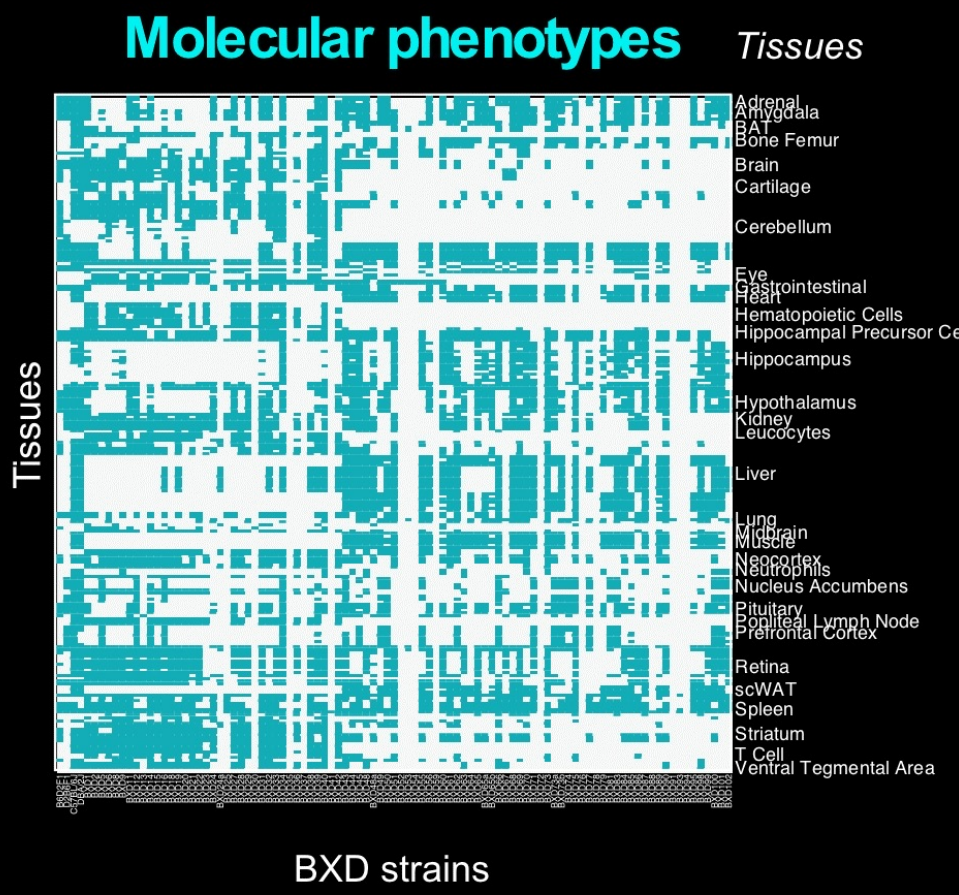
BXD Phenome - Clinical & Molecular





The BXD phenome has > 500 million datapoints

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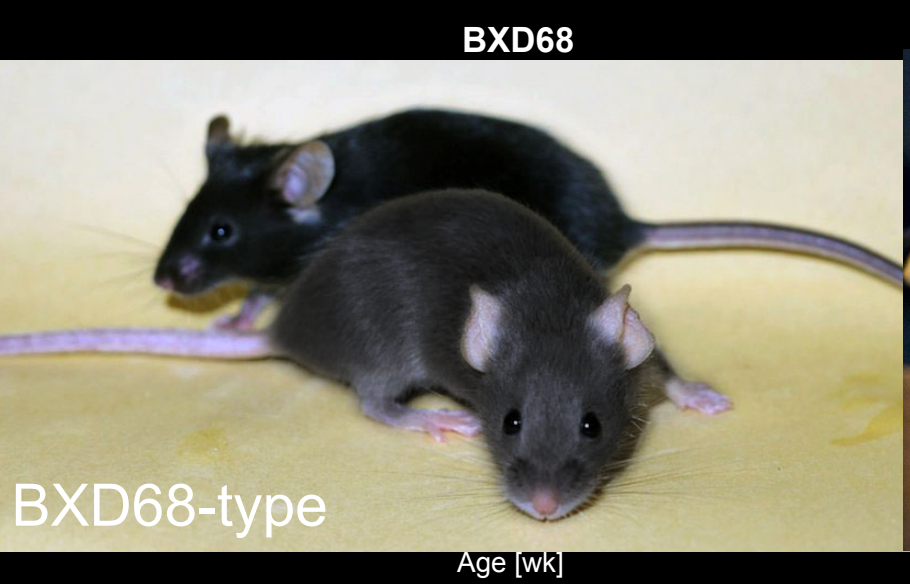
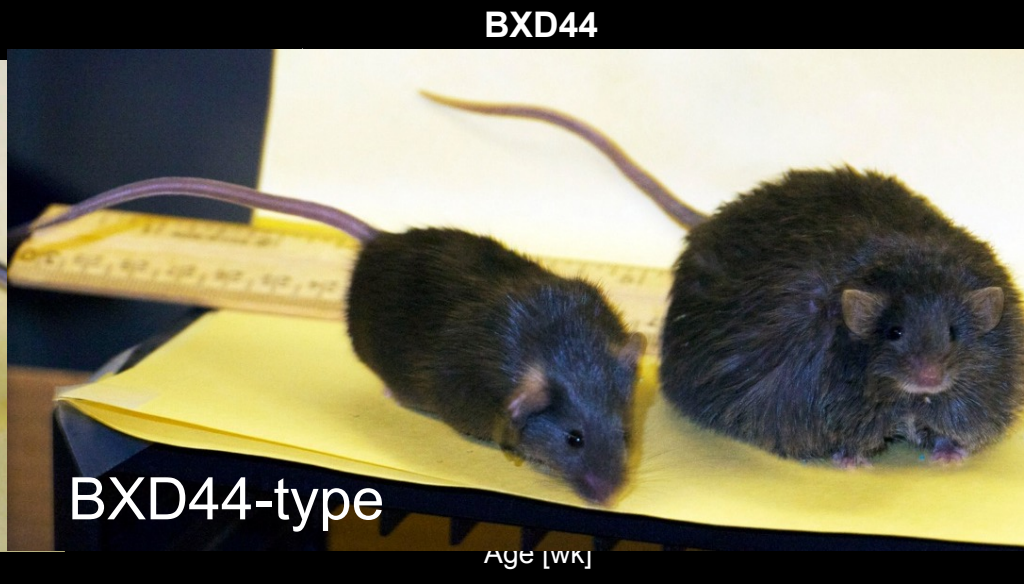
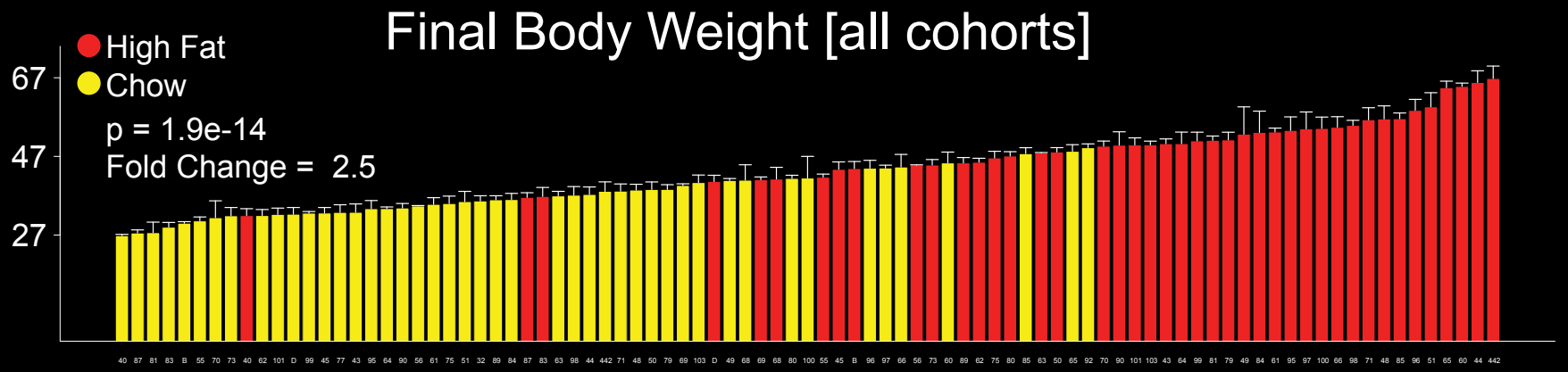
www.systems-genetics.org

Li et al, *Cell Systems*, 2018, 6, 90-102

Body weight (week 8-29) - examples







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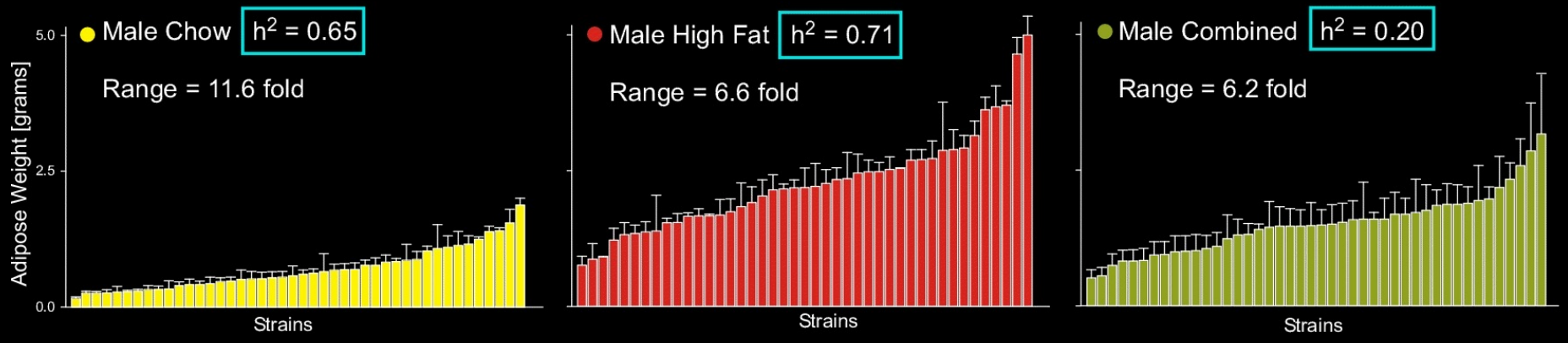
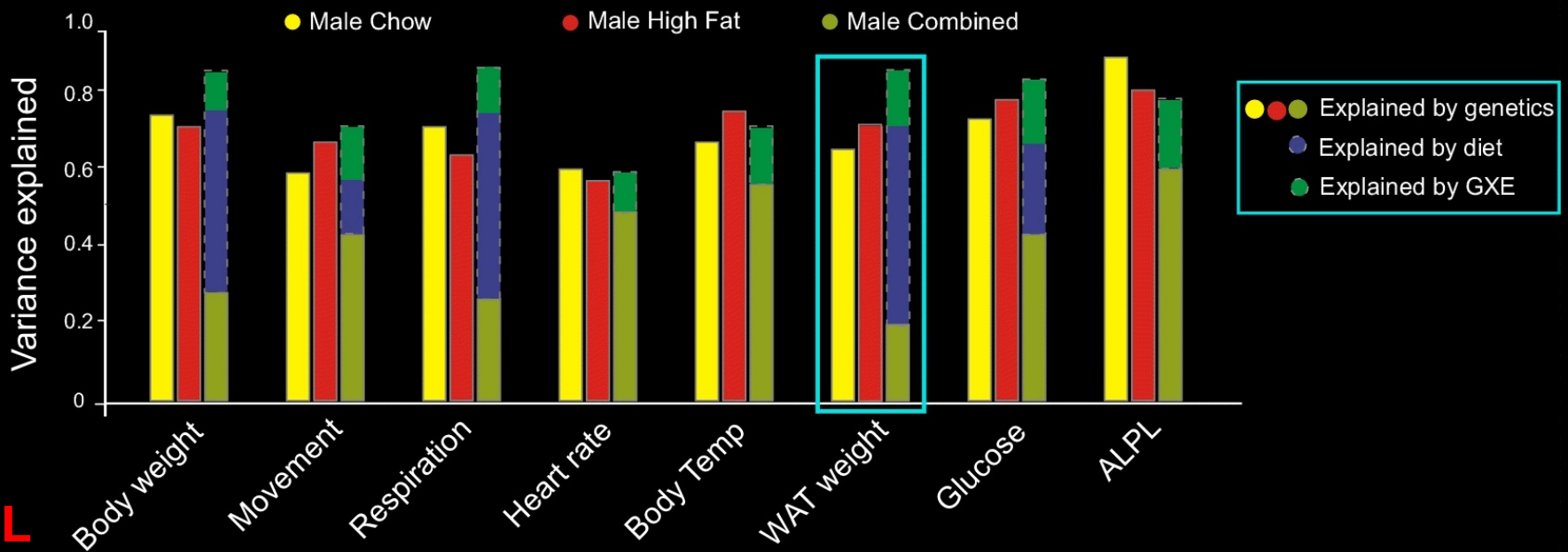
Wu et al, *Cell*, 2014, 158, 1415-1430

Heritability & environment

Heritability is the percentage of observed trait variation that can be attributed to genetic factors





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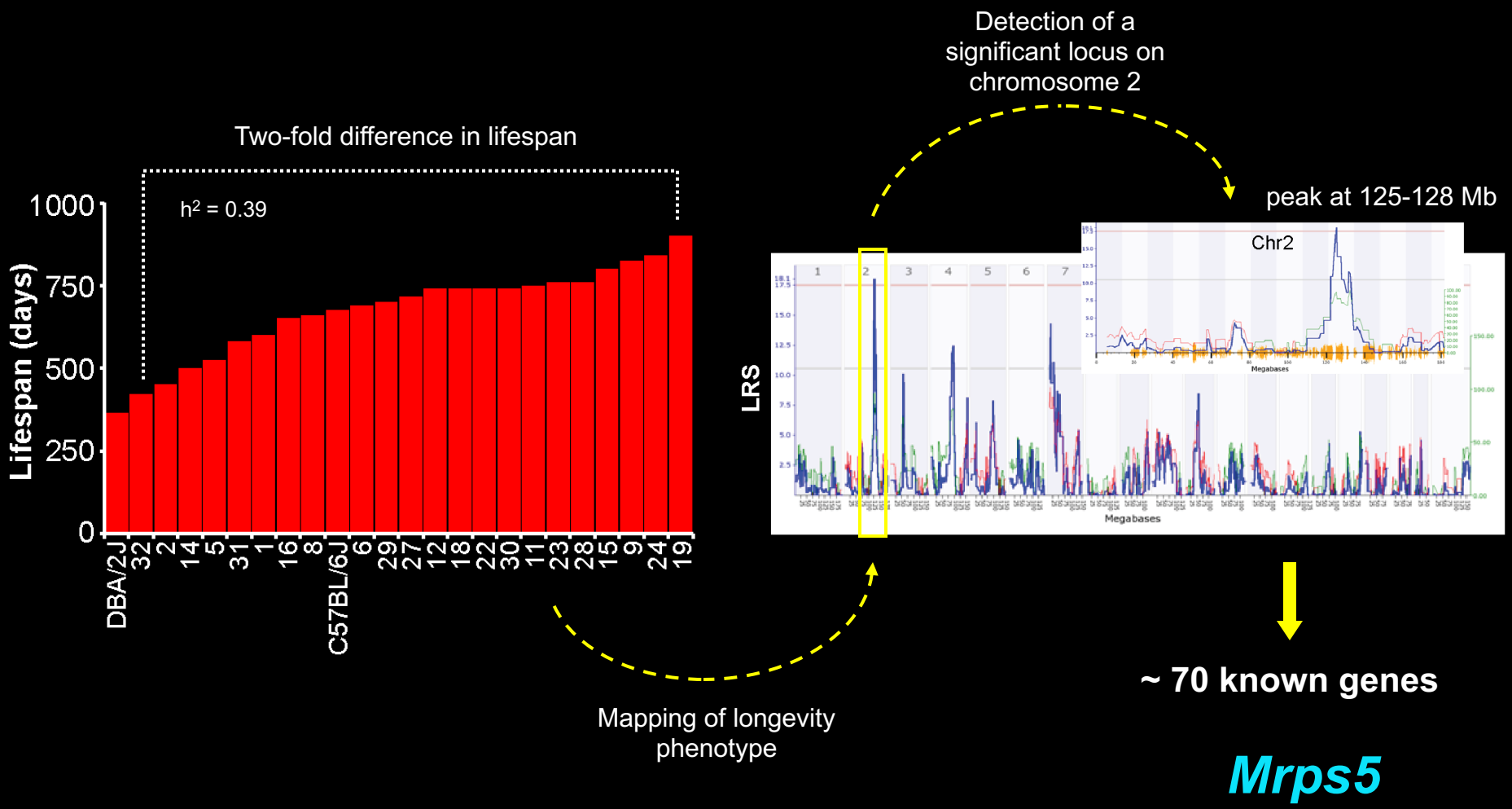
Lifespan variation maps to *Mrps5*

Forward genetic strategy



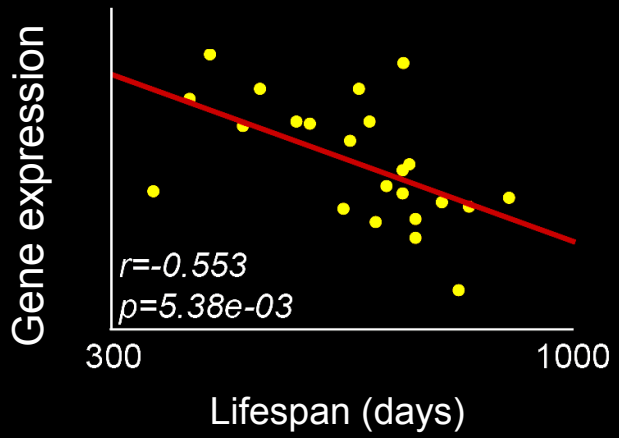
De Haan & Van Zant, *FASEB J,* 1999

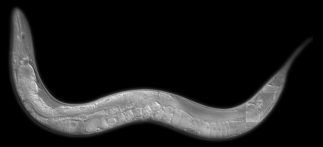
Houtkooper et al, *Nature,* 2013, 497, 451-7

The MRP family and longevity

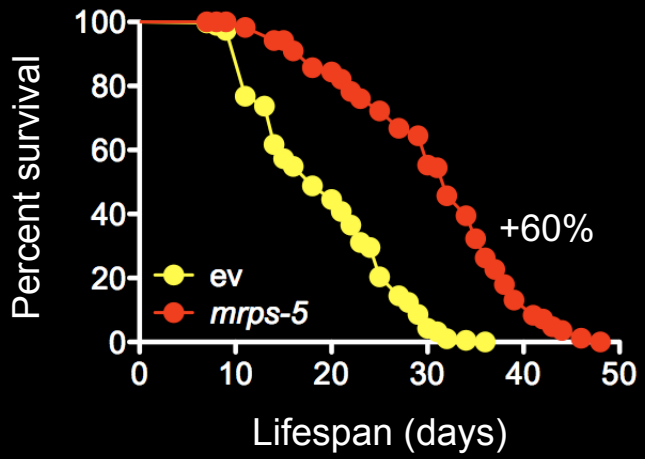
Integration of protein synthesis and mitochondrial metabolism

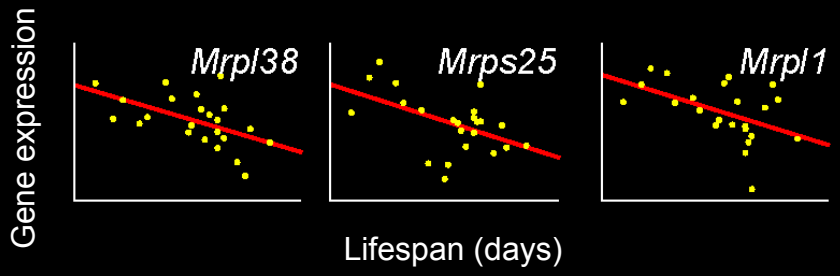
Mrps5

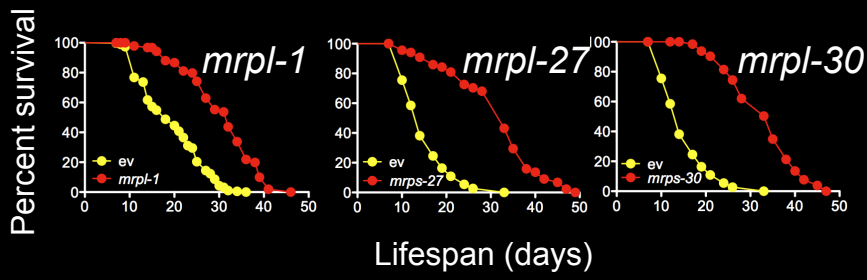




mrps-5







Houtkooper et al, *Nature,* 2013, 497, 451-7

..and also in humans MRPs are aging genes

Peters et al, *Nature Comm*, 2015, 6.8570

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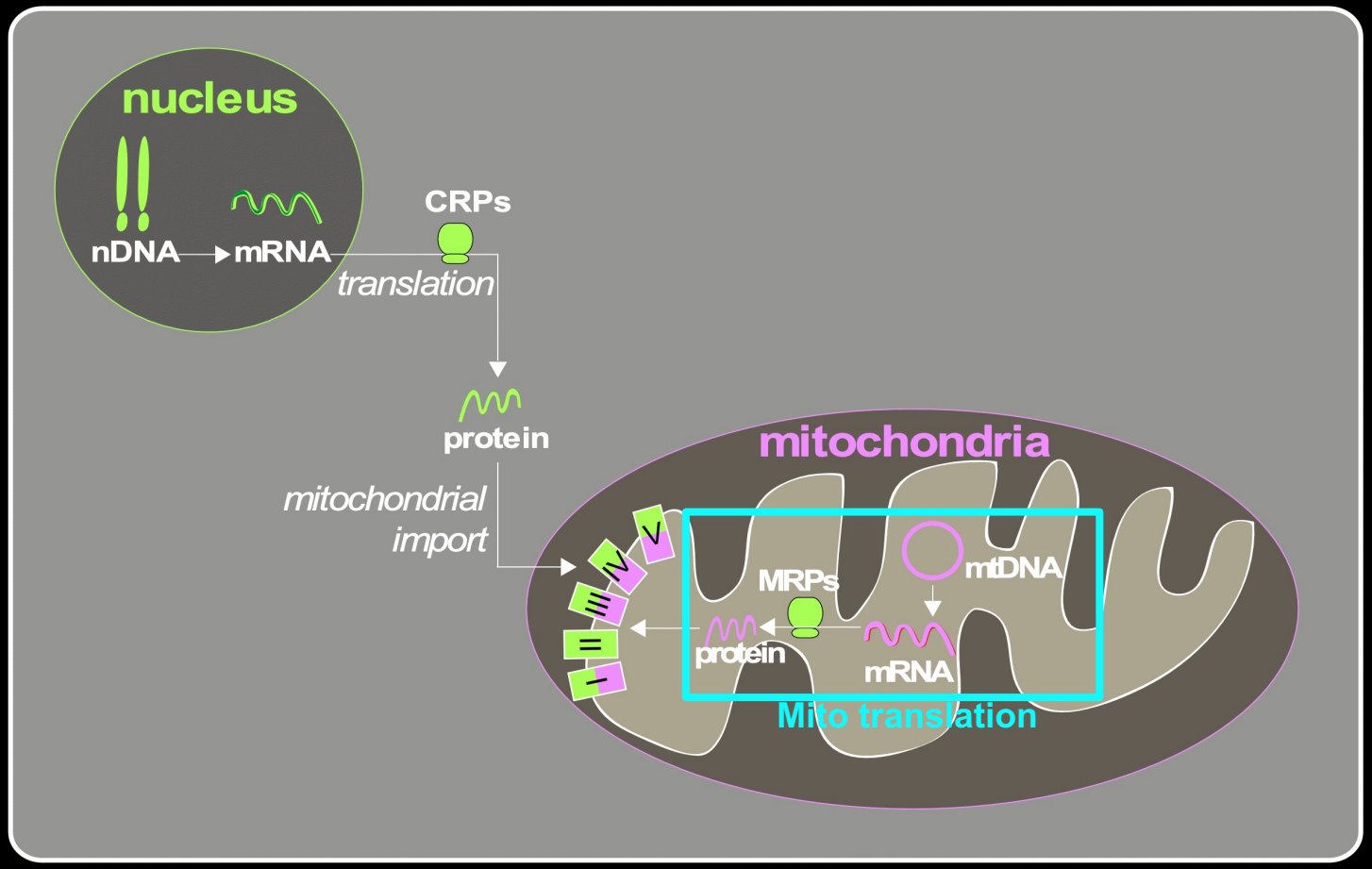
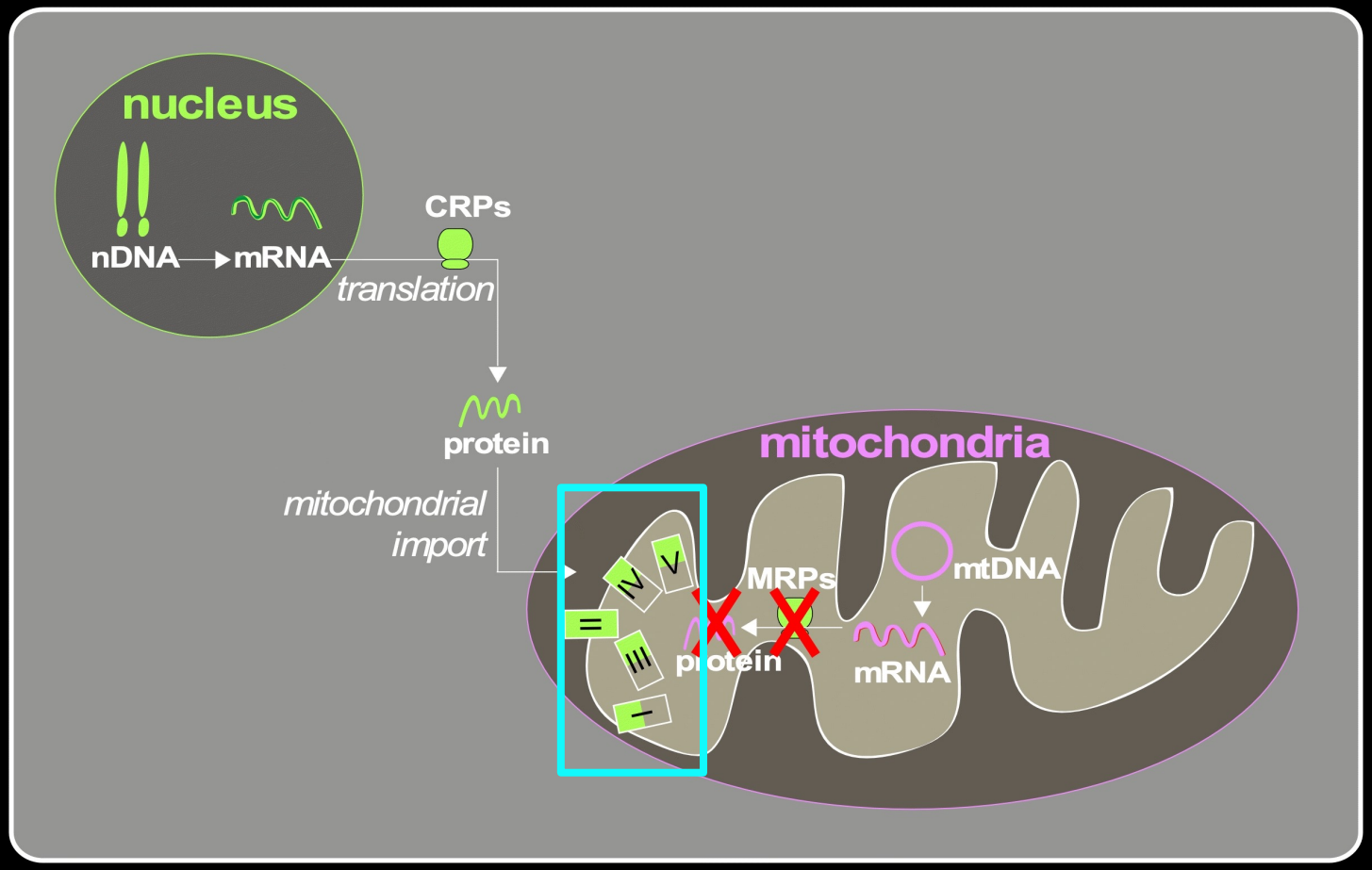
Mito-nuclear communication



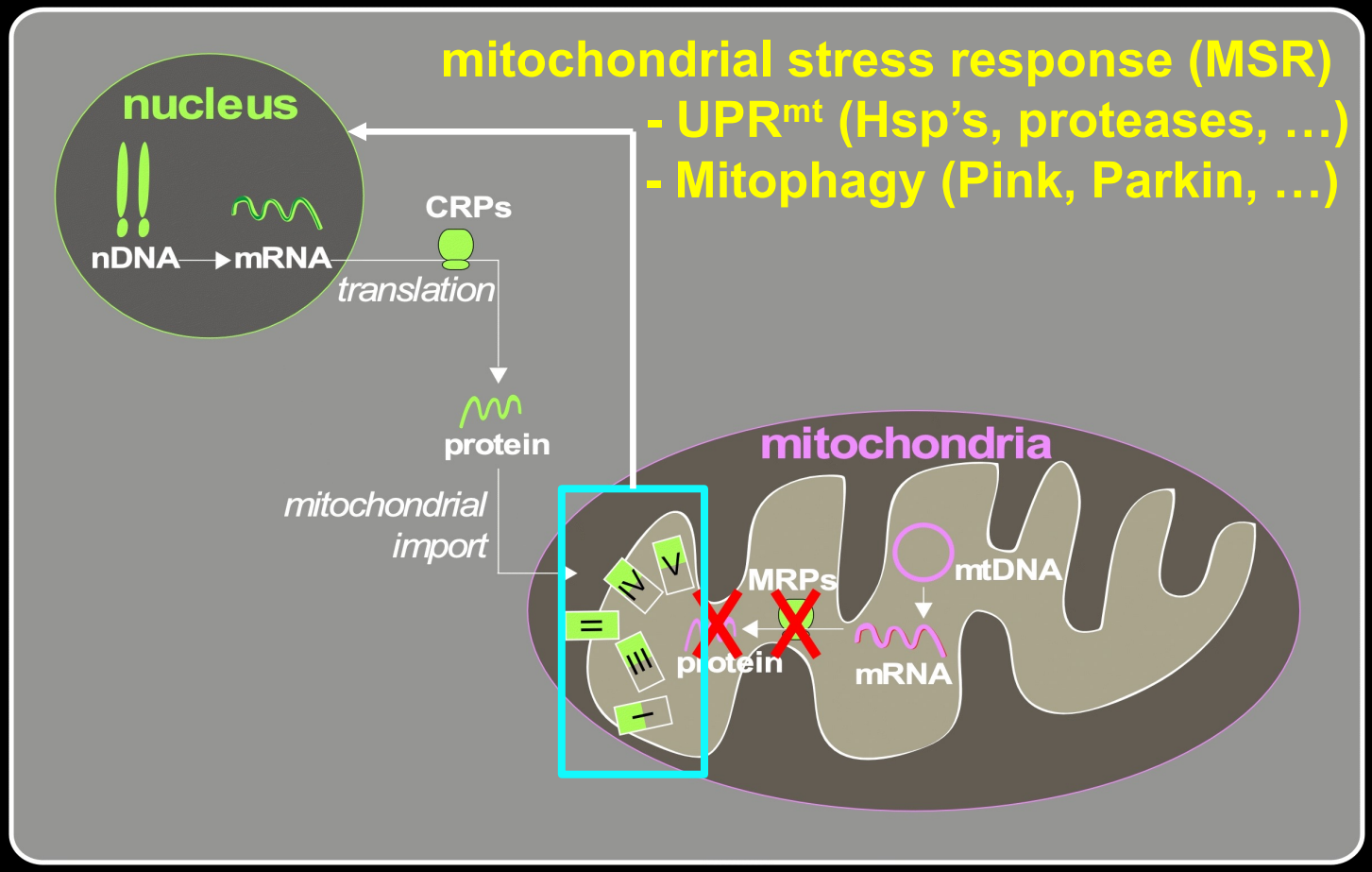
Mito-nuclear communication

Mito-nuclear protein imbalance – perturbed coordination of 2 genomes

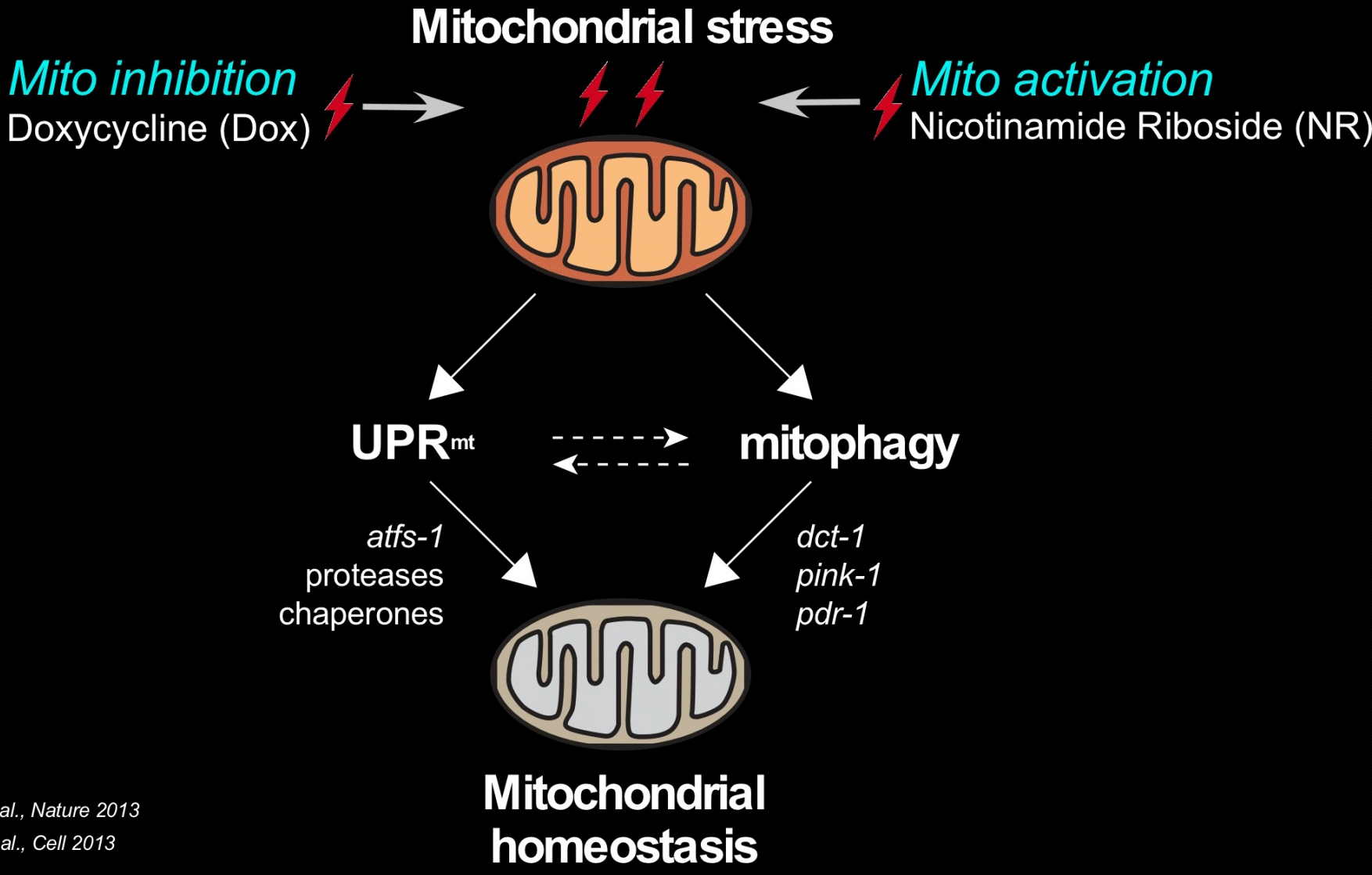


Mito-nuclear communication

Mito-nuclear protein imbalance – perturbed coordination of 2 genomes



Pharmacological enhancing the mitochondrial stress response (MSR)



Houtkooper et al., Nature 2013
Mouchiroud et al., Cell 2013

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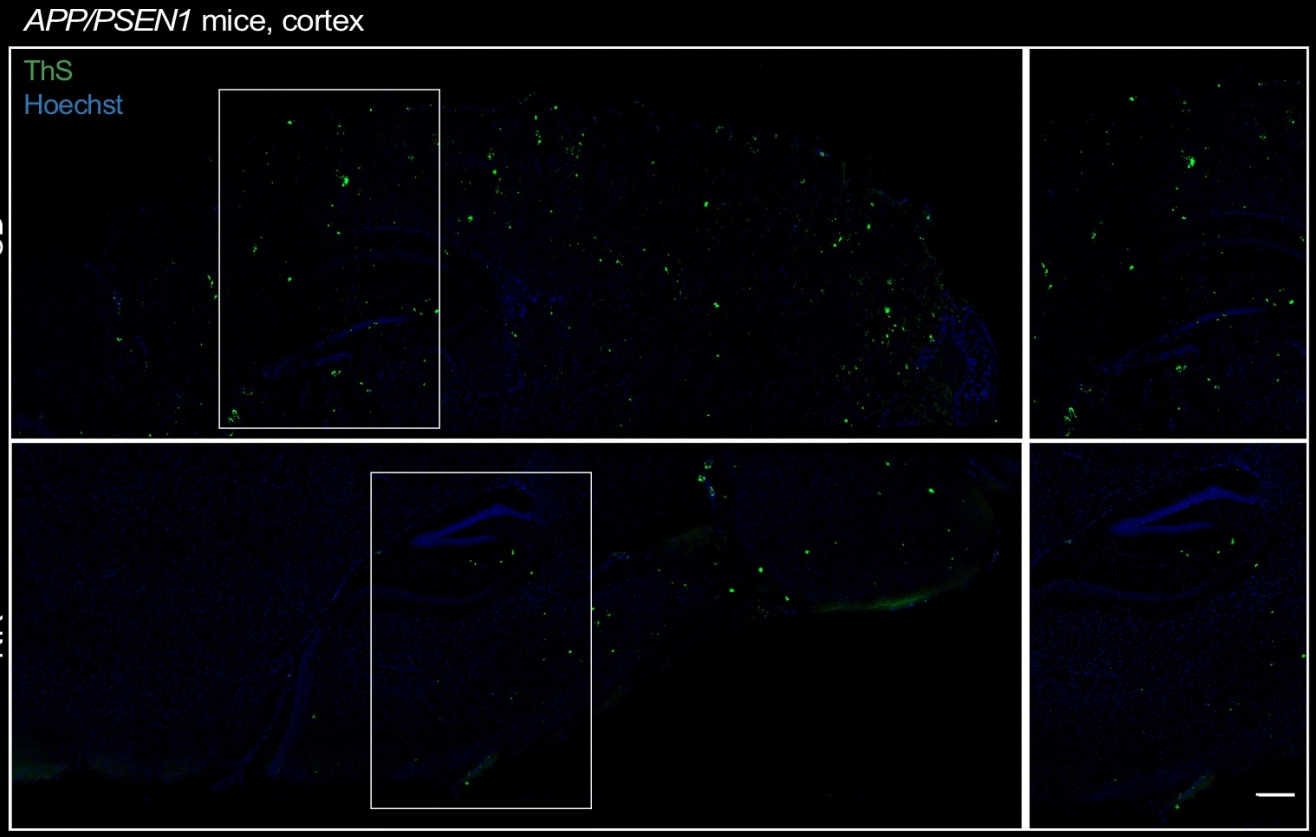
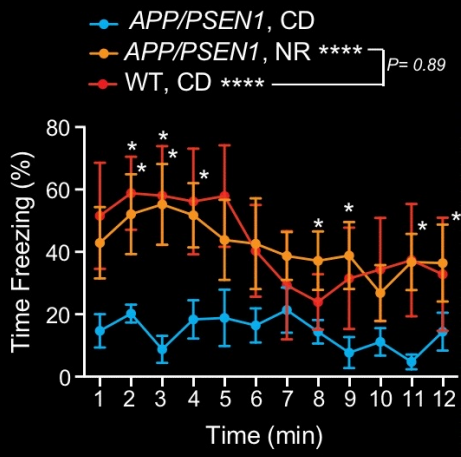
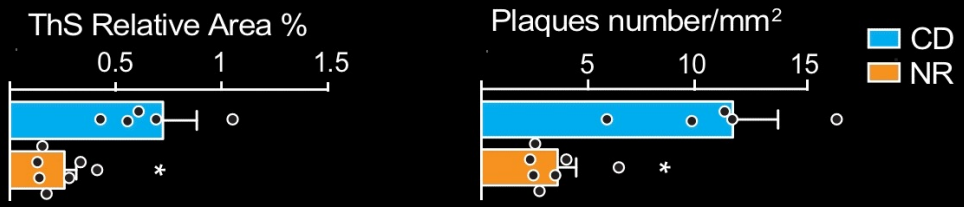
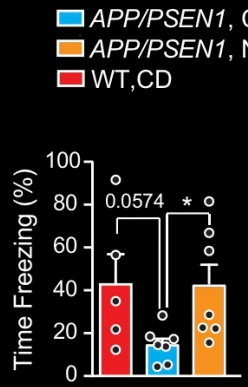
NR reduces aggregates and improves memory in an AD mouse model









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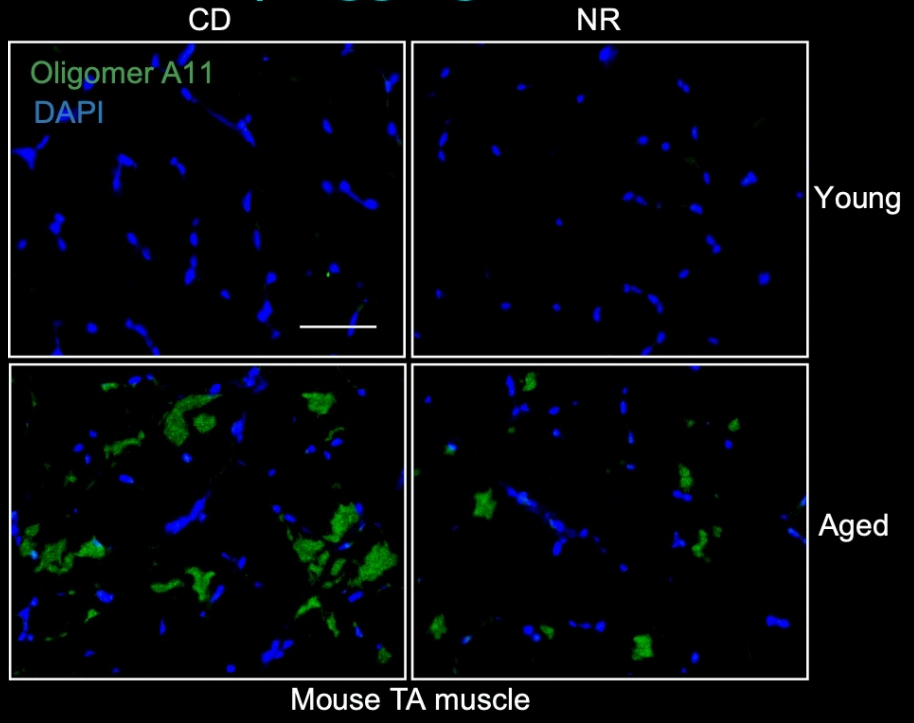
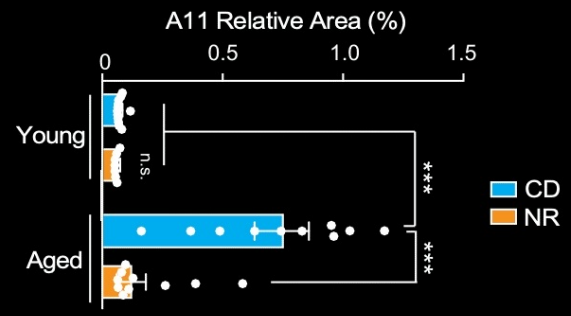
Sorrentino et al, *Nature,* 2017, 552, 187-93

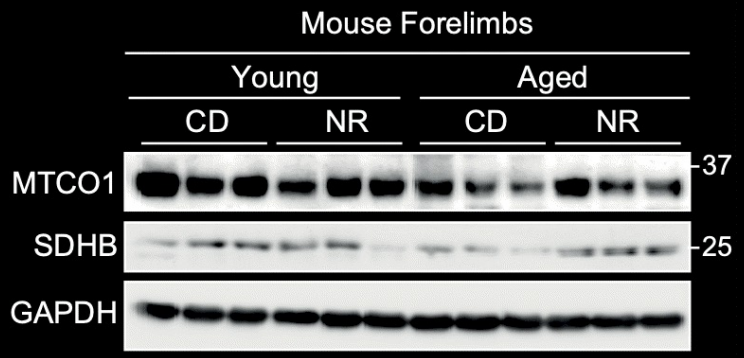
NAD boosting activates the MSR and reduces aggregates in aged mouse muscle

Aβ aggregation





Mitochondrial proteins



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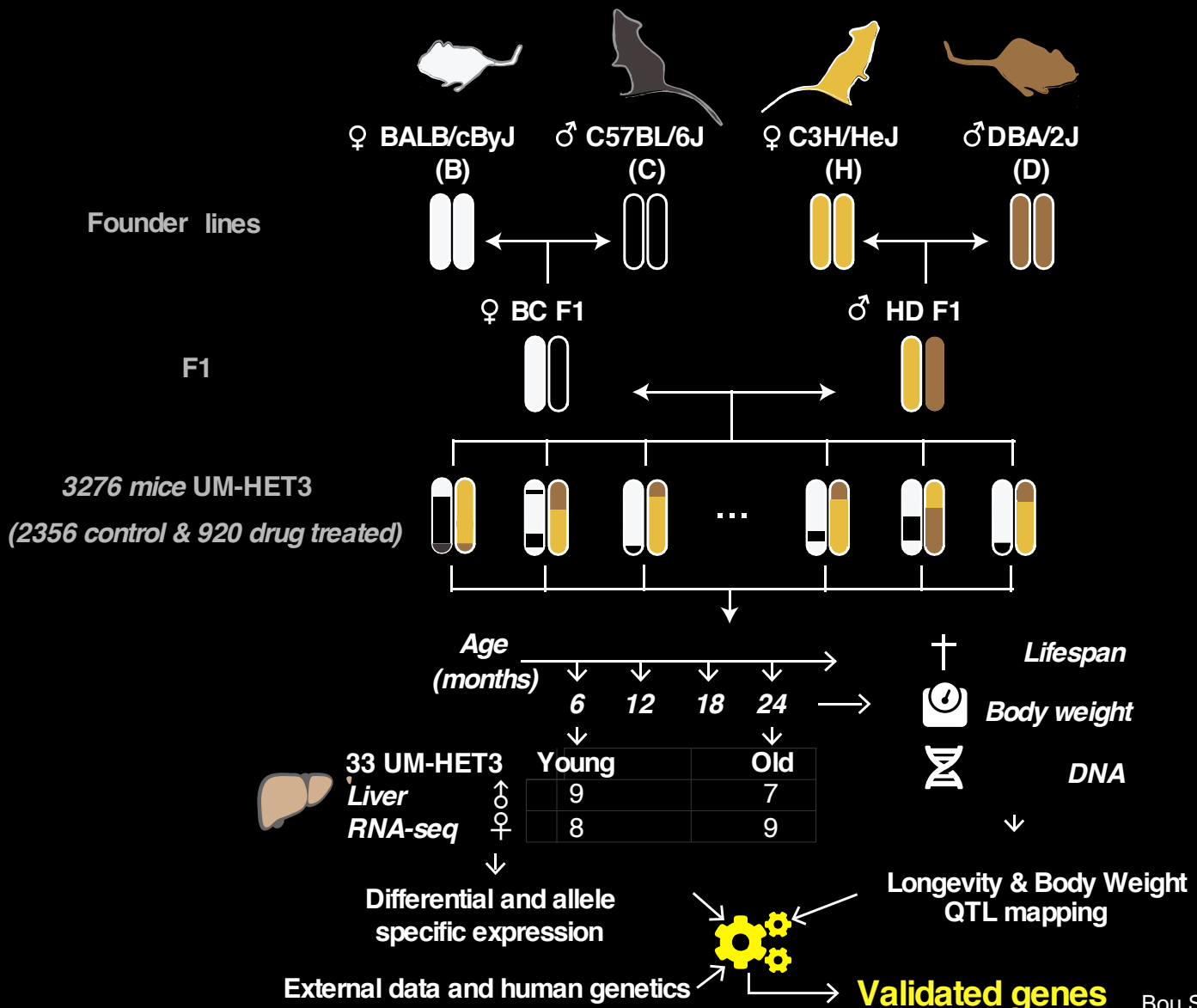
Romani et al, *Cell Rep,* 2021, 34, 108660

Genetic reference populations
Intervention Testing Program

- Metabolic phenotypes in male & female BXDs
- Intensive metabolic phenotypes for chow and high fat-fed BXDs
- Lifespan in BXDs
- NASH and CKD in the CC founders and F2 cross
- Lifespan in ITP controls
- Healthspan and mito stress in the HDPs

The ITP study - the elusive search for *bona fide* aging genes



Bou Sleiman et al, *Science*, 2022

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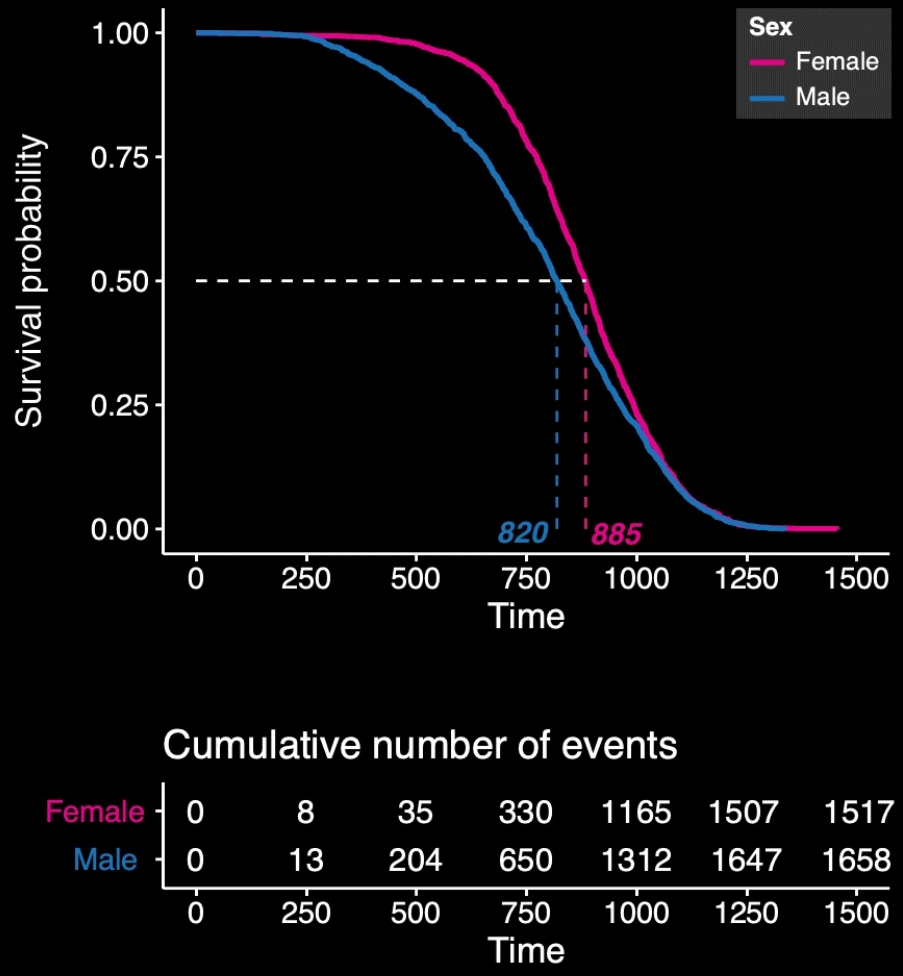
Females have higher median survival and males have higher early mortality



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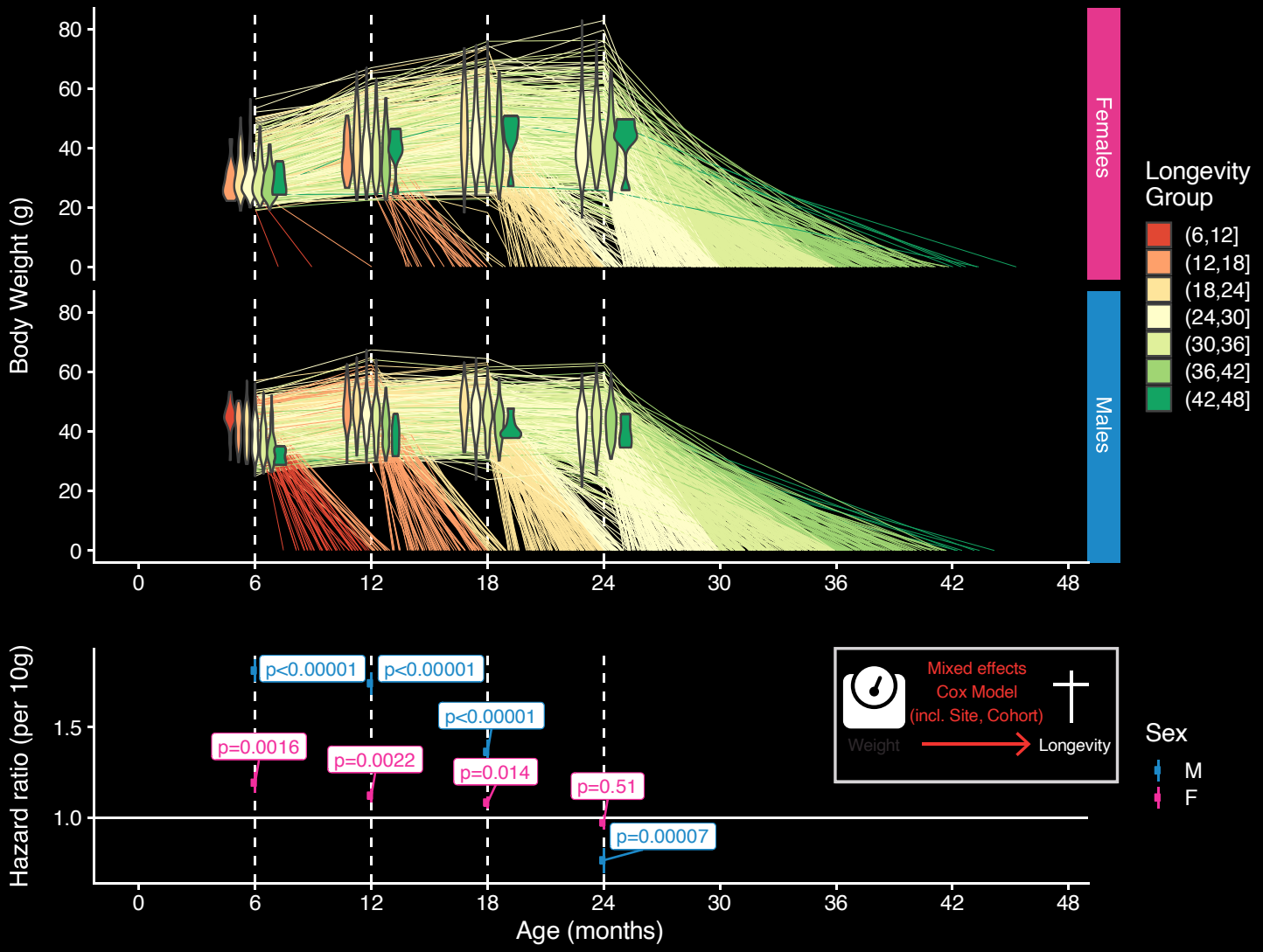
Bou Sleiman et al, *Science*, 2022, abo3191

Weight gain early in life shortens lifespan in male mice



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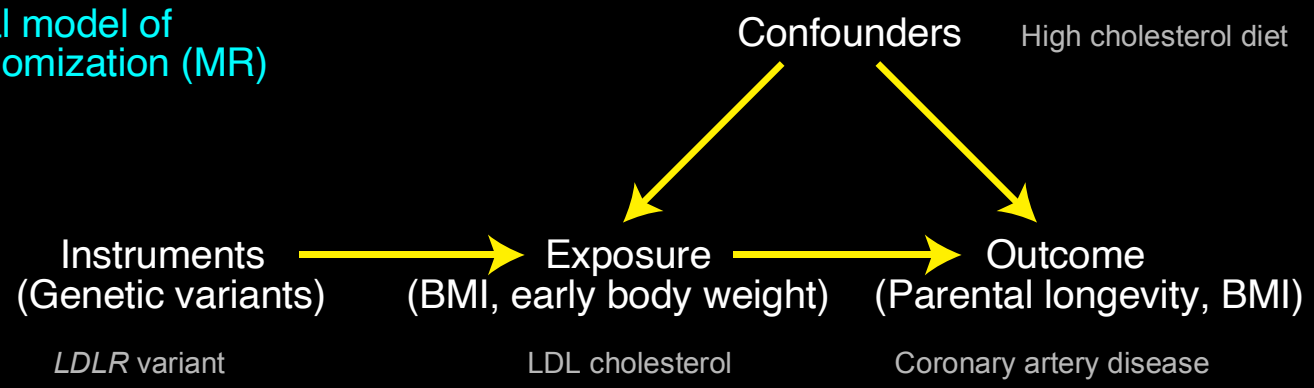
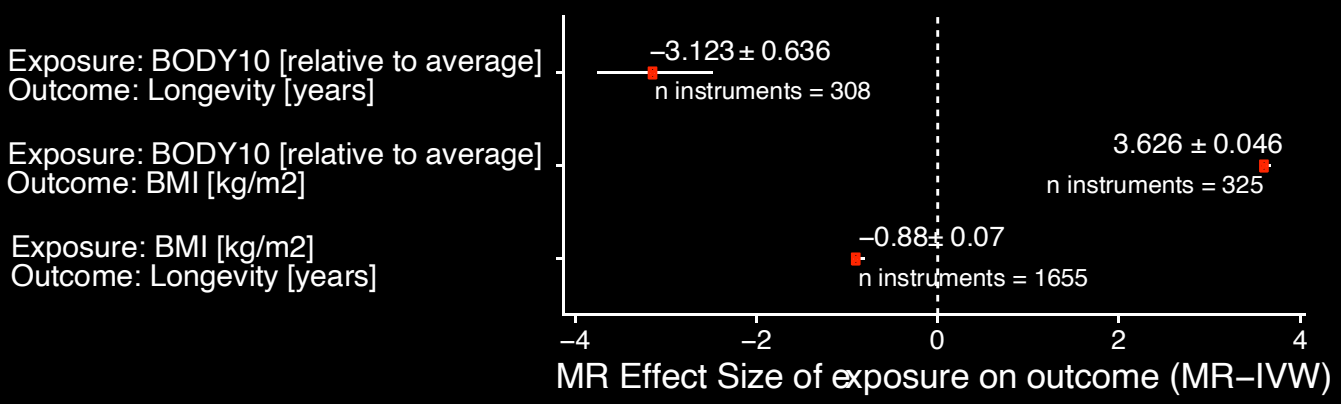
Bou Sleiman et al, *Science*, 2022, abo3191

Higher perceived body weight at 10 yrs associates with shorter parental lifespan

Conceptual model of
Mendelian Randomization (MR)





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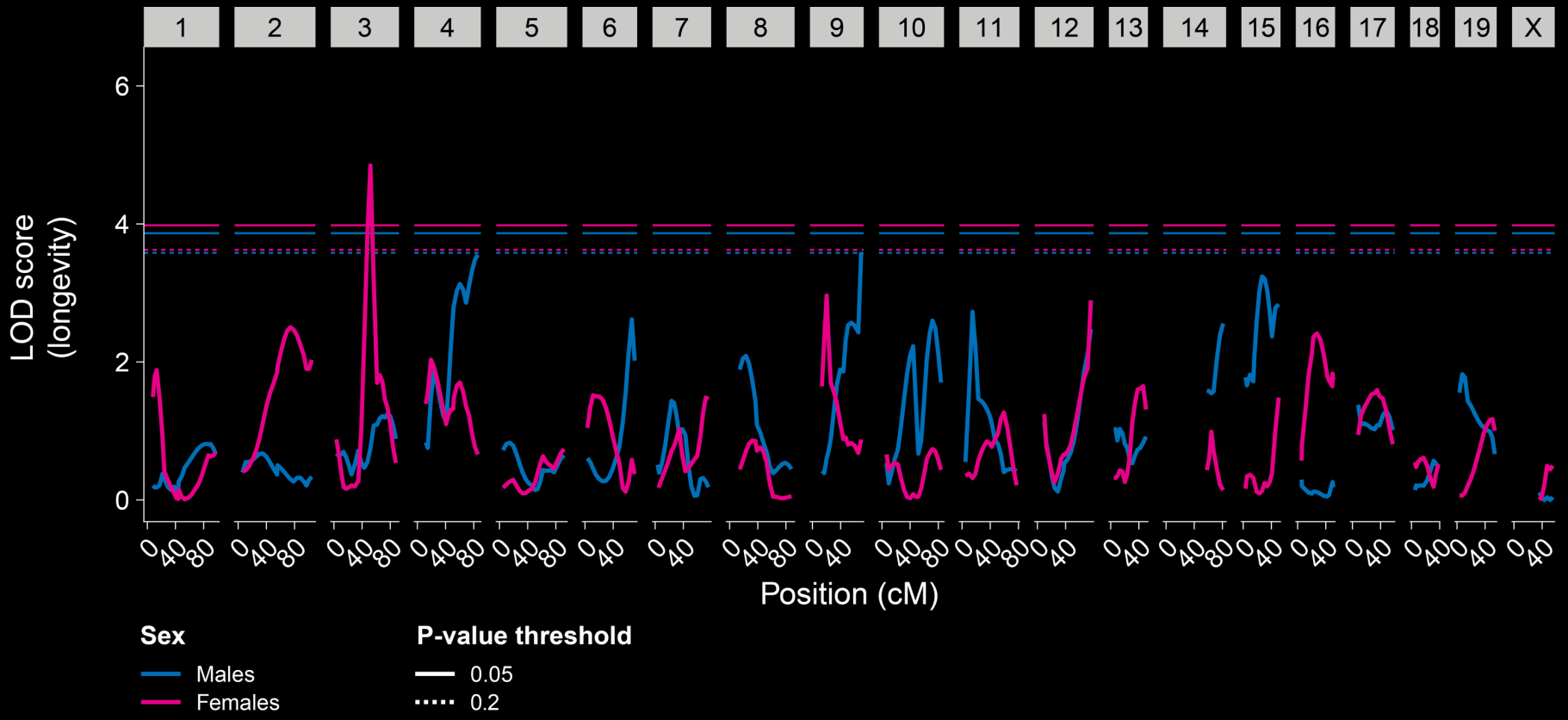
Bou Sleiman et al, *Science*, 2022, abo3191

Different male & female longevity genetics



- Sex-specific QTL scans do not overlap
- A female specific longevity locus on Chr3
- No male loci in full population

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Bou Sleiman et al, *Science*, 2022, abo3191

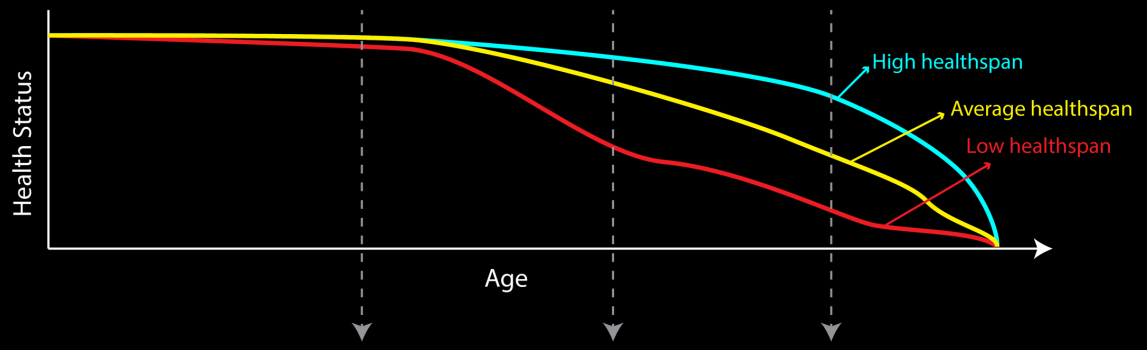
Genetic reference populations

Hybrid Diversity Panel (HDP)

- Metabolic phenotypes in male & female BXDs
- Intensive metabolic phenotypes for chow and high fat-fed BXDs
- Lifespan in BXDs
- NASH and CKD in the CC founders and F2 cross
- Lifespan in ITP controls
- Healthspan and mito stress in the HDPs

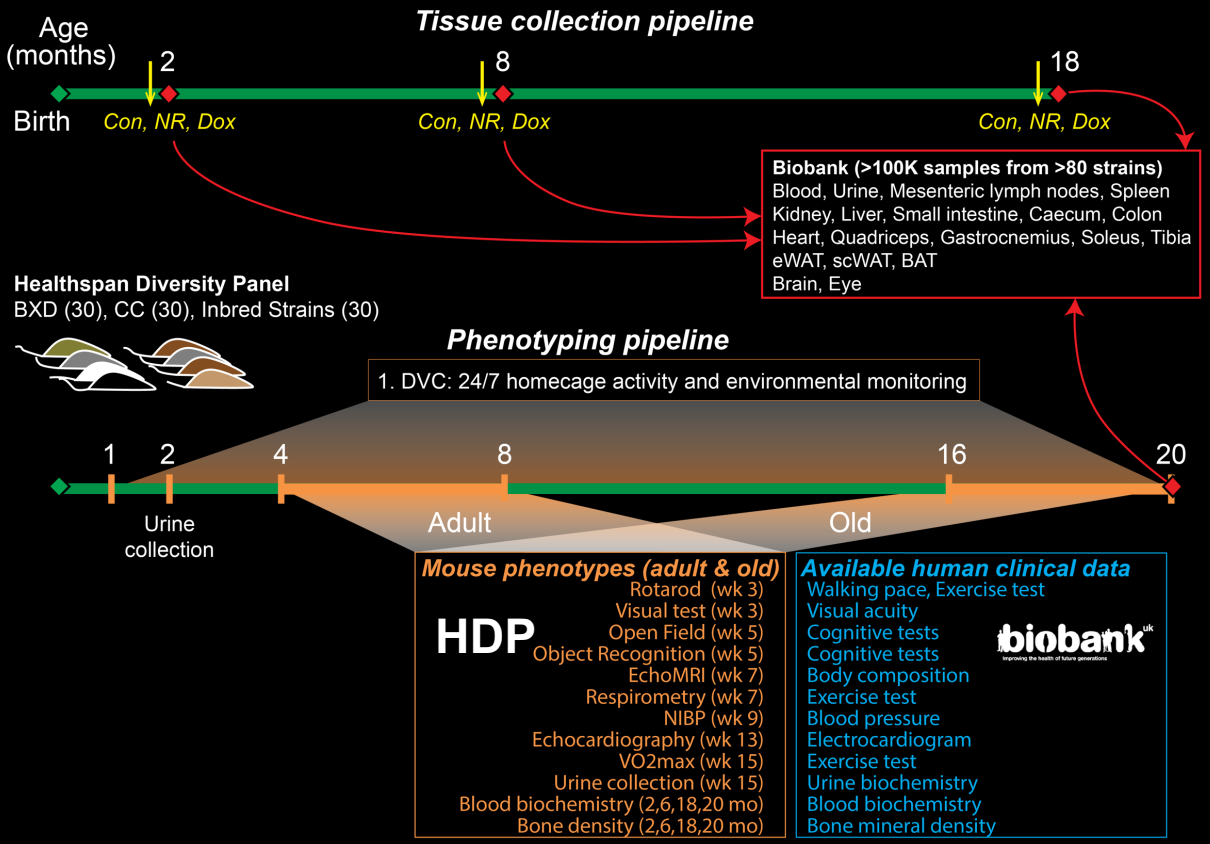
Healthspan, not lifespan, matters – can we measure it?

- Most studies are focused on longevity or lifespan, yet what is arguably more important is how long health is maintained. This is referred to as **healthspan**, the period of life that is disease-free.
- Studies in animal models and ultimately in humans will need to assess how the health degrades in a longitudinal manner during aging and define **the healthspan trajectory**.
- We need precise **healthspan metrics**, defined both in animal models and humans, that will allow us to search for underlying causes of its decline.
- Finding **common molecular denominators of aging differences** is critical. Lifespan and health are under genetic control that varies both within and between species. Once defined we can then intervene rationally.



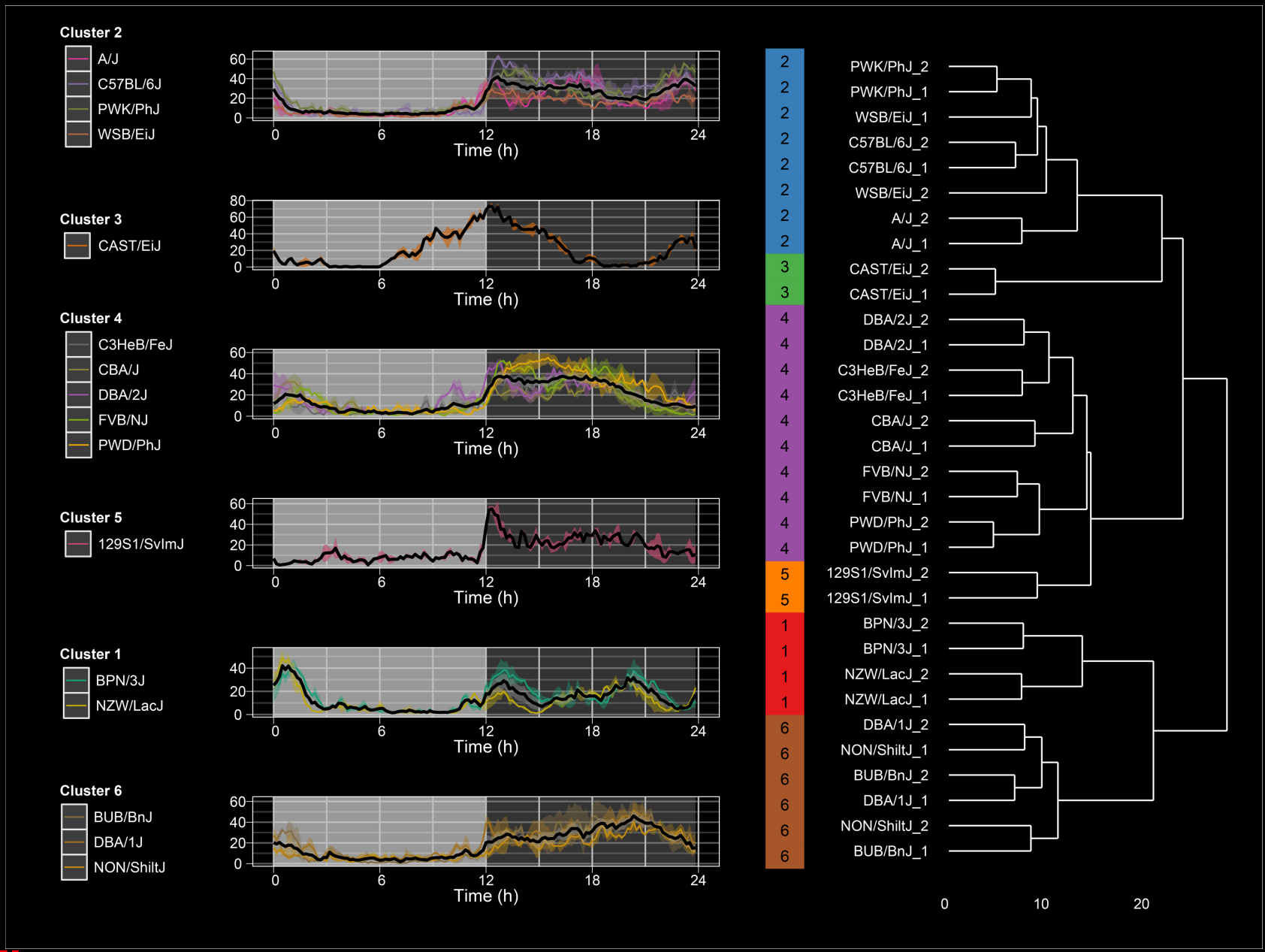
Longitudinal study design with frequent sampling and phenotyping in genetically diverse subjects is required to understand healthspan

The Healthspan Diversity Project (HDP) – collect healthspan metrics & define healthspan trajectories



- Longitudinal study – young, adult, old
- Started in 2018→ Q1 2023; >6500 mice; 23 tissues; >150,000 samples biobanked
- Clinical and molecular phenotypes (basal and challenged)
- Mice are monitored 24/7 – clinical, molecular, and genetic
- Design is complimentary to the UK Biobank, enabling seamless transition from mouse to man
- Data and sample management infrastructure established
- Ideal to generate digital twins

DVC – monitoring mice 24/7 throughout life



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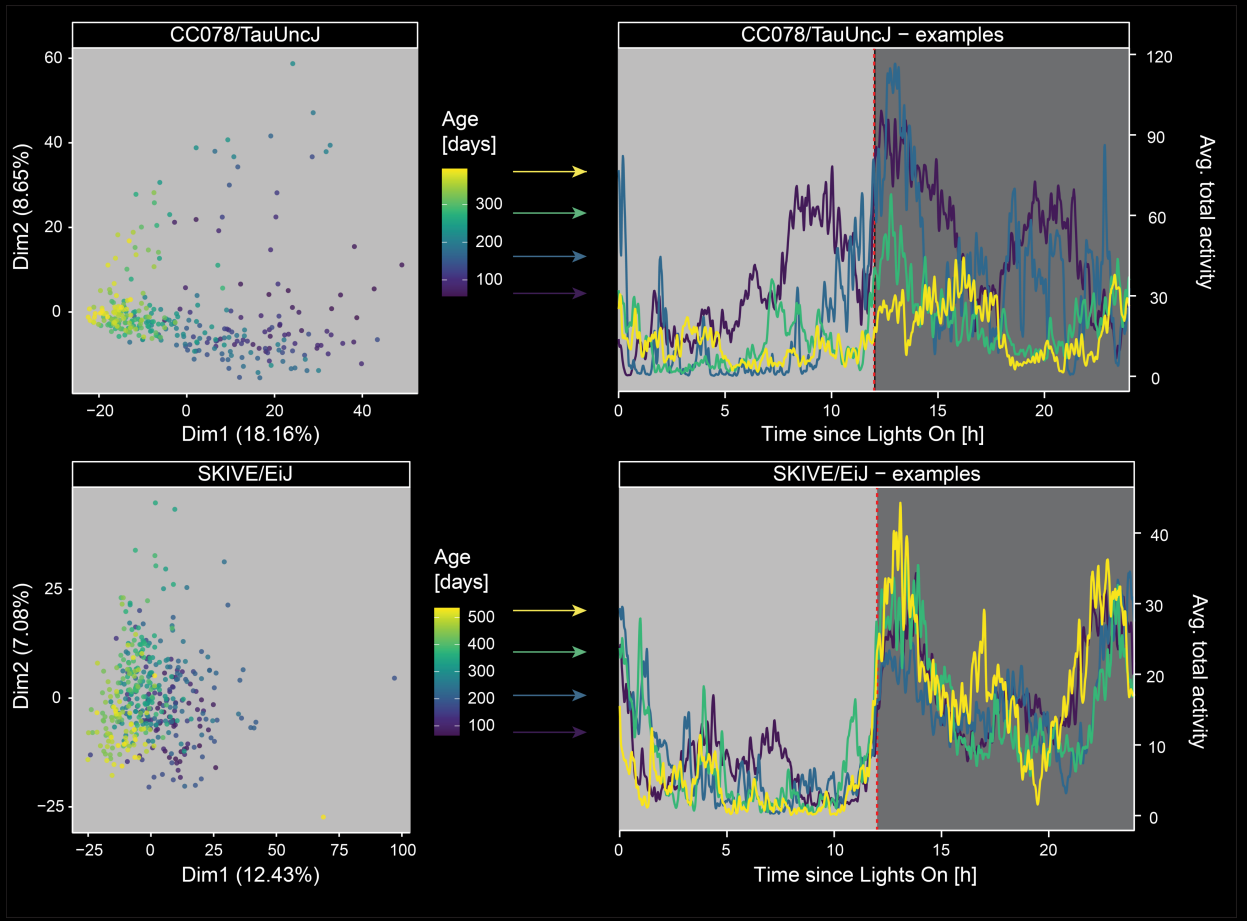
DVC reveals strain-specific changes in activity throughout life

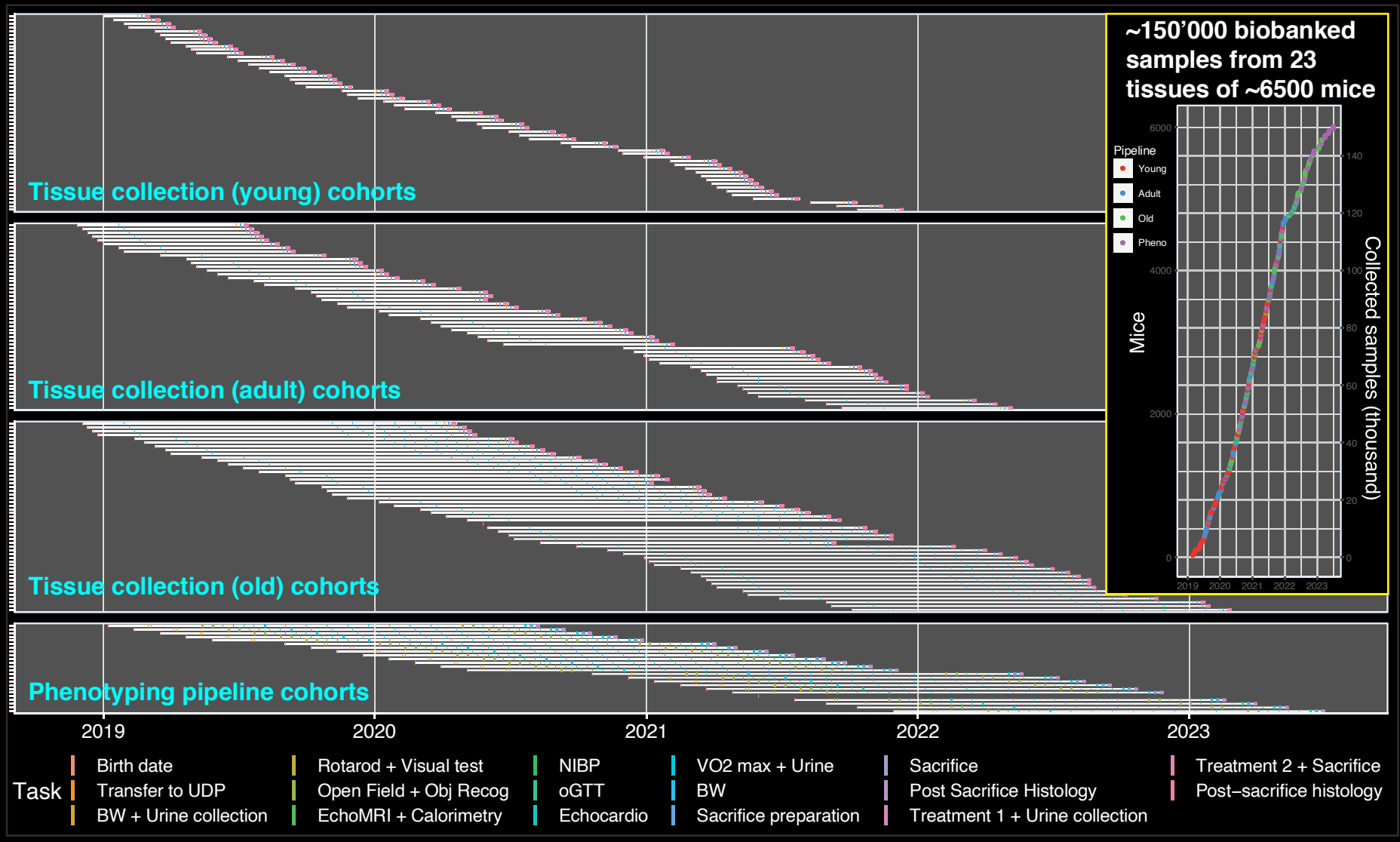
Fragmented sleep upon aging

No sleep fragmentation upon aging



Calculation of the sample entropy (aka as the Regularity Disruption Index – RDI) indicates age-linked sleep fragmentation only in the CC078, but not in the SKIVE, strain

The logistics of a longitudinal study



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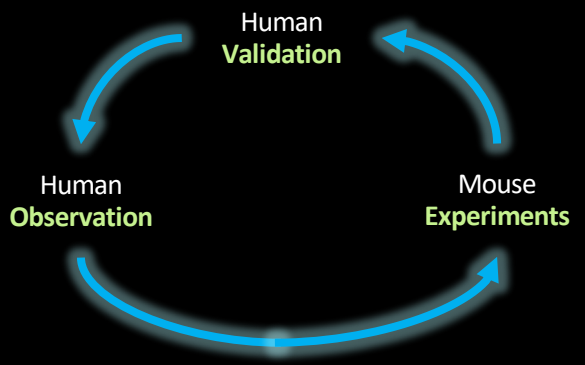
Conclusions

- GRPs provide flexible gene and pathway discovery platforms, allowing the dissection of complex traits and GXE interactions that are impossible in humans

- Experiments in GRPs can be seamlessly integrated with human studies creating a virtuous cycle fueling target discovery
  - ❖ Genetic (*Mrps-5* LOF) or pharmacological (tetracyclines, NAD^+ boosters) activation of the MSR reduces proteotoxic stress and increases health- and lifespan;
  - ❖ Elevated body weight at young age, but not adult BMI, determines lifespan;
  - ❖ Processes (e.g. mitohormesis, proteostasis, energy homeostasis, inflammation,..) rather than individual genes determine health- and lifespan;
  - ❖ These processes can be targeted to interfere with age-related diseases,as illustrated by efficacy in infection/inflammation, Alzheimer's disease, IBM and sarcopenia



Nadeau & Auwerx, *Nat. Rev. Drug Disc.*, 2019

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NIA - ITP collaborators

Rob Williams
Richard Miller & many others

University of Lausanne

Zoltan Kutalik

Janssen Pharmaceuticals

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Disclosure: Mitobridge, OrsoBio, NOV