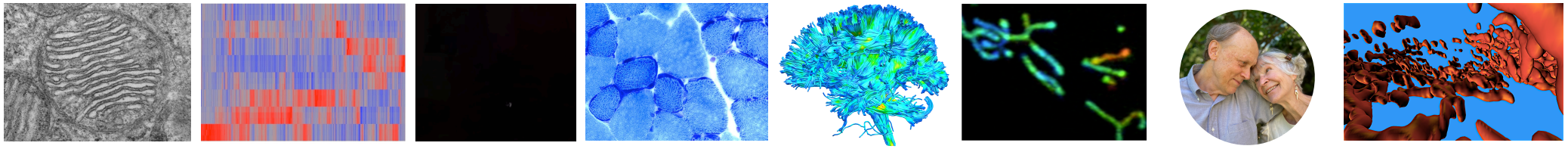
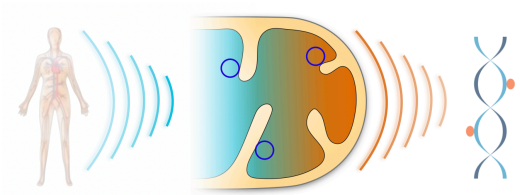


Energy → Mitochondria → Health

↗ Stress

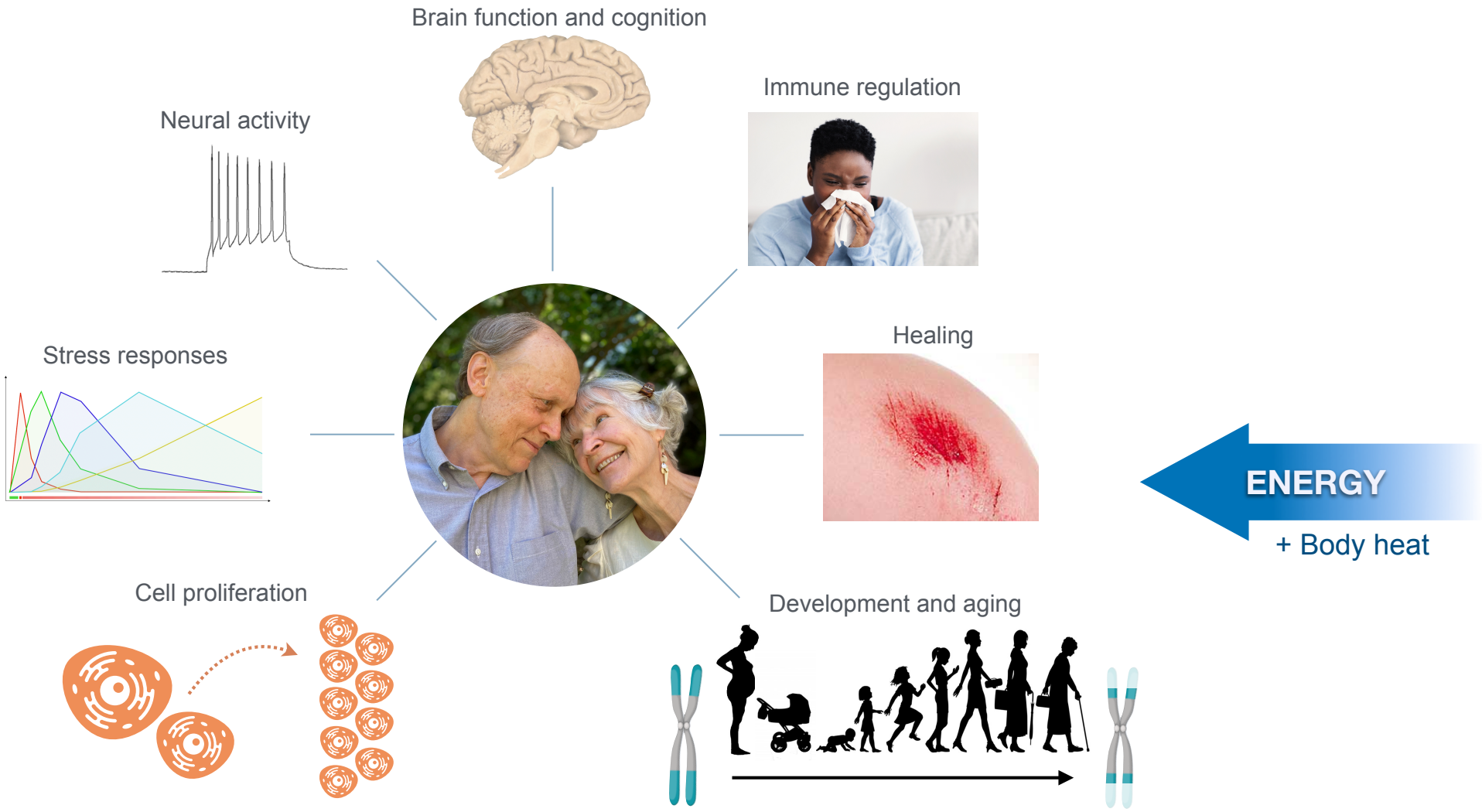


GSRNet Stress and Resilience Meeting - Lausanne 2024

Martin Picard, Ph.D.
Department of Psychiatry, Division of Behavioral Medicine
Department of Neurology, H. Houston Merritt Center
Columbia Translational Neuroscience Initiative
New York State Psychiatric Institute (NYSPI)
Robert N Butler Columbia Aging Center

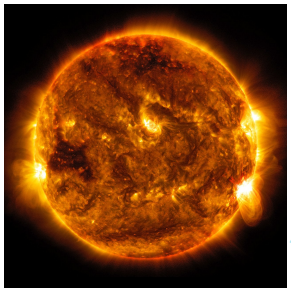
COLUMBIA
COLUMBIA UNIVERSITY
IRVING MEDICAL CENTER

NEW YORK STATE OF OPPORTUNITY. New York State Psychiatric Institute



BIOLOGY, PHYSIOLOGY, COGNITION, CONSCIOUSNESS

PSYCHOBIOLOGICAL ALLOSTATIC PROCESSES



Nuclear fusion
Quantum electrodynamics

Photons and heat

Oils and fats, proteins, carbohydrates

CO_2 + H_2O = $C_{17}H_{33}COOH$ + O_2

ENERGY STORED AS CHEMISTRY

Food

O_2

EATING and BREATHING

CO_2 H_2O

'Waste' products

Brain function and cognition

Neural activity

Immune regulation

Stress responses

Healing

Cell proliferation

Development and aging

ENERGY
+ Body heat

Electricity and Chemiosmosis
$\Delta\Psi m + \Delta pH$

Protons (H+)

Electrons

TCA Cycle

Beta Oxidation

Carbon substrates

Electron transport chain

O_2 H_2O

ATP

mtDNA

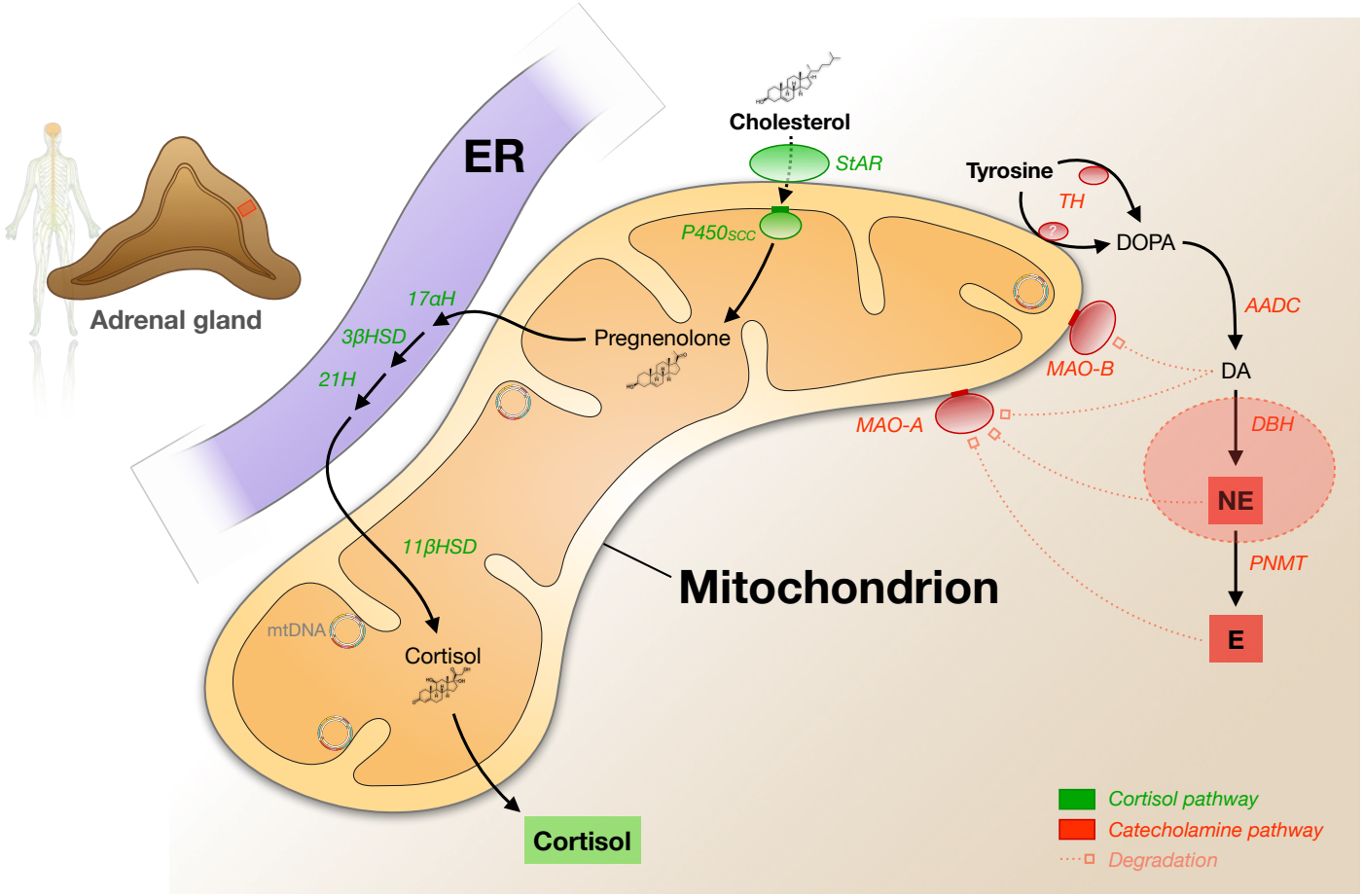
BIOLOGY, PHYSIOLOGY, COGNITION, CONSCIOUSNESS
PSYCHOBIOLOGICAL ALLOSTATIC PROCESSES

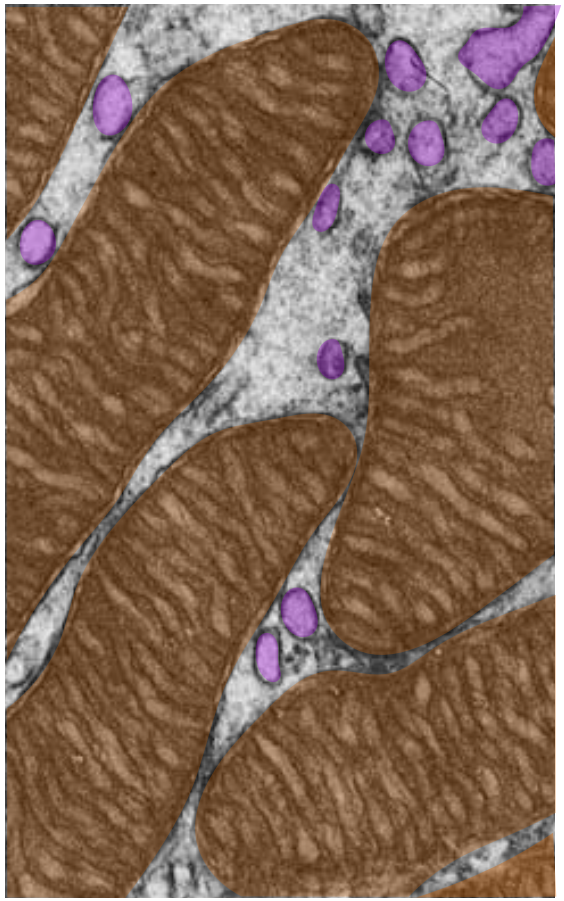
CHEMICAL ENERGY TRANSFORMED INTO
ELECTROCHEMICAL FORCE

Biochemistry 2022

Mitochondria and stress hormone synthesis?

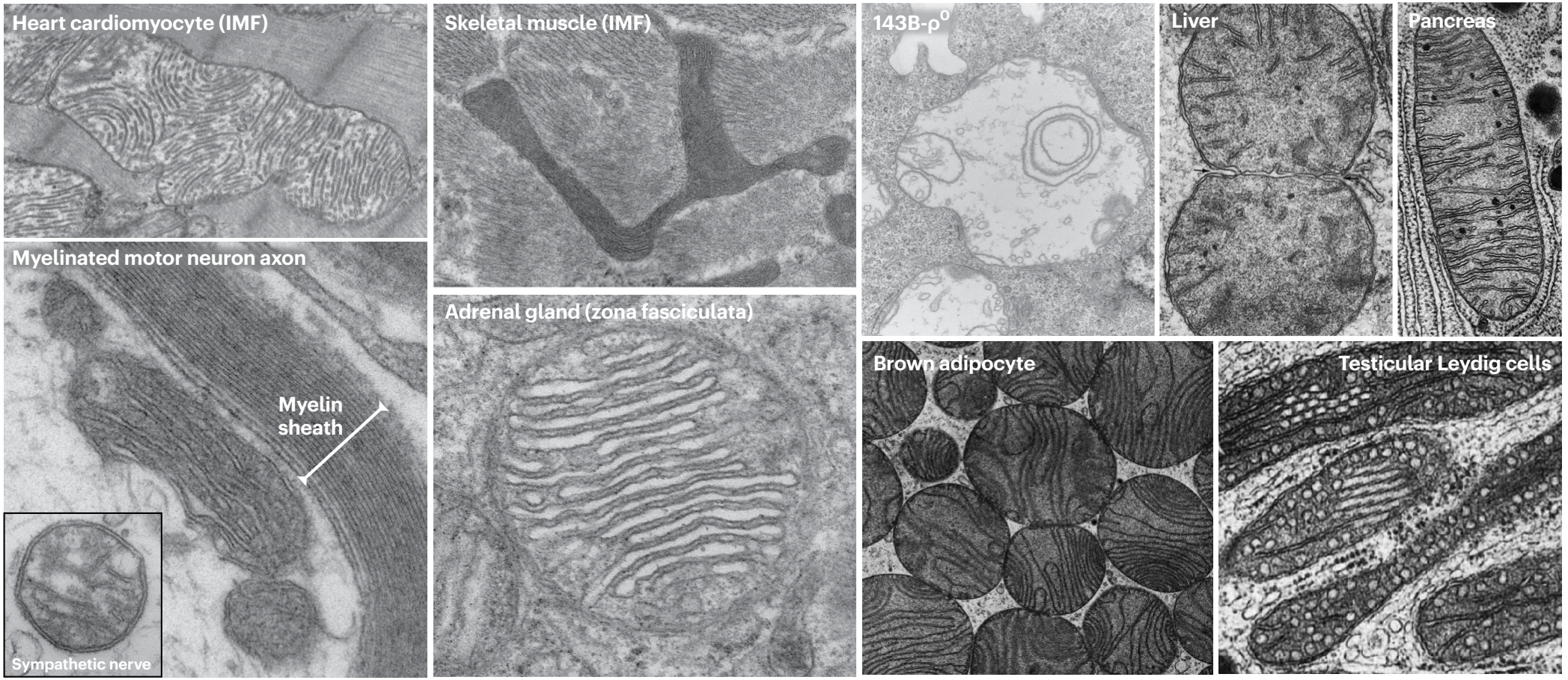
Mitochondria synthesize glucocorticoid and sex hormones

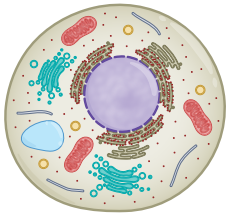




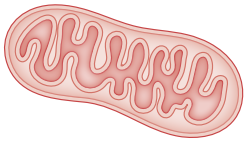
Picard, McEwen, Epel, Sandi. **An energetic view of stress.** *Front Neuroendocrinol* 2018

Different mitochondria types (mitotypes)





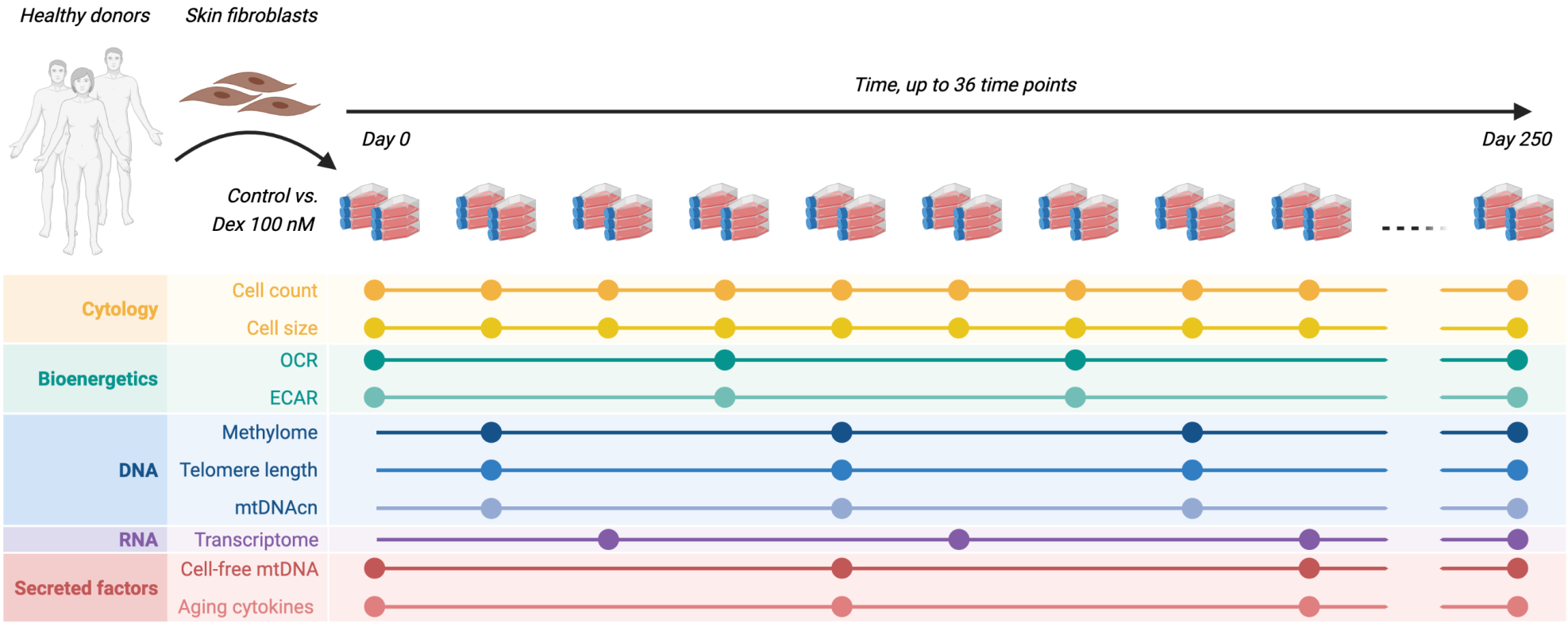
Cell types and subtypes

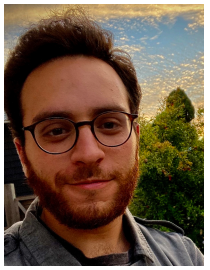


Mitochondrial phenotypes

Monzel et al.
Nat Metab 2023

Cellular lifespan model of chronic stress





Gabriel Sturm

Natalia Bobba-Alves

scientific data

OPEN

DATA DESCRIPTOR

A multi-omics longitudinal aging dataset in primary human fibroblasts with mitochondrial perturbations

Gabriel Sturm[1,2], Anna S. Monzel[1], Kalpita R. Karan[1], Jeremy Michelson[1], Sarah A. Ware[3], Andres Cardenas[4], Jue Lin[2], Céline Bris[5,6], Balaji Santhanam[7], Michael P. Murphy[8], Morgan E. Levine[9,10], Steve Horvath[10,11], Daniel W. Belsky[12], Shuang Wang[13], Vincent Procaccio[5,6], Brett A. Kaufman[3], Michio Hirano[14] & Martin Picard[1,14,15] ✉

Aging is a process of progressive change. To develop biological models of aging, longitudinal datasets with high temporal resolution are needed. Here we report a multi-omics longitudinal dataset for cultured primary human fibroblasts measured across their replicative lifespans. Fibroblasts were sourced from both healthy donors (n = 6) and individuals with lifespan-shortening mitochondrial disease (n = 3). The dataset includes cytological, bioenergetic, DNA methylation, gene expression, secreted proteins, mitochondrial DNA copy number and mutations, cell-free DNA, telomere length, and whole-genome sequencing data. This dataset enables the bridging of mechanistic processes of aging as outlined by the "hallmarks of aging", with the descriptive characterization of aging such as epigenetic age clocks. Here we focus on bridging the gap for the hallmark mitochondrial metabolism. Our dataset includes measurement of healthy cells, and cells subjected to over a dozen experimental manipulations targeting oxidative phosphorylation (OxPhos), glycolysis, and glucocorticoid signaling, among others. These experiments provide opportunities to test how cellular energetics affect the biology of cellular aging. All data are publicly available at our webtool: https://columbia-picard.shinyapps.io/shinyapp-Lifespan_Study/

columbia-picard.shinyapps.io

Cellular Lifespan Study

Mitochondrial Psychobiology Lab, Columbia University Medical Center

Type/Select one or more Cell Lines:

Cell Lines

HC1 (hFB12): primary human fibroblast, breast, healthy, male, 18yo

SURF1_2 (hFB7): primary human fibroblast, upper arm, SURF1 Mutation, male, 11yo

Type/Select one or more Treatments:

Treatments

Untreated Control (HC1,2,3,4,5,6, SURF1_1,2,3)

- [x] Show Legend

Select one or more phases of the study (for matching ctrls):

- [x] Phase I (mitoQ,NAC,a-keto)
- [x] Phase II (DEX,mitoNUIts,Oligo)
- [ ] Phase III (contact inhibition,hypoxia)
- [ ] Phase IV (galactose,hydroxybuturate,2DG)
- [ ] Phase V (SURF1 hypoxia)

Normalize to:

- [ ] Cell Volume
- [ ] Divisions
- [ ] Age of Donor

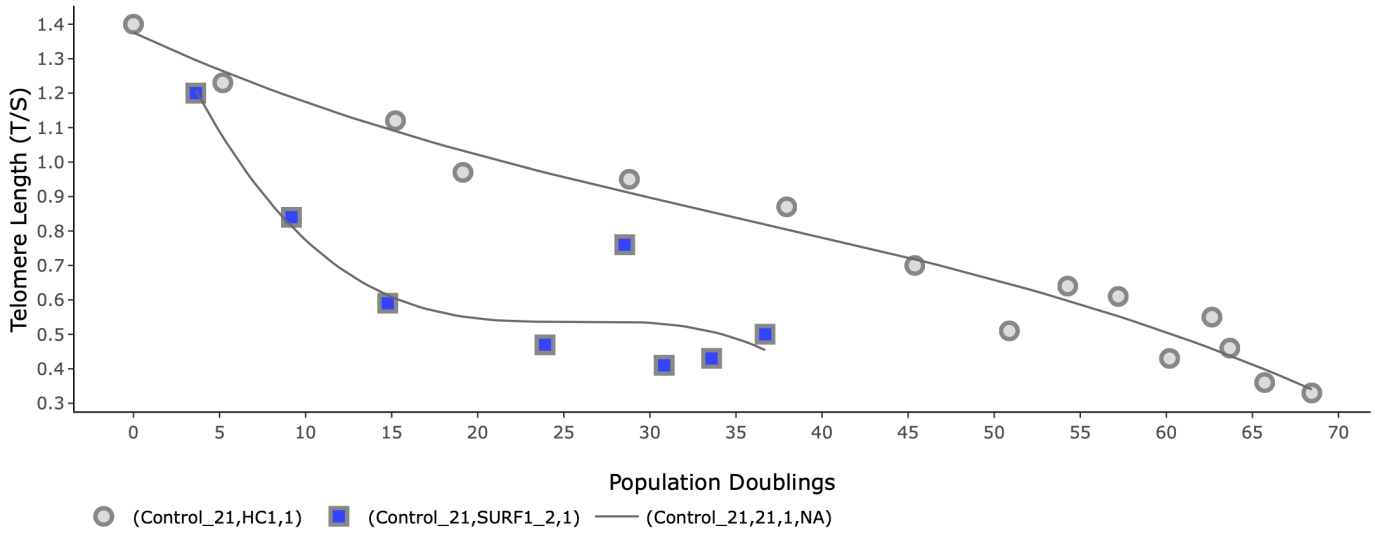
Select Y-axis scale:

- (•) Linear
- ( ) Log

Growth Curves | DNAmethylation | Gene expression | Telomere Length | mtDNA | cell-free DNA

Cytokines | Seahorse Bioenergetics | Correlations | Download Data | Available Data | About

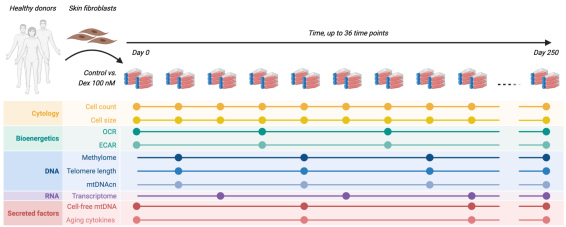
Telomere Length

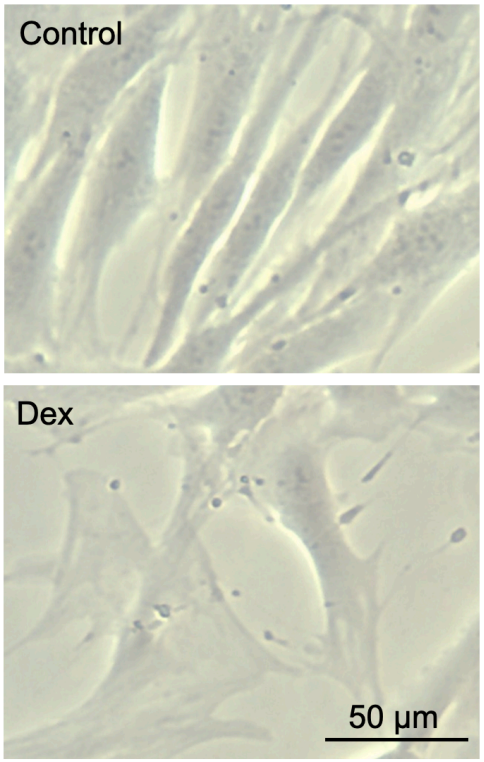


hover to see method details

https://columbia-picard.shinyapps.io/shinyapp-Lifespan_Study/

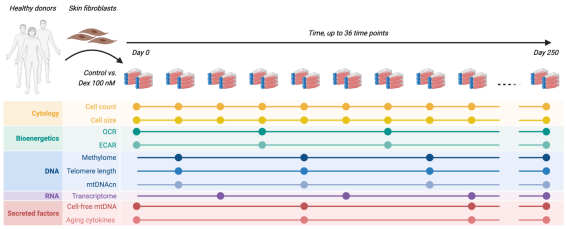
Trajectories of cellular aging ± Dex

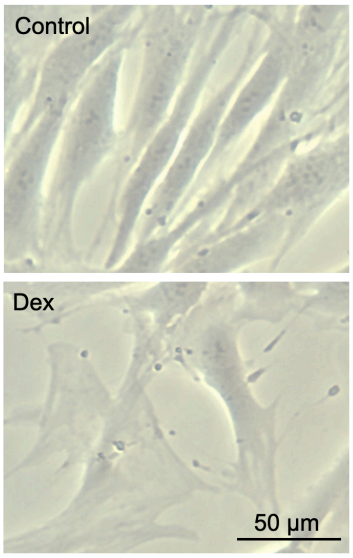


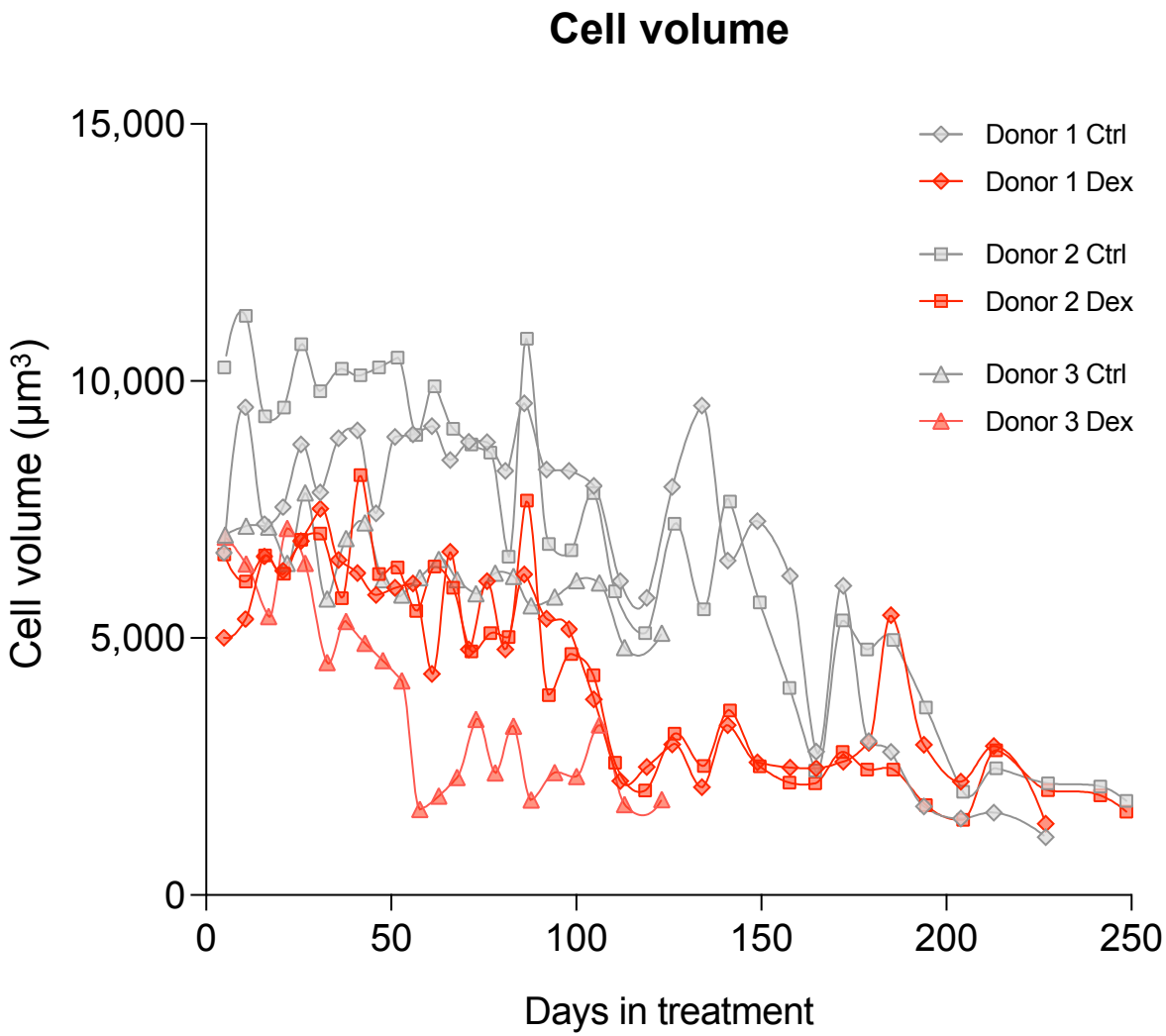


Bobba-Alves et al. *PNEC* 2023

Trajectories of cellular aging ± Dex

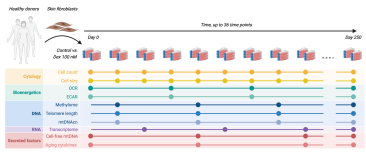


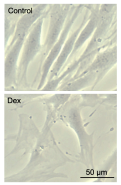


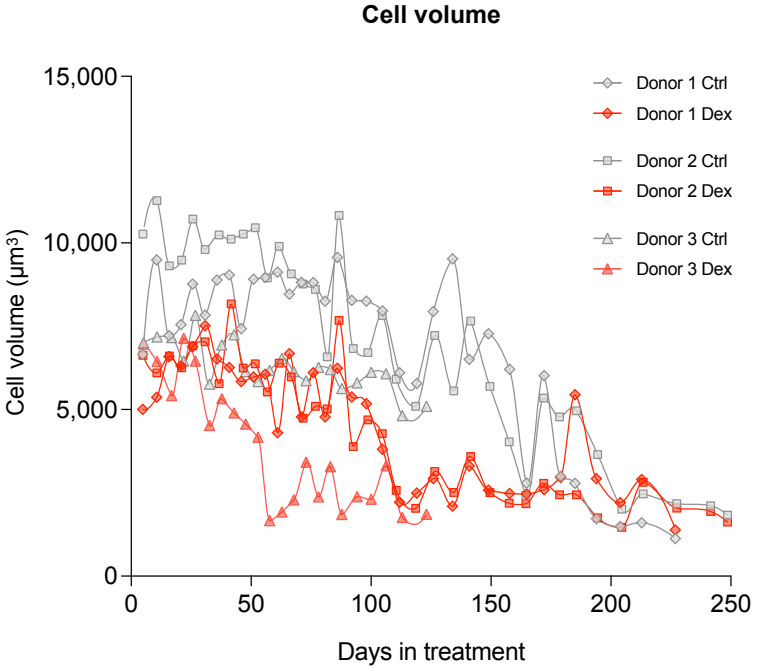


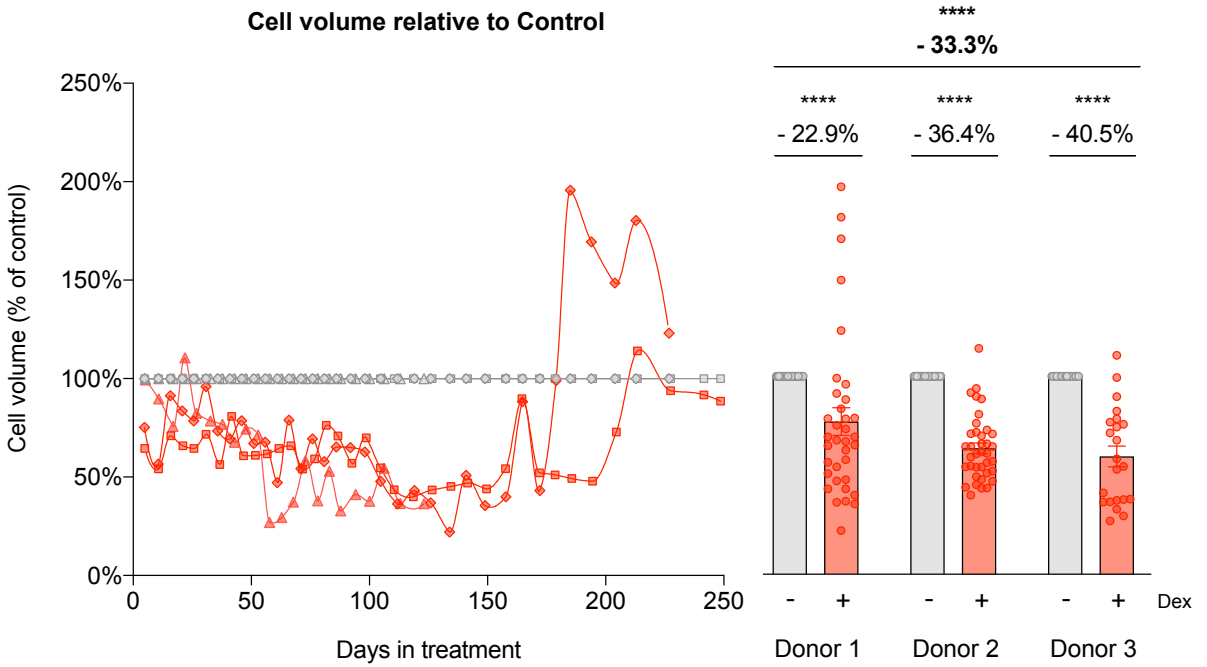
Bobba-Alves et al. *PNEC* 2023

Trajectories of cellular aging ± Dex



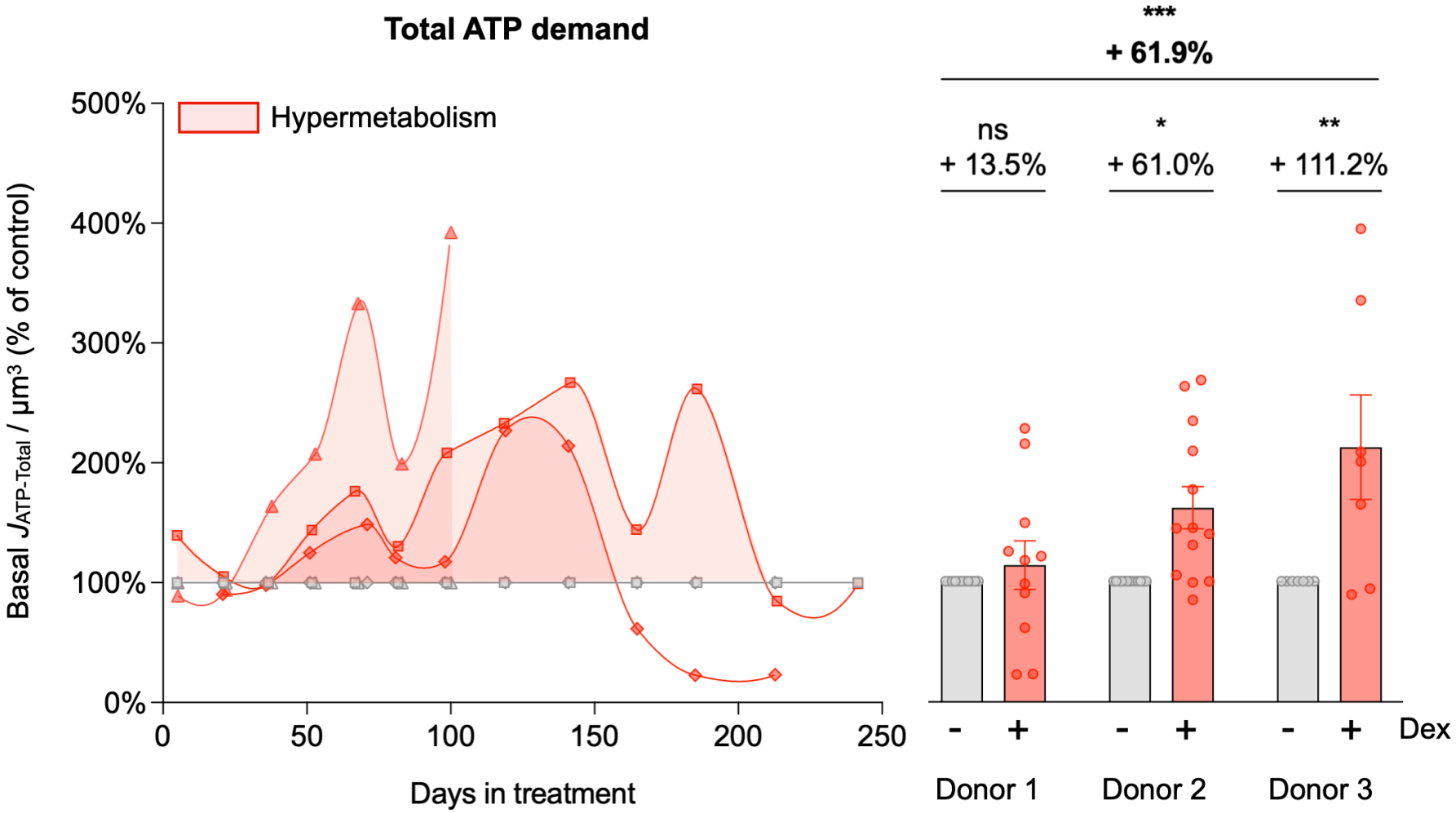






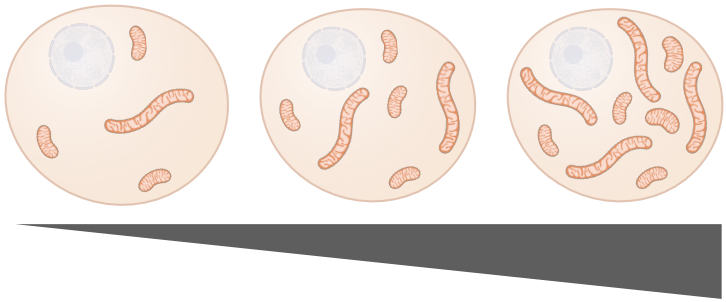
Bobba-Alves et al. *PNEC* 2023

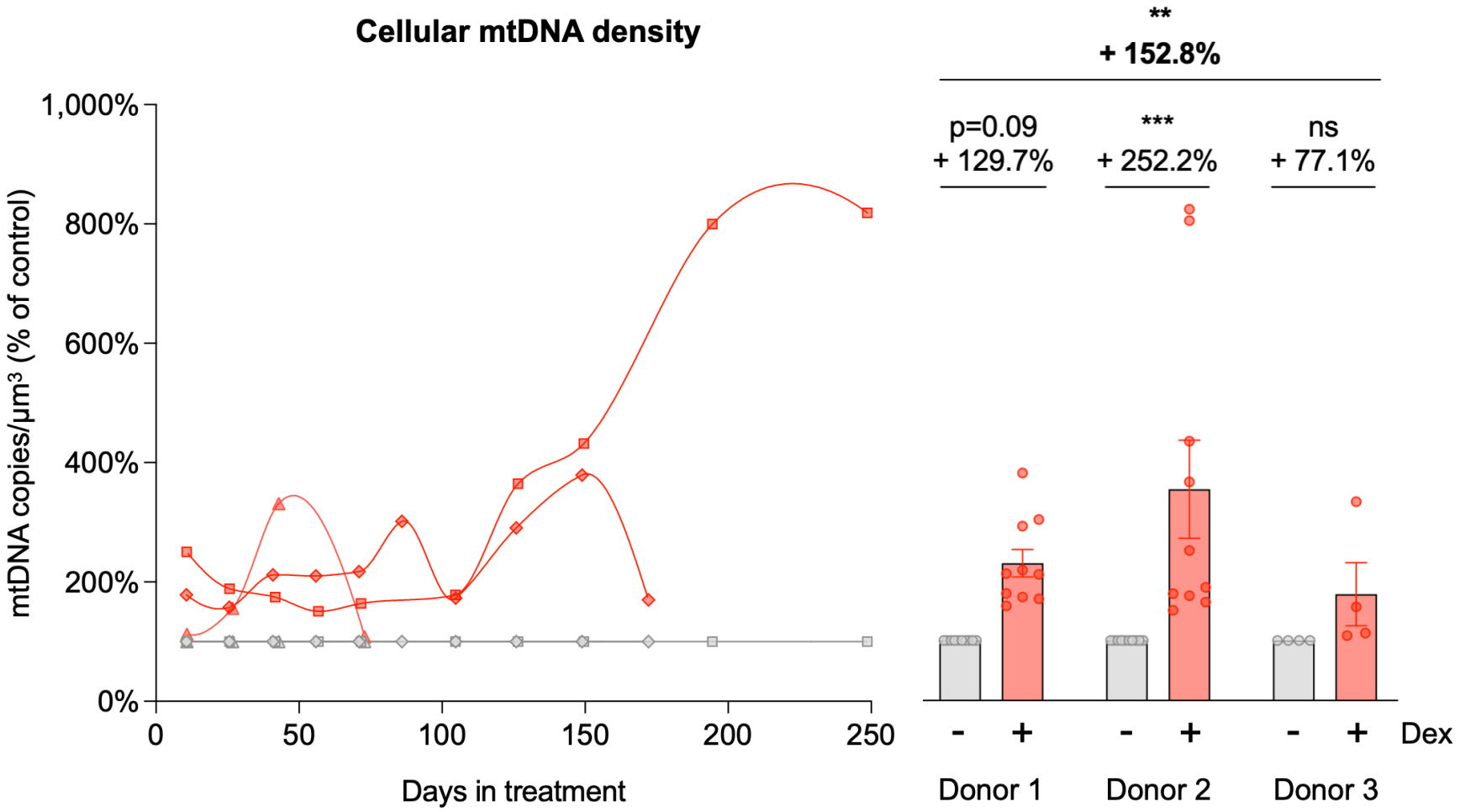
Chronic Dex treatment causes hypermetabolism



Bobba-Alves et al. *PNEC* 2023

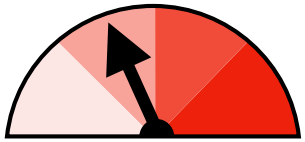
Mitochondrial DNA content

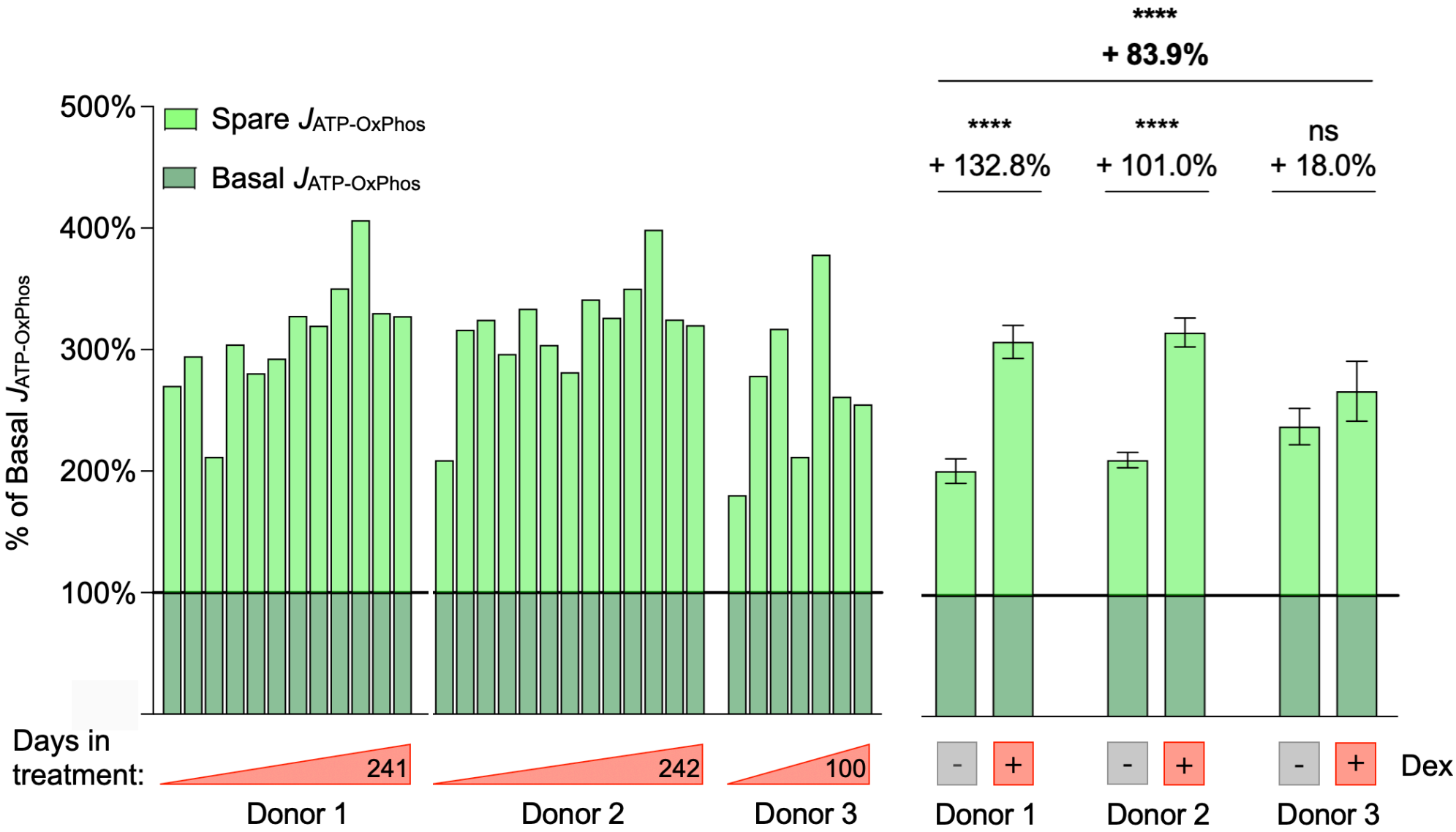




Bobba-Alves et al. *PNEC* 2023

Spare energy transformation capacity





Bobba-Alves et al. *PNEC* 2023

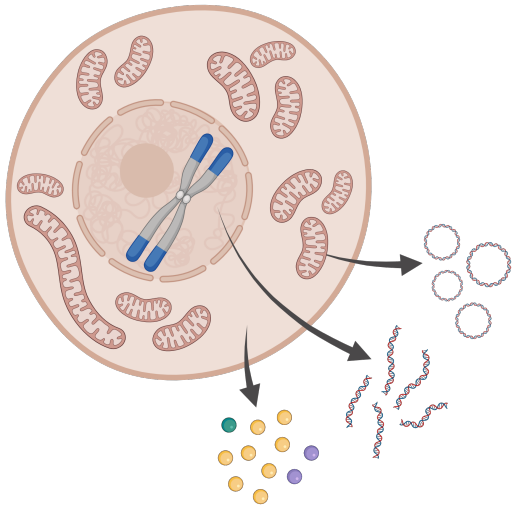
Increased ATP demand

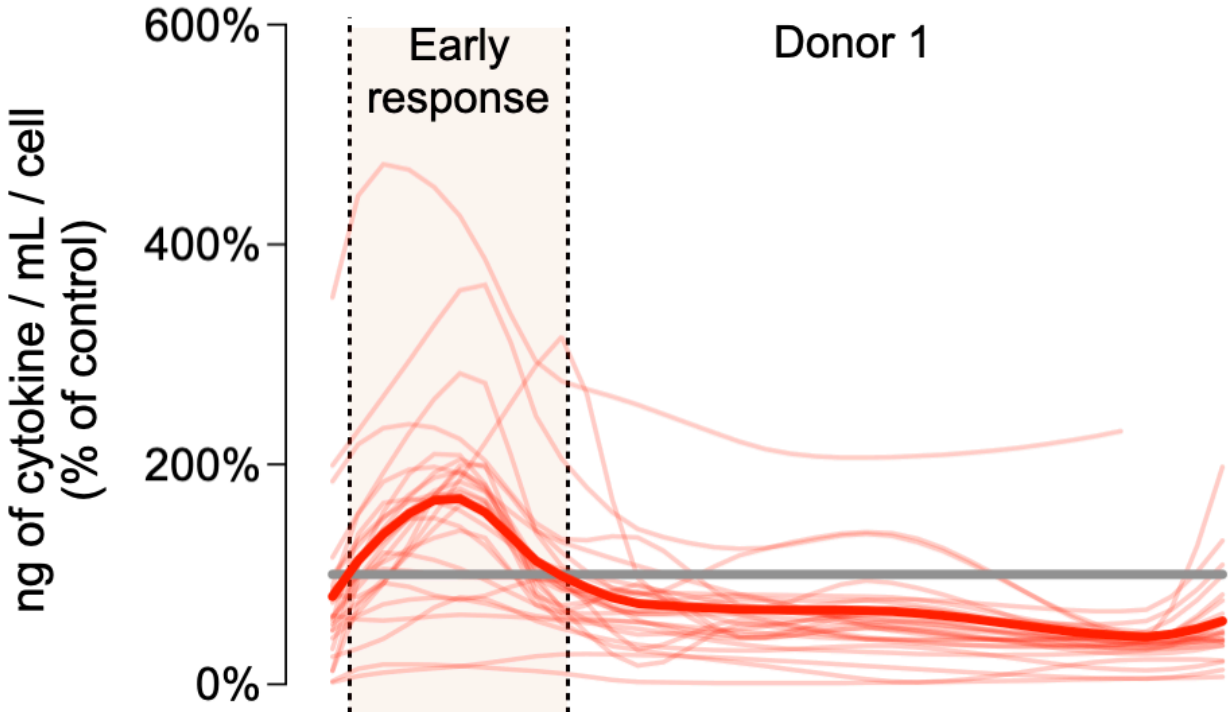
Increased mtDNA density

Increased energetic reserve capacity

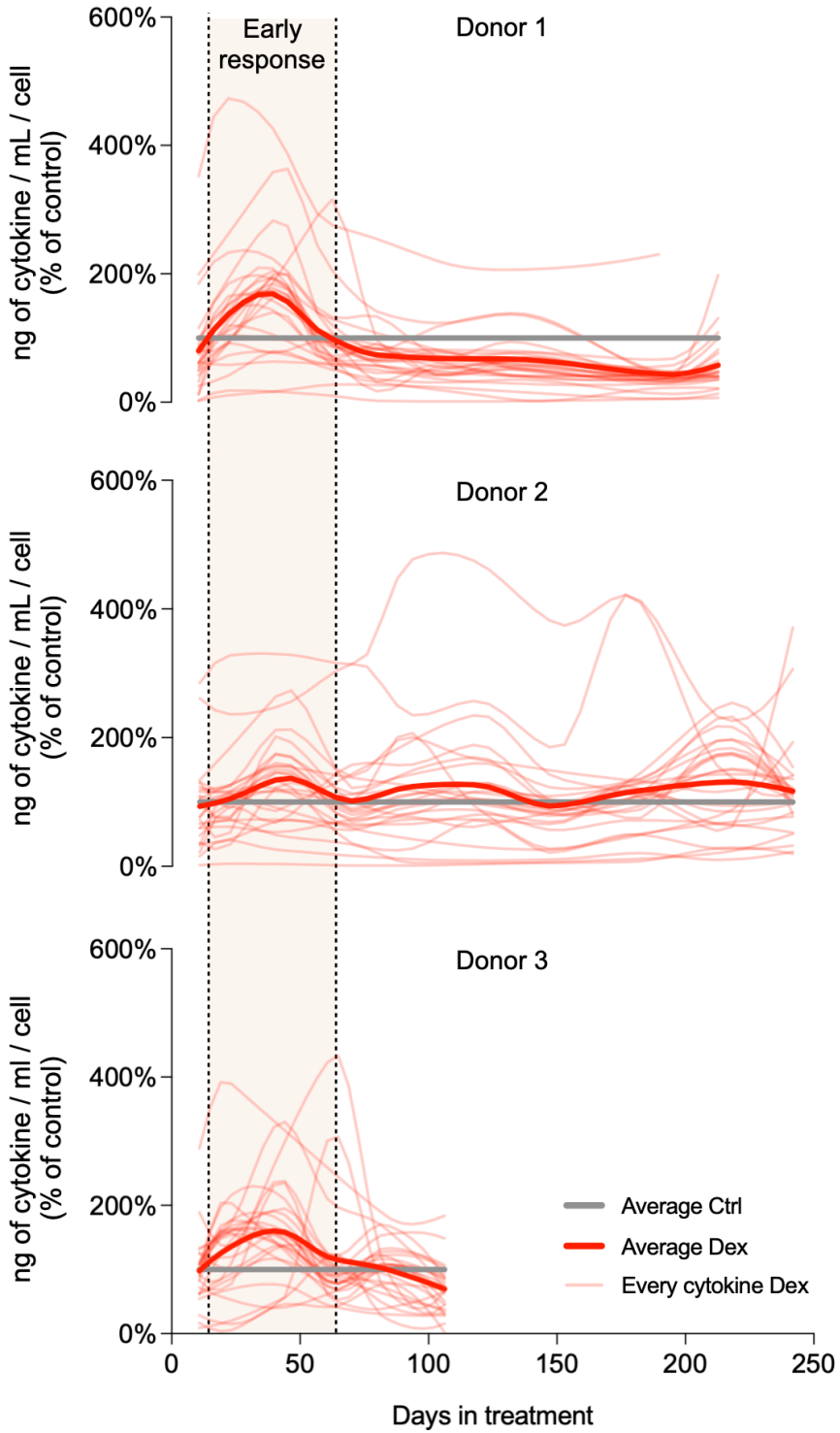
What is costing excess energy?

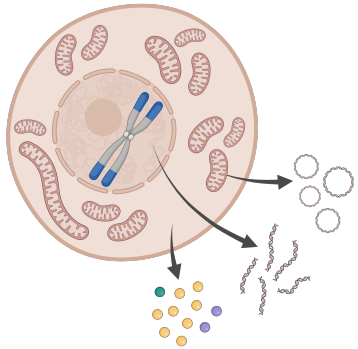
Extracellular secretion



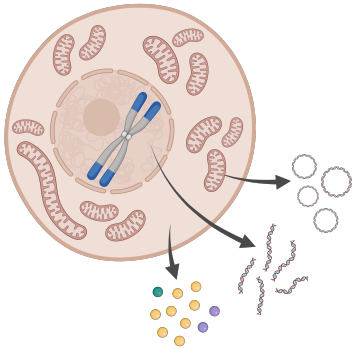


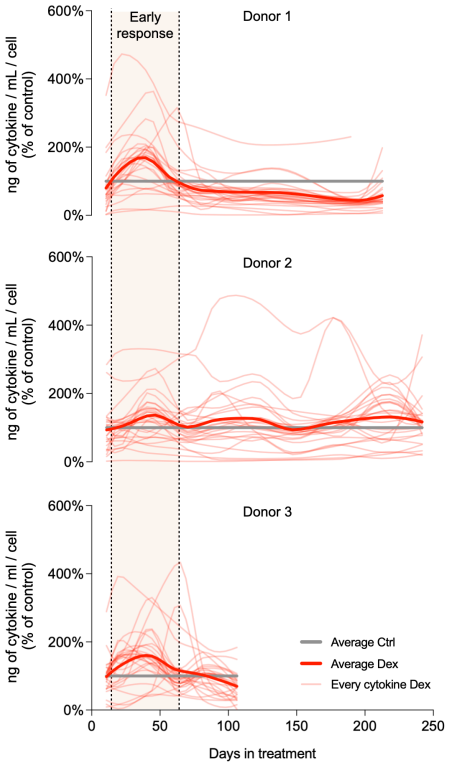
Bobba-Alves et al. *PNEC* 2023

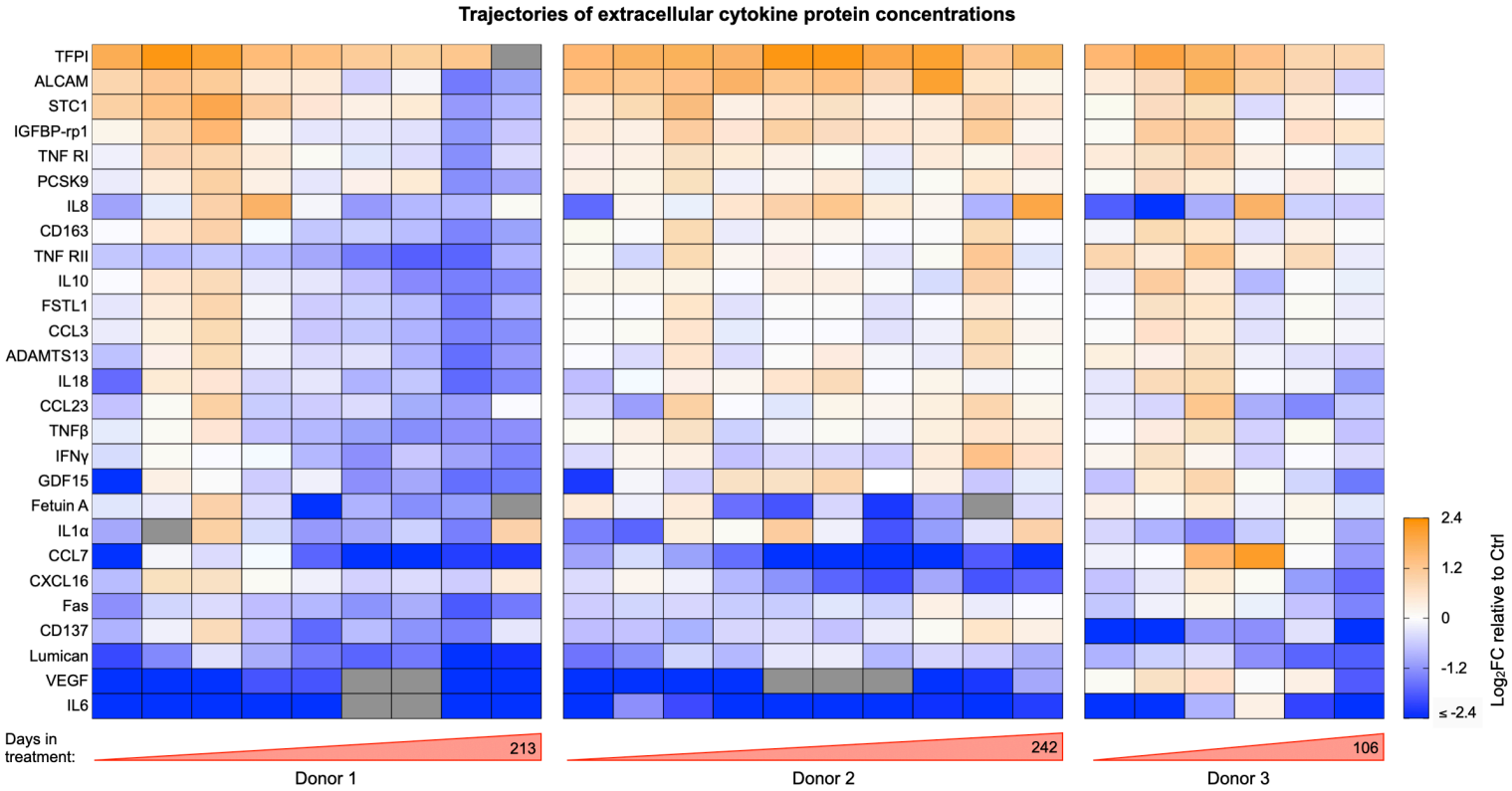


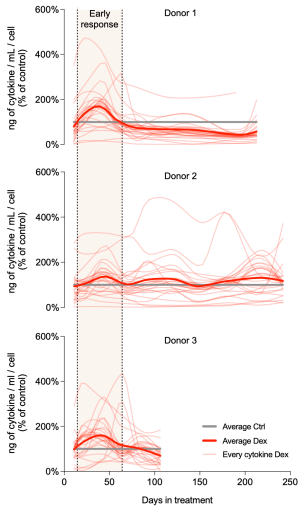


Bobba-Alves et al. *PNEC* 2023




Early response
Donor 1
Donor 2
Donor 3
ng of cytokine / mL / cell (% of control)
ng of cytokine / ml / cell (% of control)
600%
400%
200%
0%
0
50
100
150
200
250
Days in treatment
Average Ctrl
Average Dex
Every cytokine Dex


Trajectories of extracellular cytokine protein concentrations
TFPI
ALCAM
STC1
IGFBP-rp1
TNF RI
PCSK9
IL8
CD163
TNF RII
IL10
FSTL1
CCL3
ADAMTS13
IL18
CCL23
TNFβ
IFNγ
GDF15
Fetuin A
IL1α
CCL7
CXCL16
Fas
CD137
Lumican
VEGF
IL6
Days in treatment:
213
242
106
Donor 1
Donor 2
Donor 3
2.4
1.2
0
-1.2
≤ -2.4
Log2FC relative to Ctrl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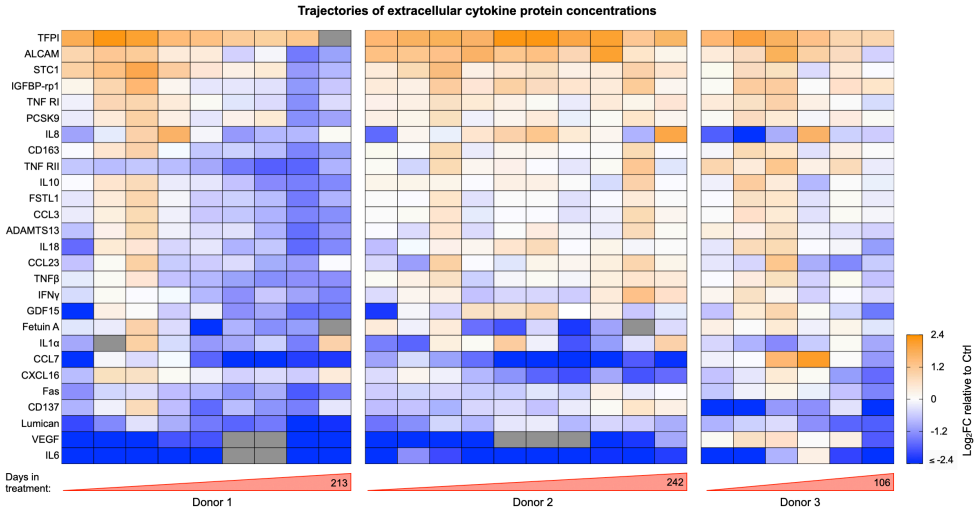
Days in treatment
Average Ctrl
Average Dex
Every cytokine Dex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CCL23
TNFβ
IFNγ
GDF15
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IL1α
CCL7
CXCL16
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Lumican
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Days in treatment:
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Donor 3
2.4
1.2
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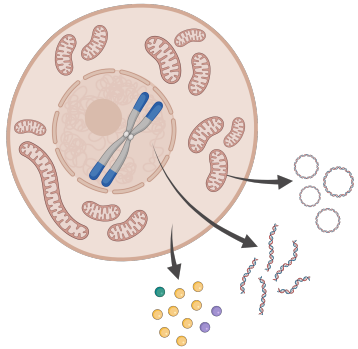
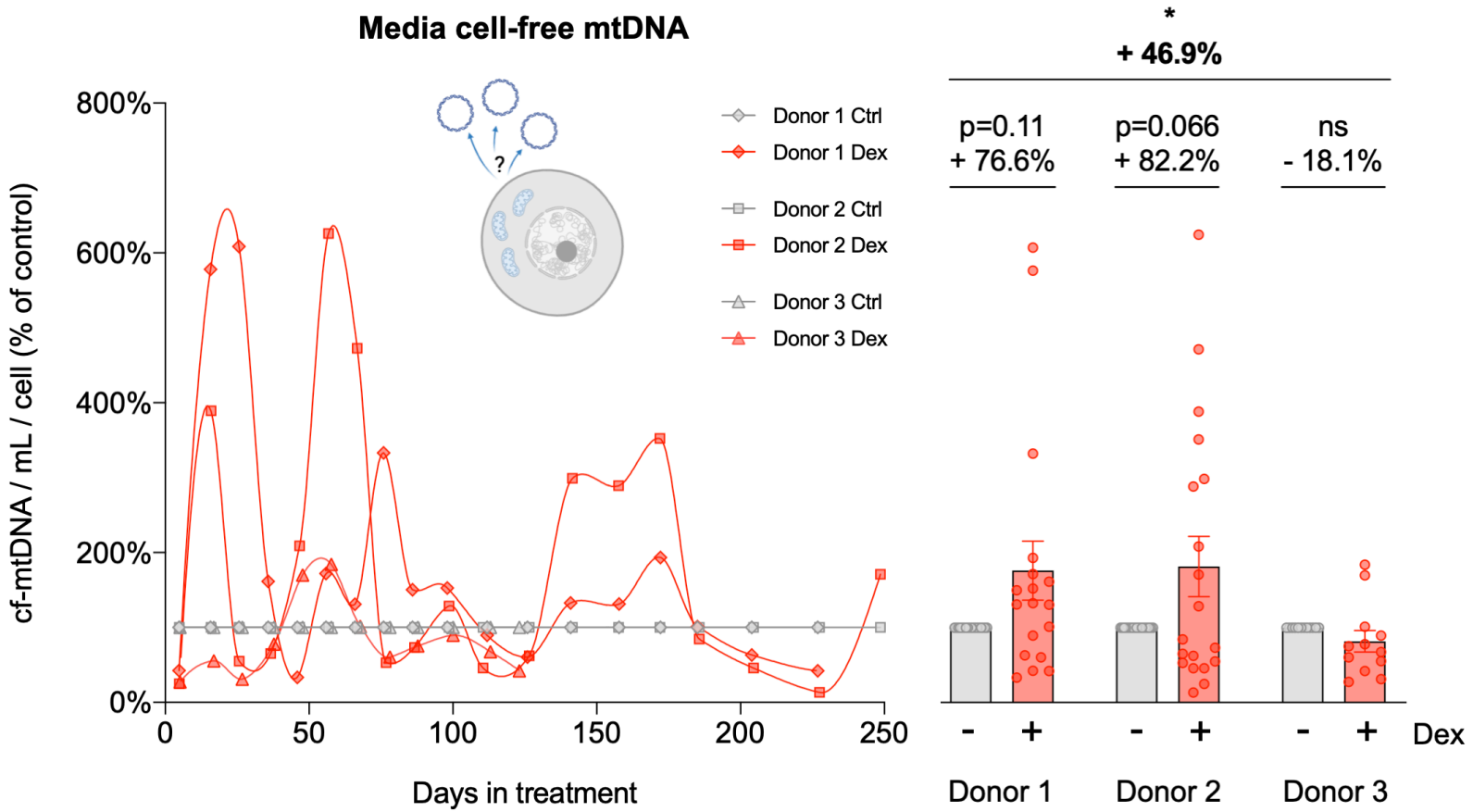
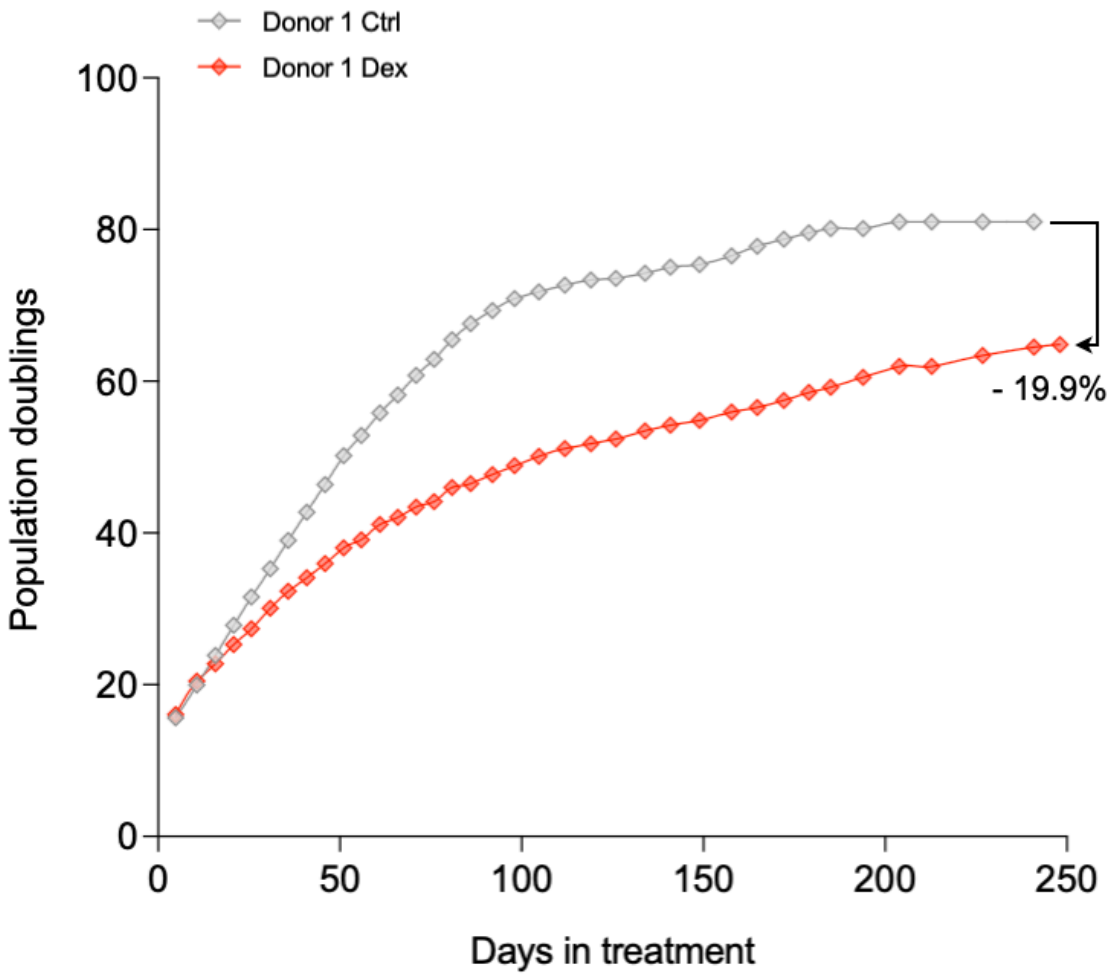
-1.2
≤ -2.4
LogFC relative to Ctrl




Media cell-free mtDNA
cf-mtDNA / mL / cell (% of control)
800%
600%
400%
200%
0%
0
50
100
150
200
250
Days in treatment
?
Donor 1 Ctrl
Donor 1 Dex
Donor 2 Ctrl
Donor 2 Dex
Donor 3 Ctrl
Donor 3 Dex
*
+ 46.9%
p=0.11
+ 76.6%
p=0.066
+ 82.2%
ns
- 18.1%
- + - + - + Dex
Donor 1
Donor 2
Donor 3

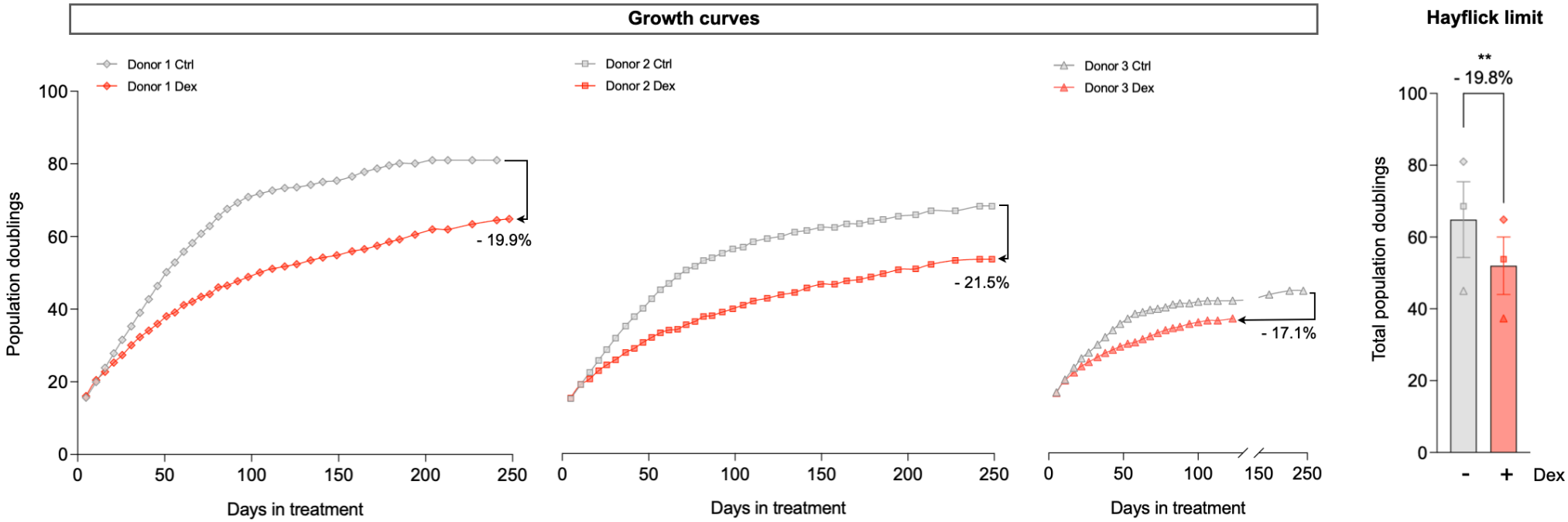
What are the consequences of hypermetabolism?

Reduced lifespan in Dex-treated cells



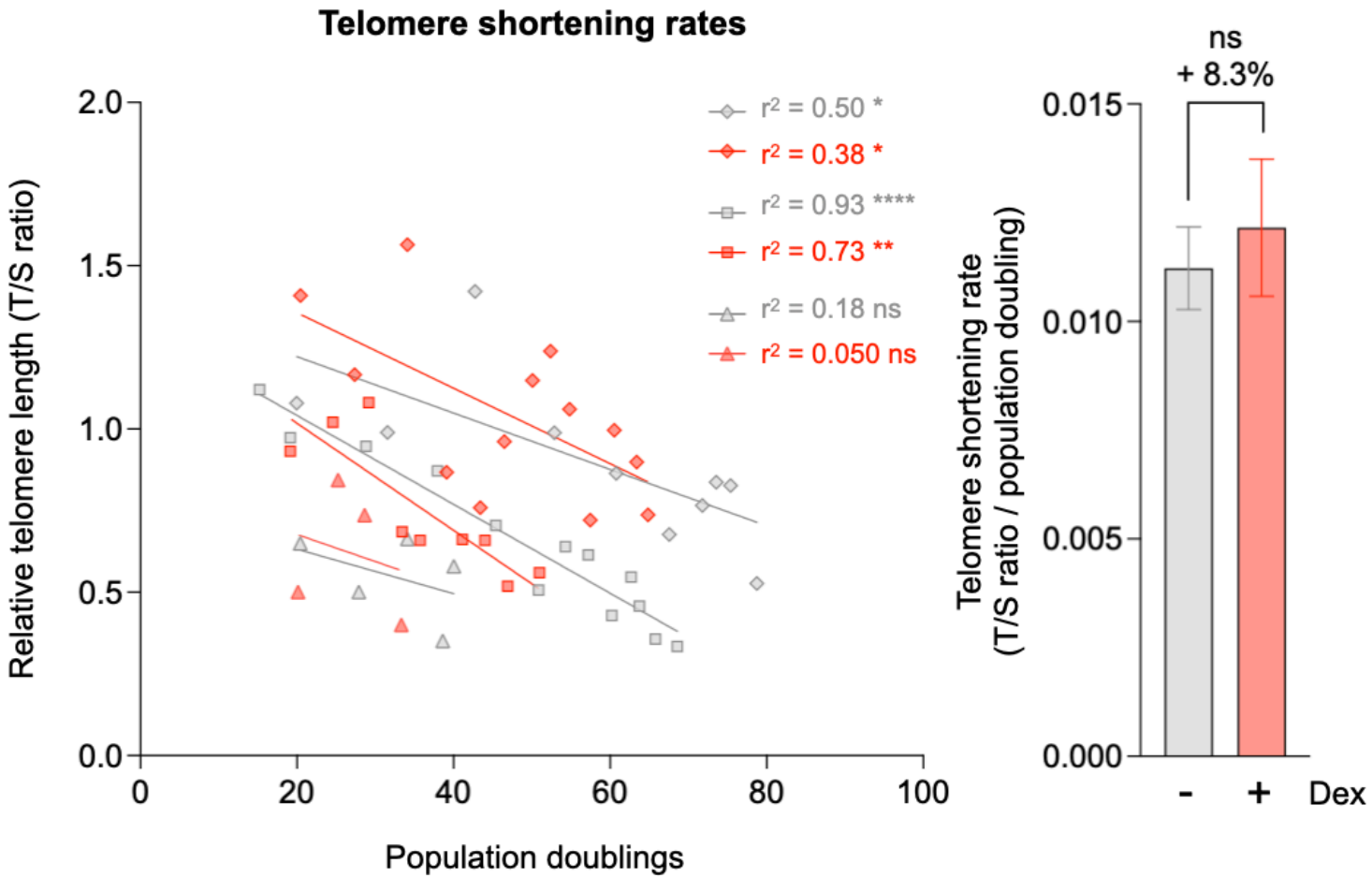
Bobba-Alves et al. *PNEC* 2023

Reduced lifespan in Dex-treated cells



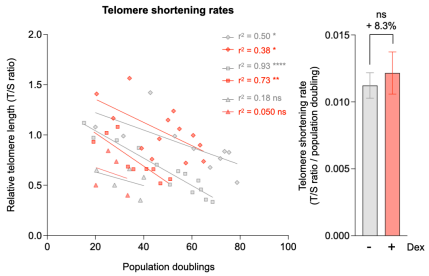
Bobba-Alves et al. *PNEC* 2023

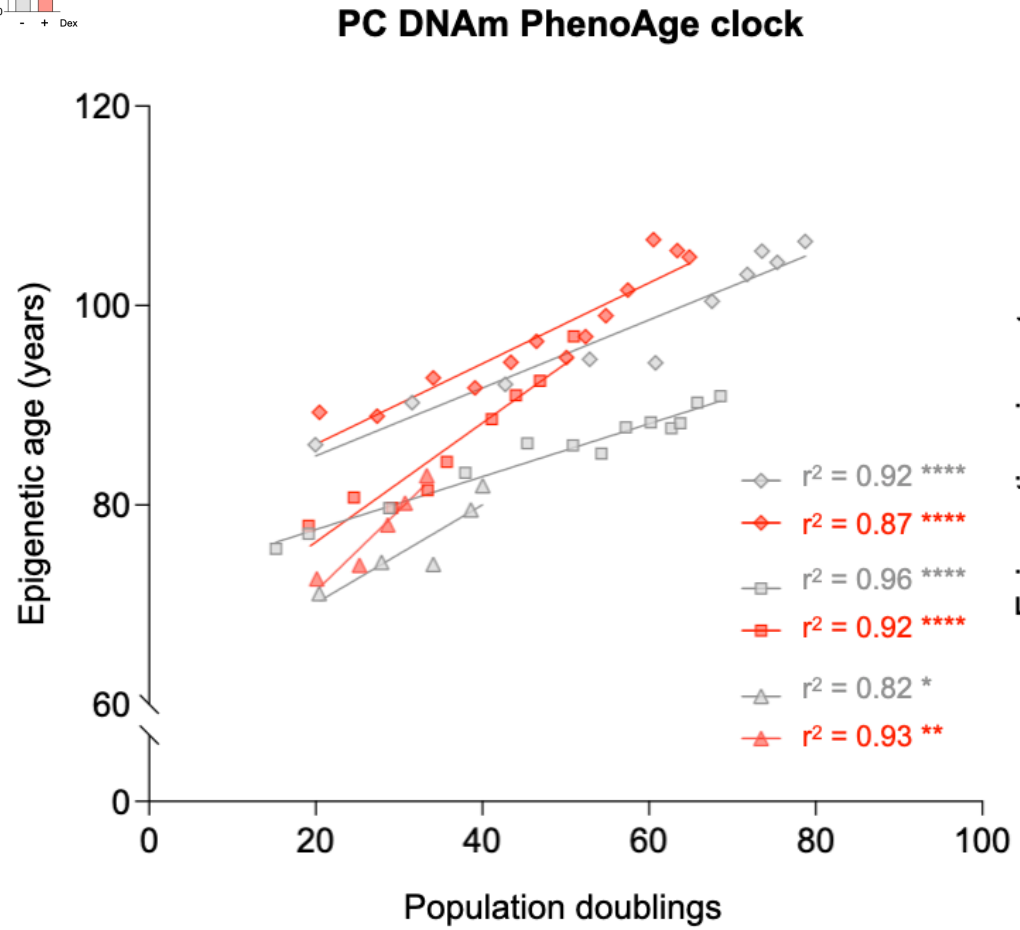
Modest acceleration in telomere shortening rate

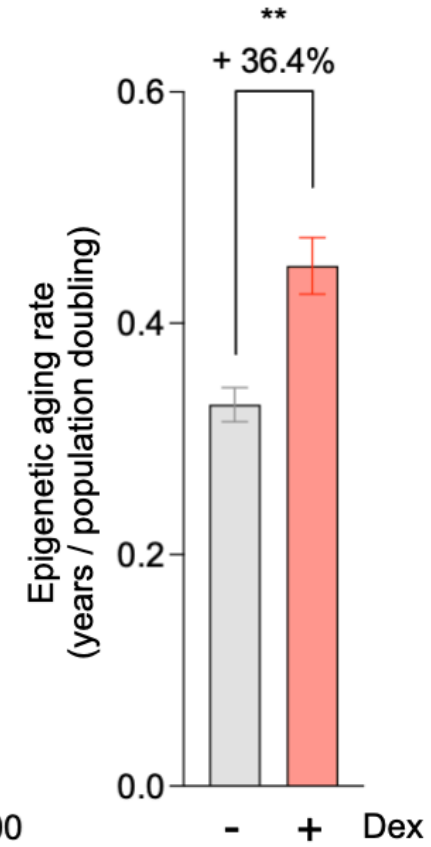


Bobba-Alves et al. *PNEC* 2023

Chronic Dex accelerates epigenetic aging

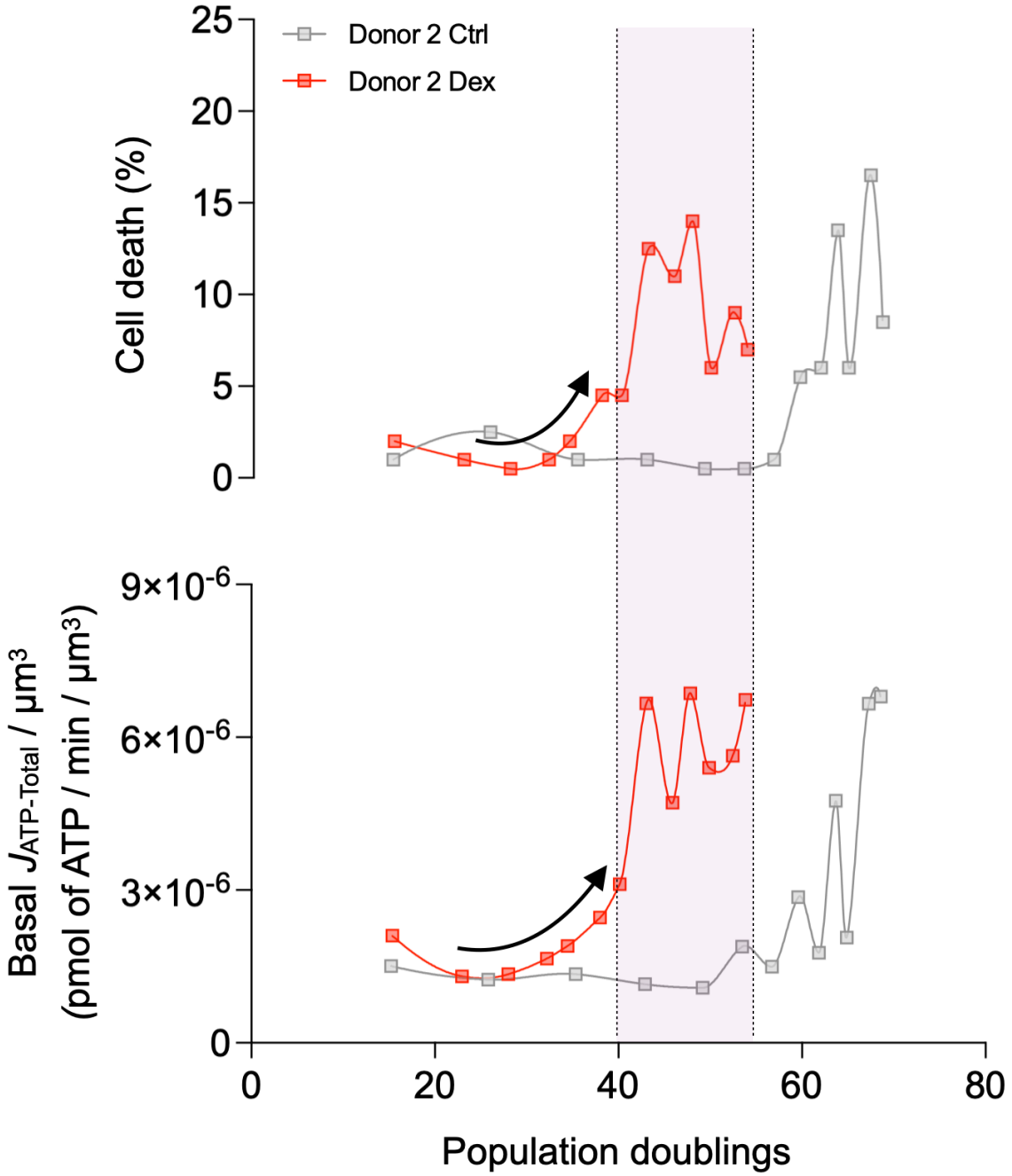






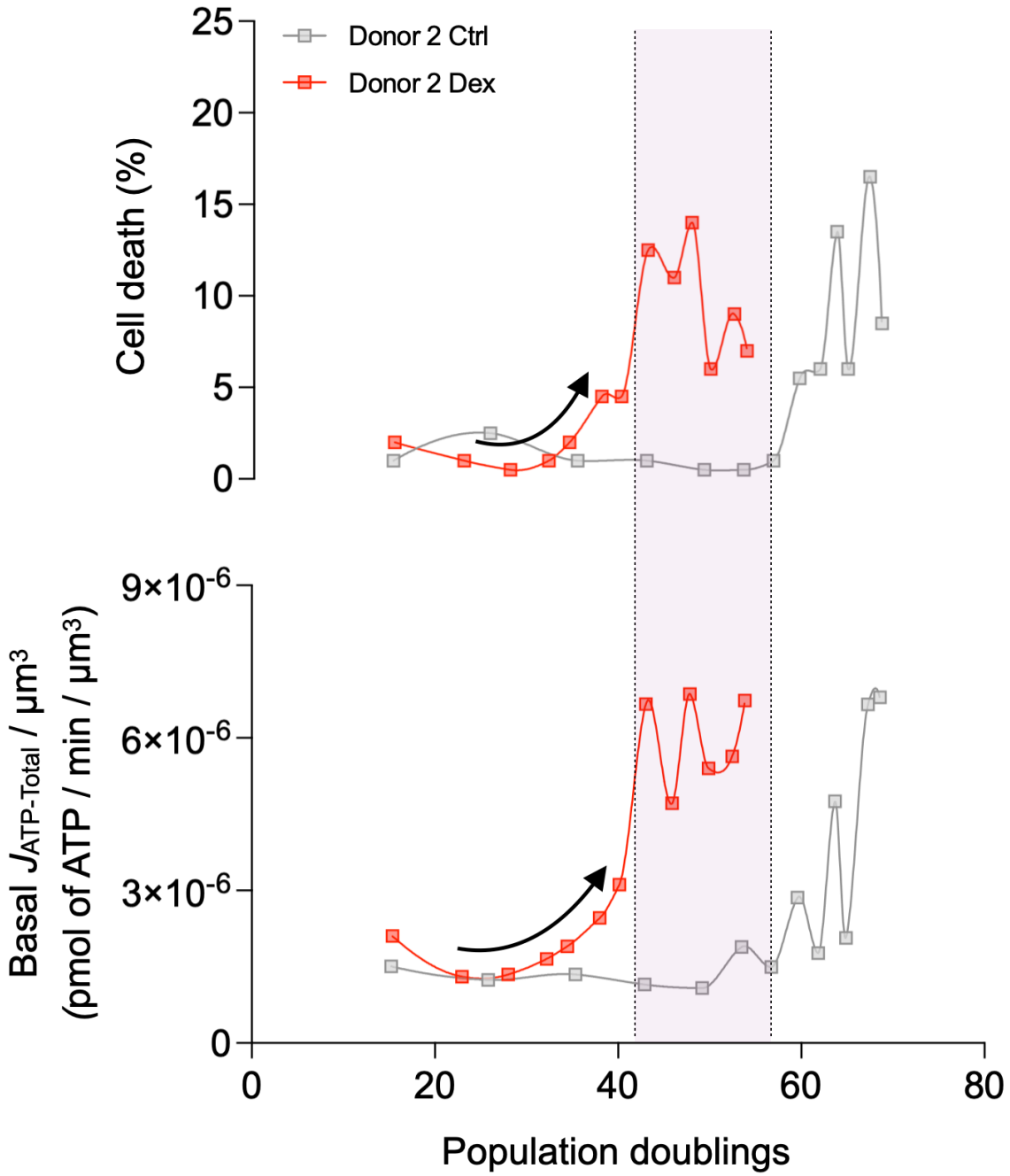
Bobba-Alves et al. *PNEC* 2023

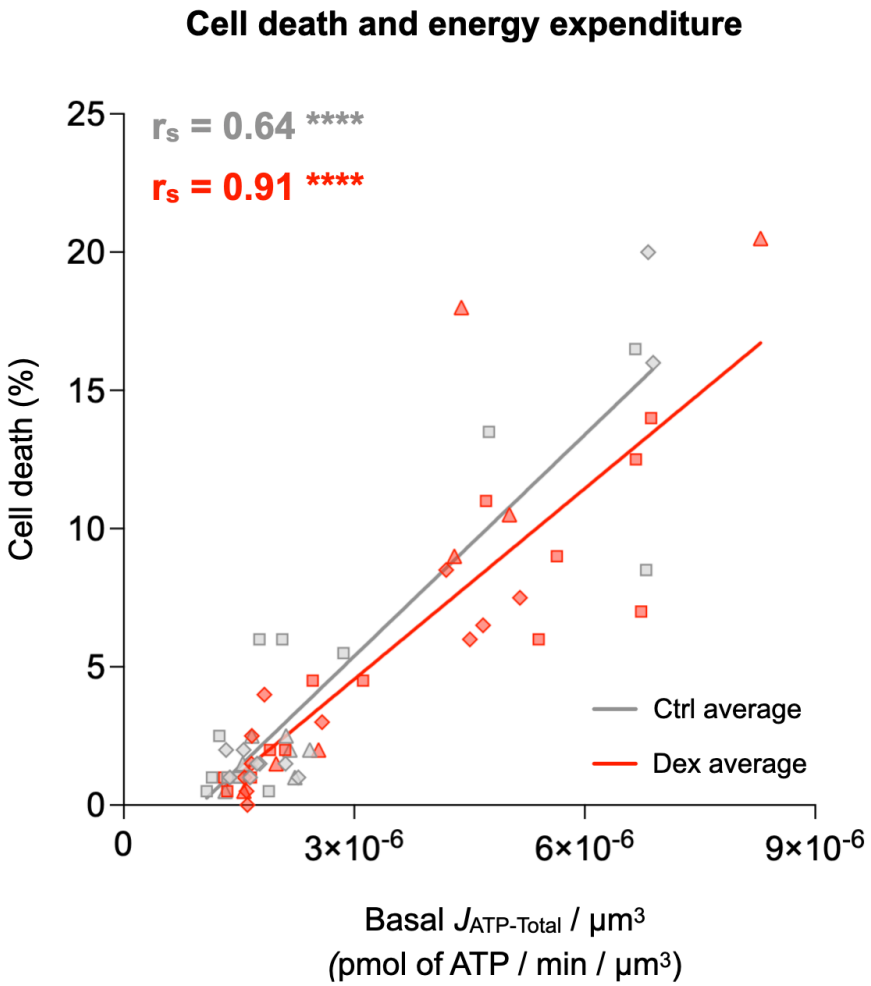
Correlation of cell death and hypermetabolism



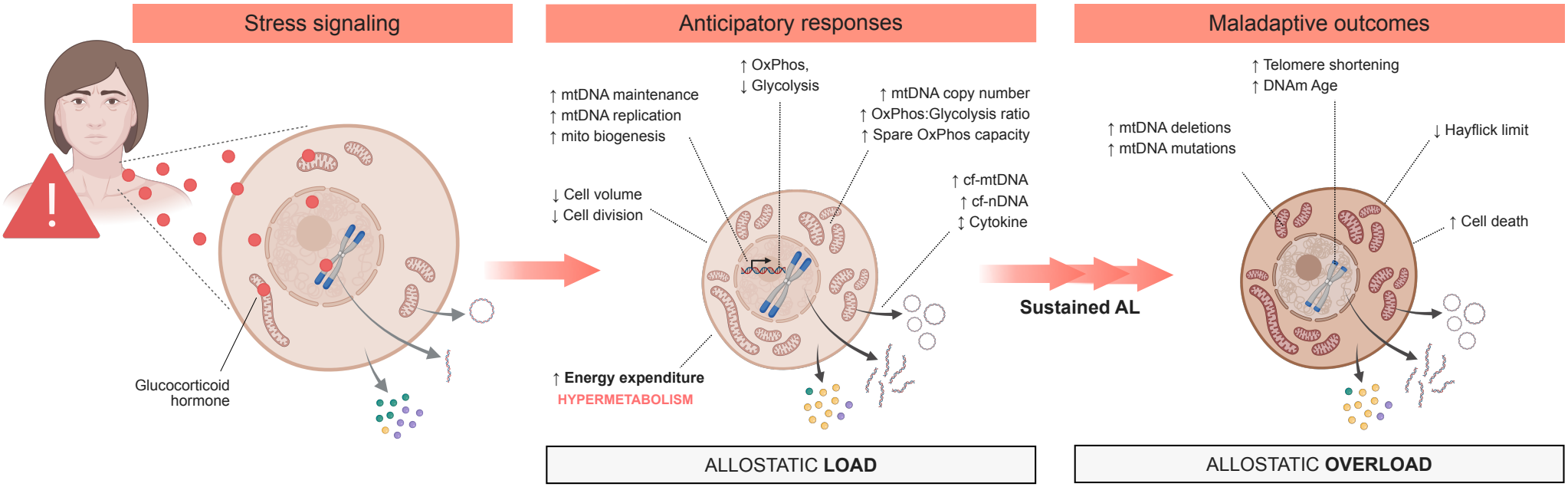
Bobba-Alves et al. *PNEC* 2023

Correlation of cell death and hypermetabolism





Bobba-Alves et al. *PNEC* 2023



Glucocorticoid signaling increases energy expenditure by **60%**

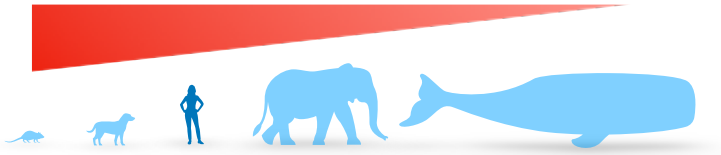
And accelerates cellular aging by **10-40%**

Bobba-Alves et al. *PNEC* 2023

Why is hypermetabolism associated with aging?

Rate of living hypothesis?

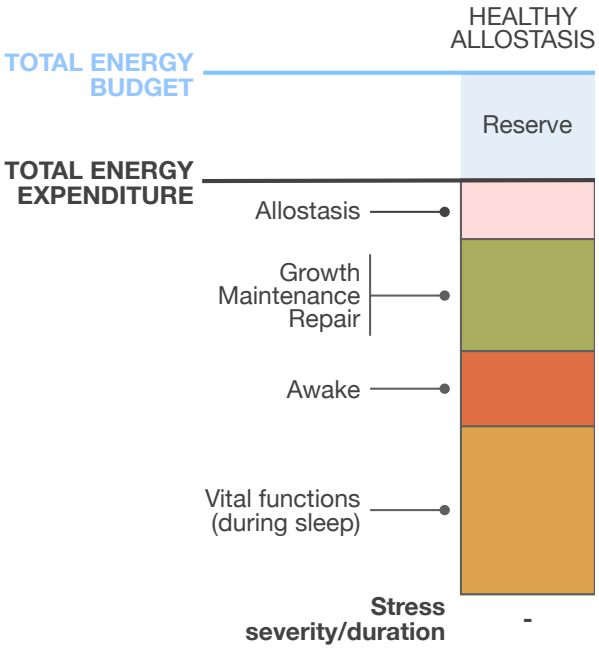
HYPERMETABOLISM

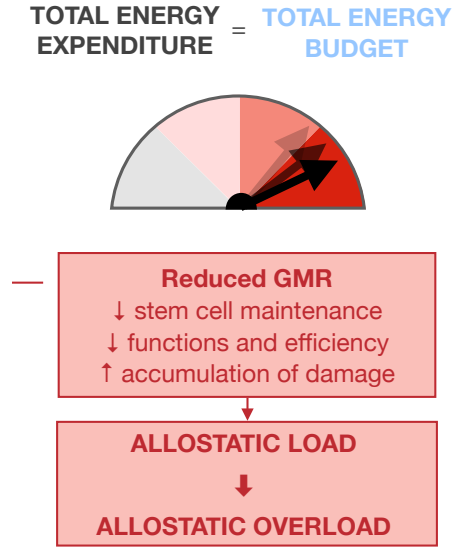


Seconds **Years / Decades** **Centuries**

Hypermetabolism is an increase in the amount of energy needed to sustain one's life over time

Model: Aging and lifespan determined by the partitioning of limited energetic resources



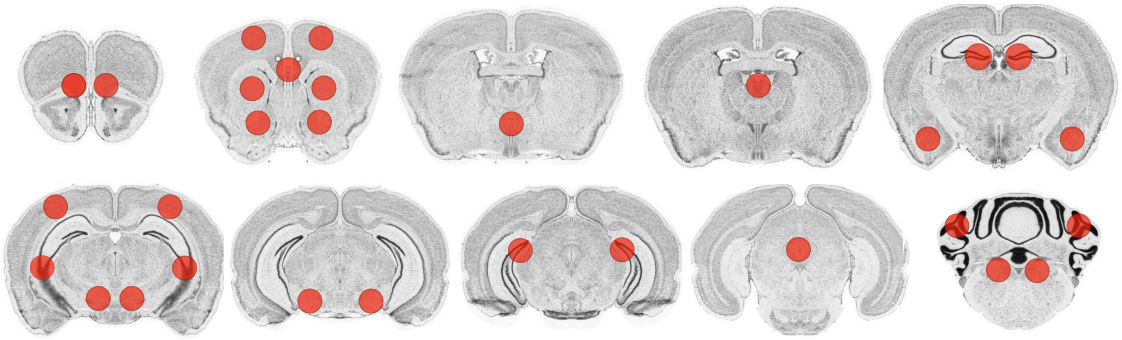


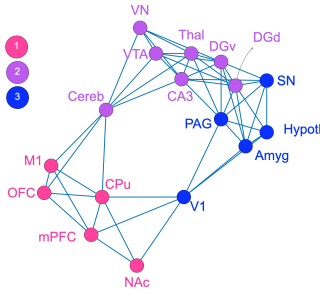
Bobba-Alves et al. The energetic cost of allostasis and allostatic load. *Psychoneuroendocrinol* 2022

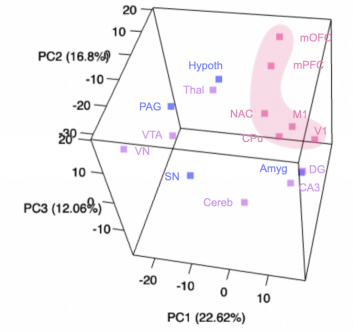
Are brain cortical mitochondrial phenotypes linked to stress, and psychosocial exposures/experiences?

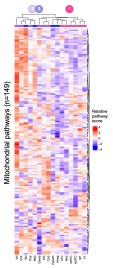
Article https://doi.org/10.1038/s41467-023-39941-0

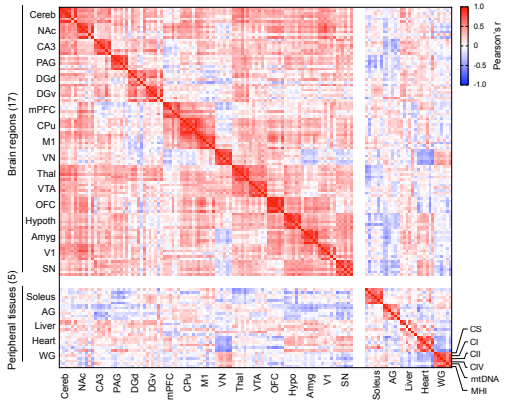
Brain mitochondrial diversity and network organization predict anxiety-like behavior in male mice

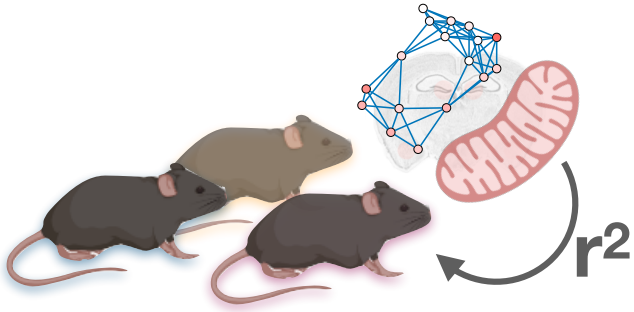




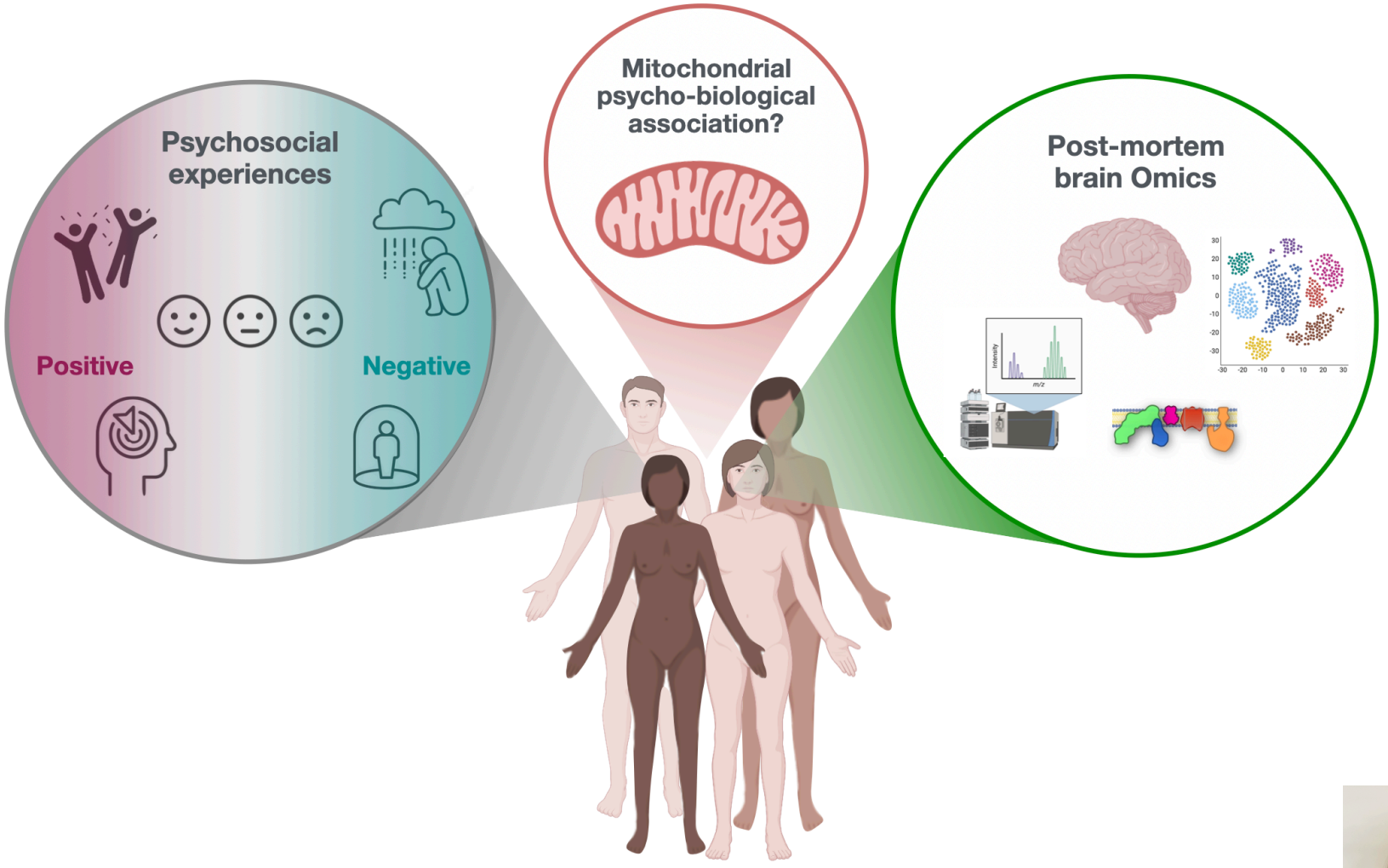




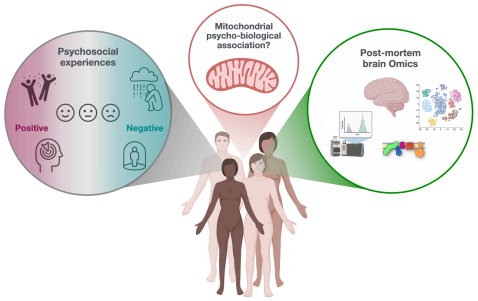




Rosenberg et al. *Nat Commun* 2023



Caroline Trumpff



ROSMAP

N=400

Women, N=281, 70%

Men, N=119, 30%

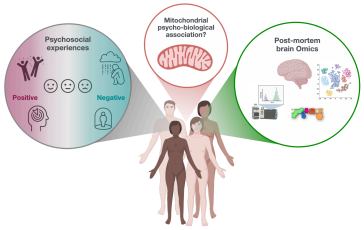
Other dementia
N=6

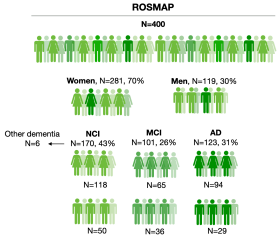
NCI
N=170, 43%
N=118
N=50

MCI
N=101, 26%
N=65
N=36

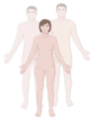
AD
N=123, 31%
N=94
N=29

Caroline Trumpff



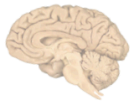


ROSMAP



Ante-mortem <1 year

Post-mortem



Up to 20 years — *Length of follow up (yearly)*

Positive Experiences

Social network size,
Late life social activity,
Purpose in life,
Satisfaction with life,
Time horizon,
Well-being

Negative Experiences

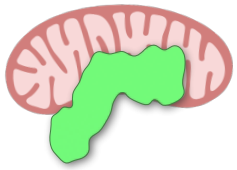
Adverse childhood experiences*,
Negative life events,
Social isolation,
Depressive symptoms,
Negative mood,
Perceived stress

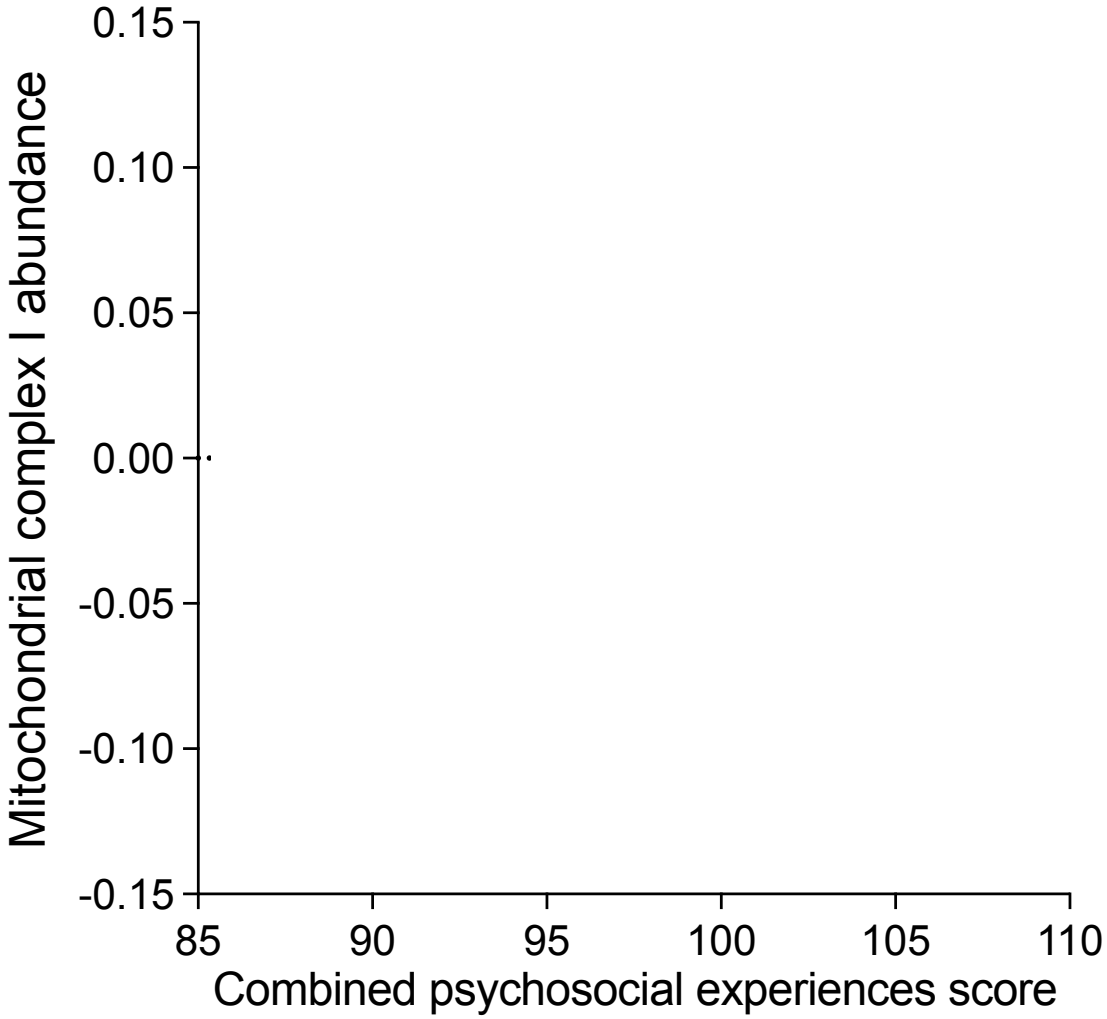
1 year

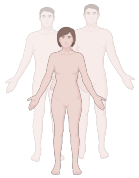
- TMT Proteomics
- SRM Proteomics
- Bulk RNA-seq
- Single-nucleus RNA-seq

Caroline Trumpff

Psychobiological associations in human brain mitochondria



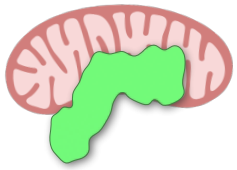


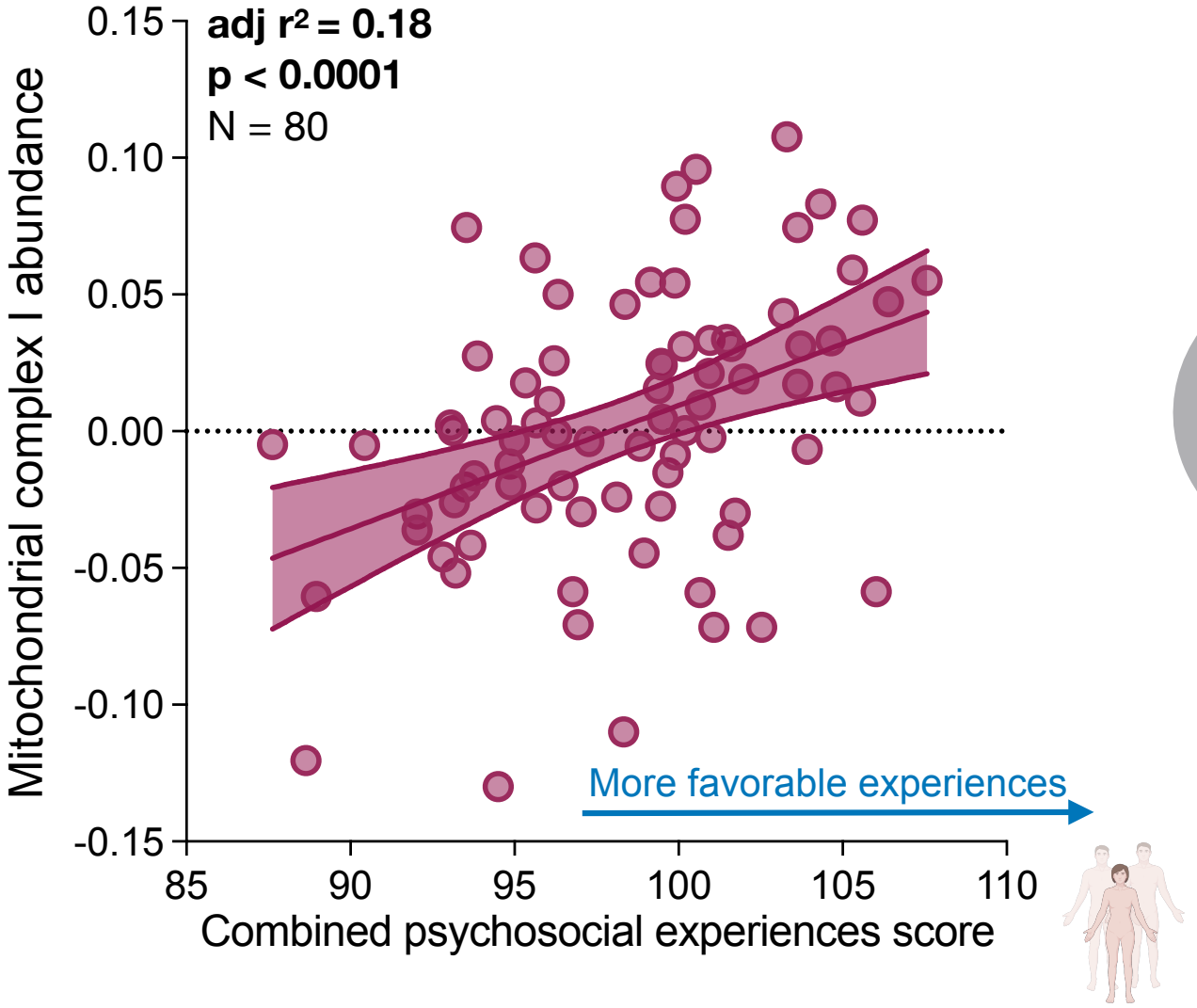


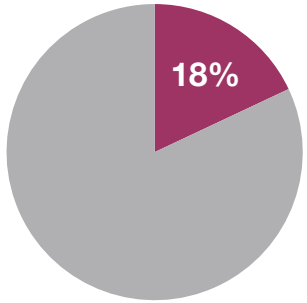
Multiple linear regression adjusted for sex and cognitive status; cell type abundances

Trumpff et al. *BioRxiv* 2023

Psychobiological associations in human brain mitochondria

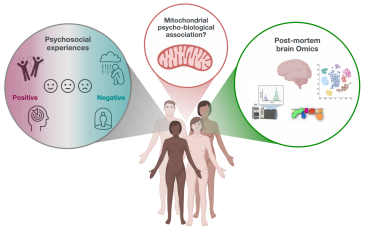


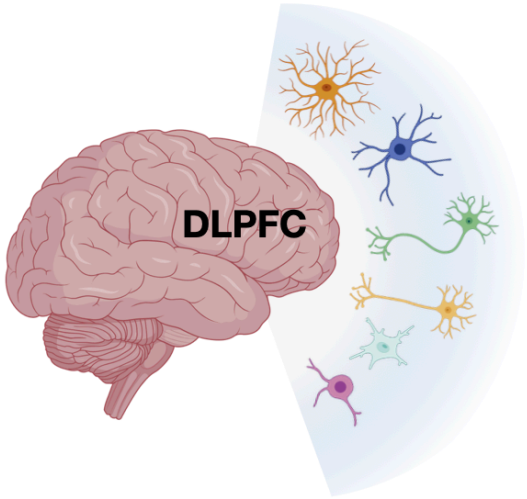




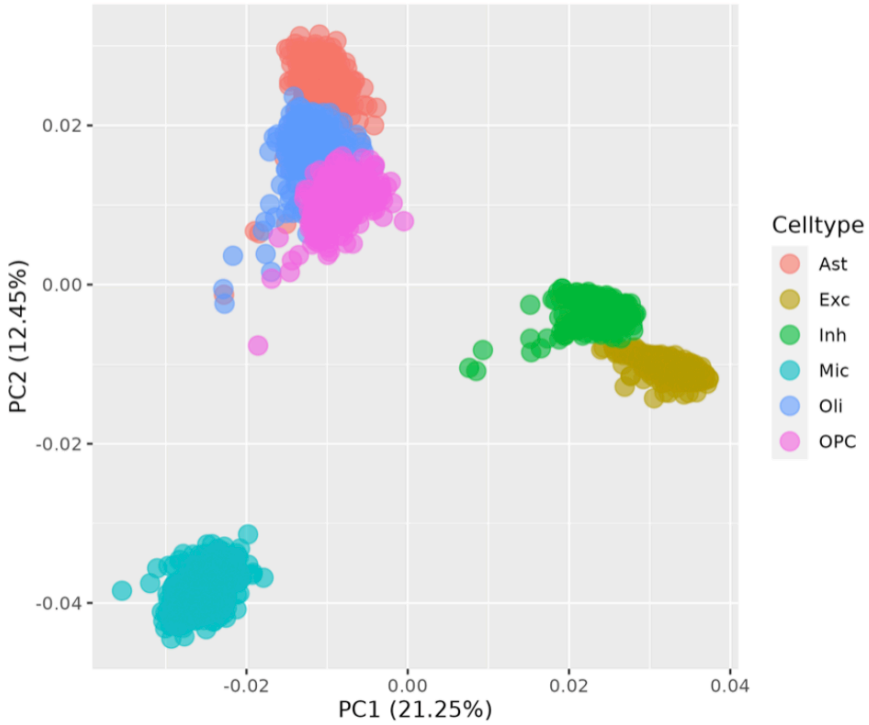
Multiple linear regression adjusted for sex and cognitive status; cell type abundances

Trumpff et al. *BioRxiv* 2023





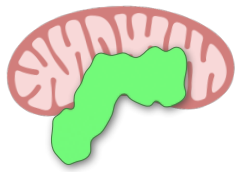
single-nucleus
RNA-seq pseudobulk data

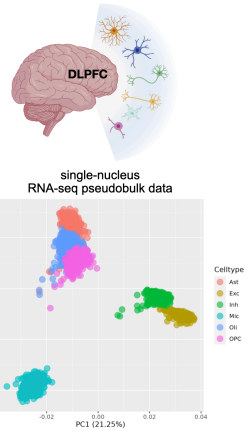


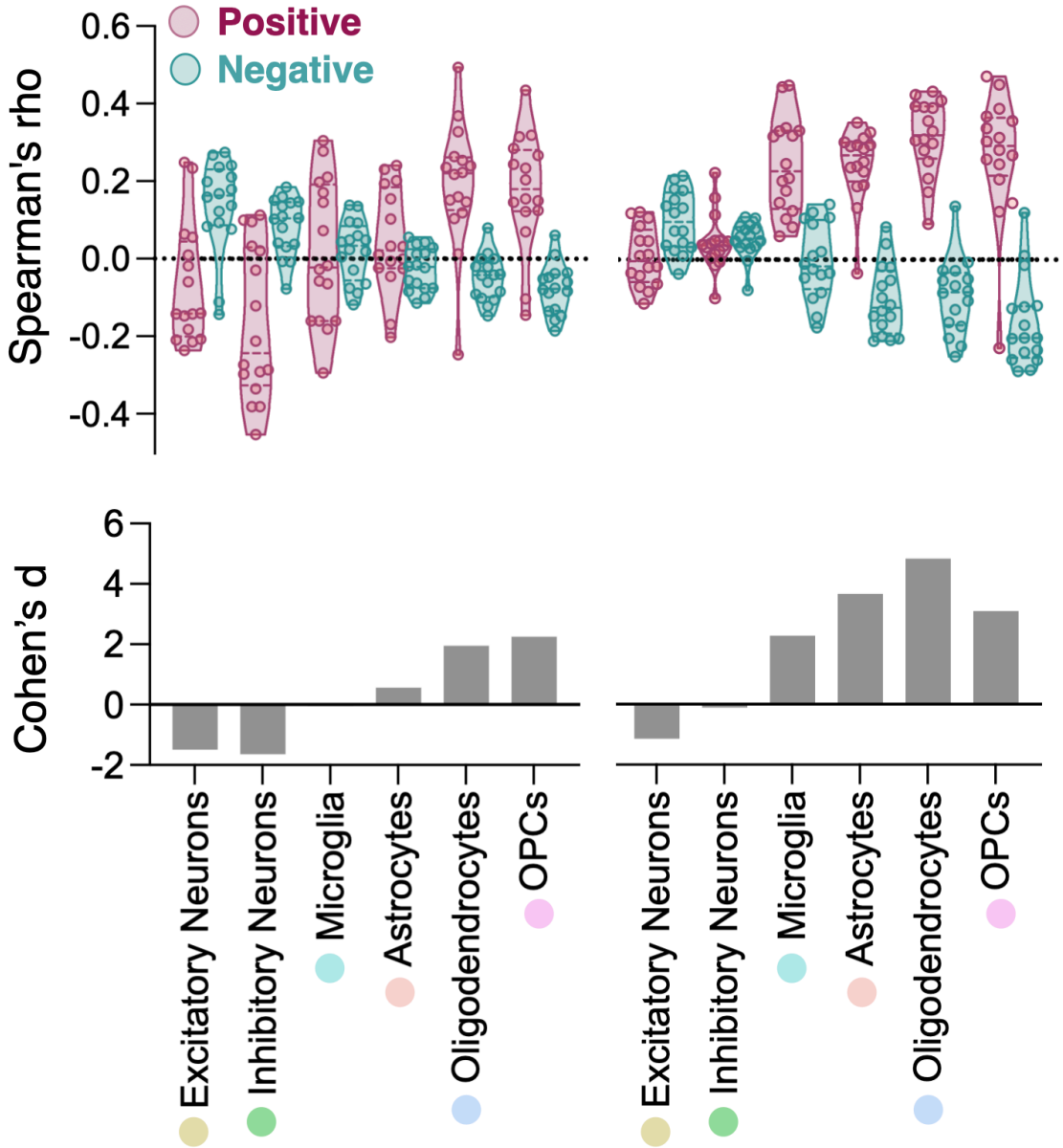
Phil de Jager

Anna Monzel

Trumpff et al. *BioRxiv* 2023







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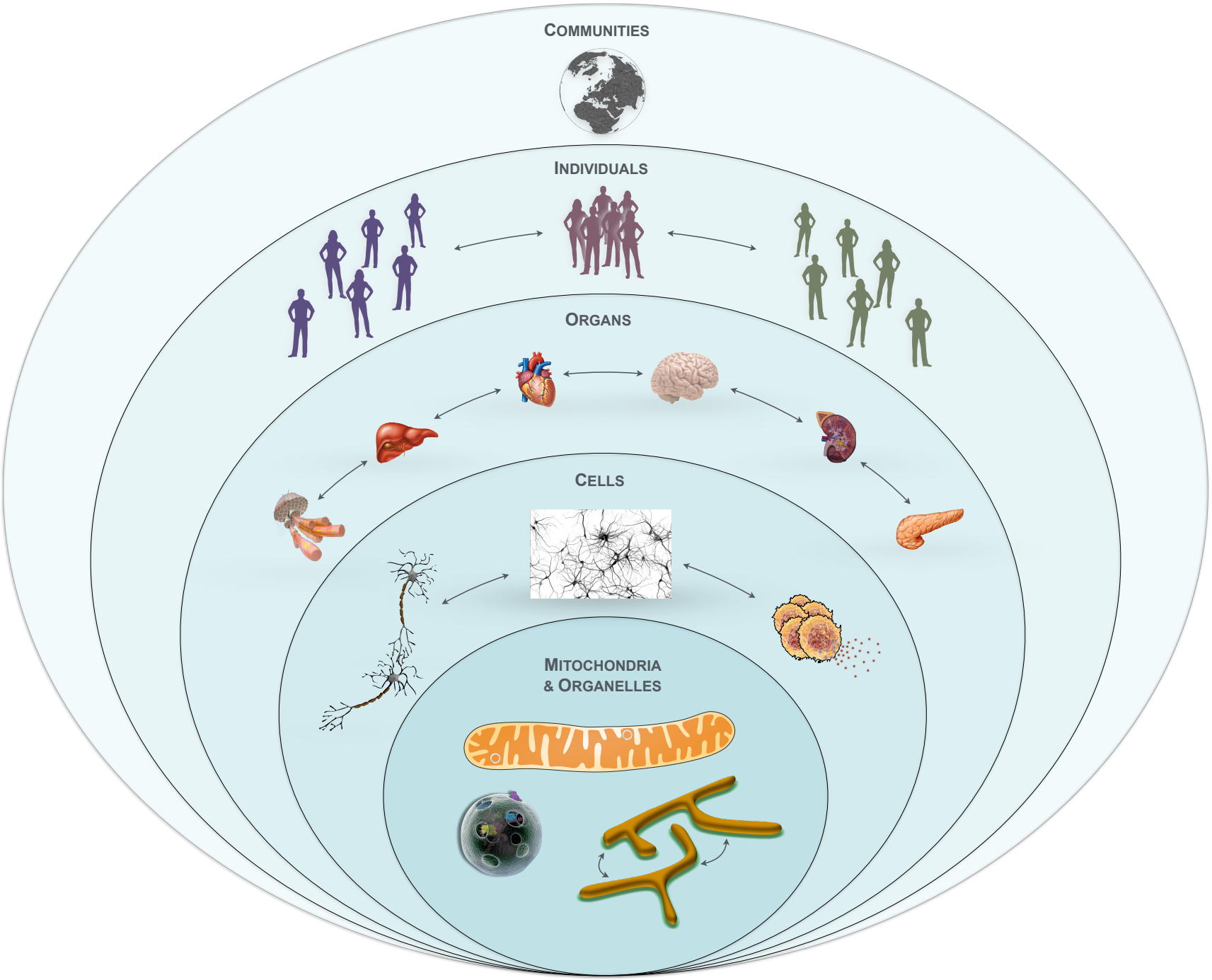
COMMUNITIES
INDIVIDUALS
ORGANS
CELLS
MITOCHONDRIA
& ORGANELLES

Mitochondrial PsychoBiology Lab

Linking molecular processes within mitochondria with the human experience

OUR RESEARCH

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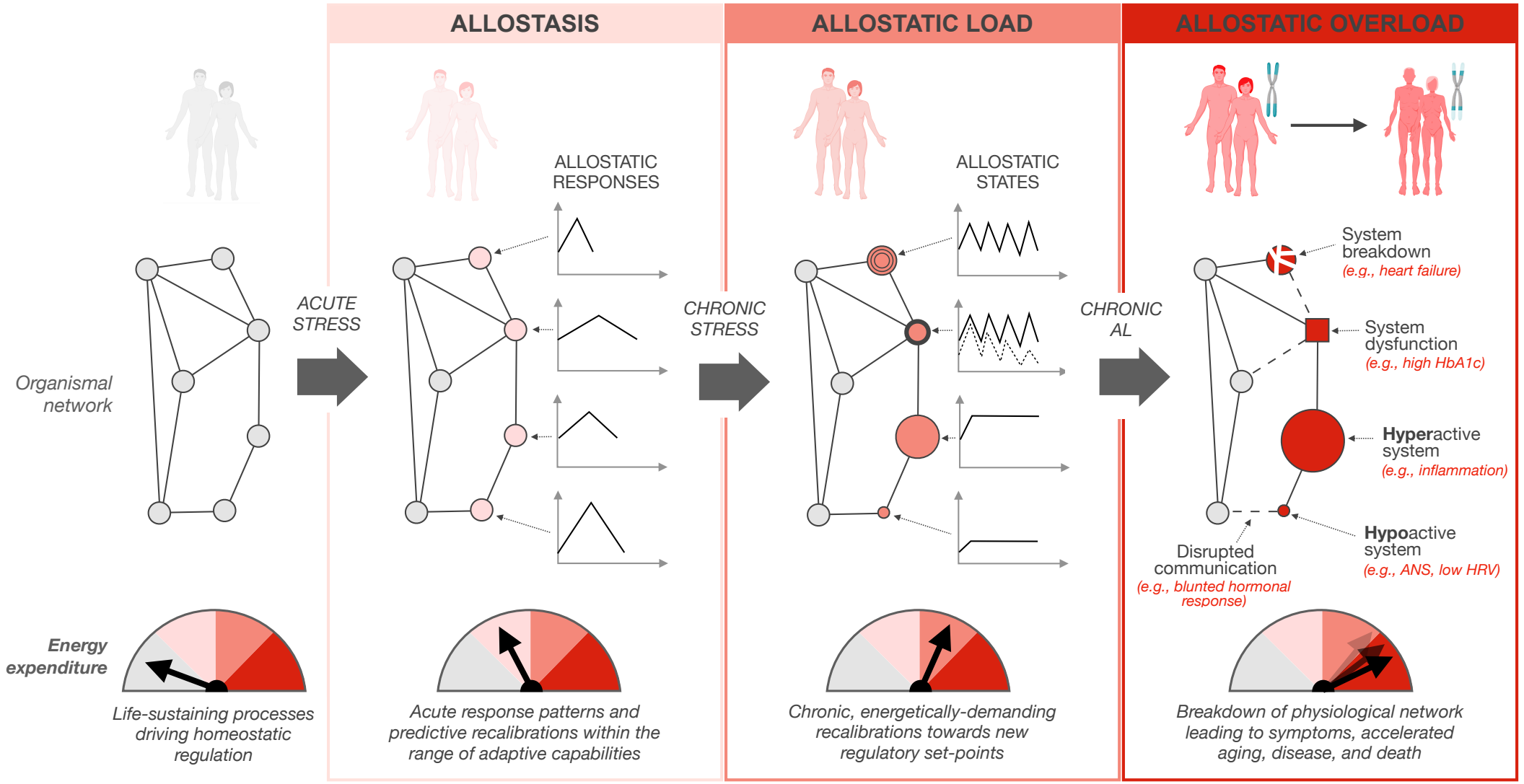
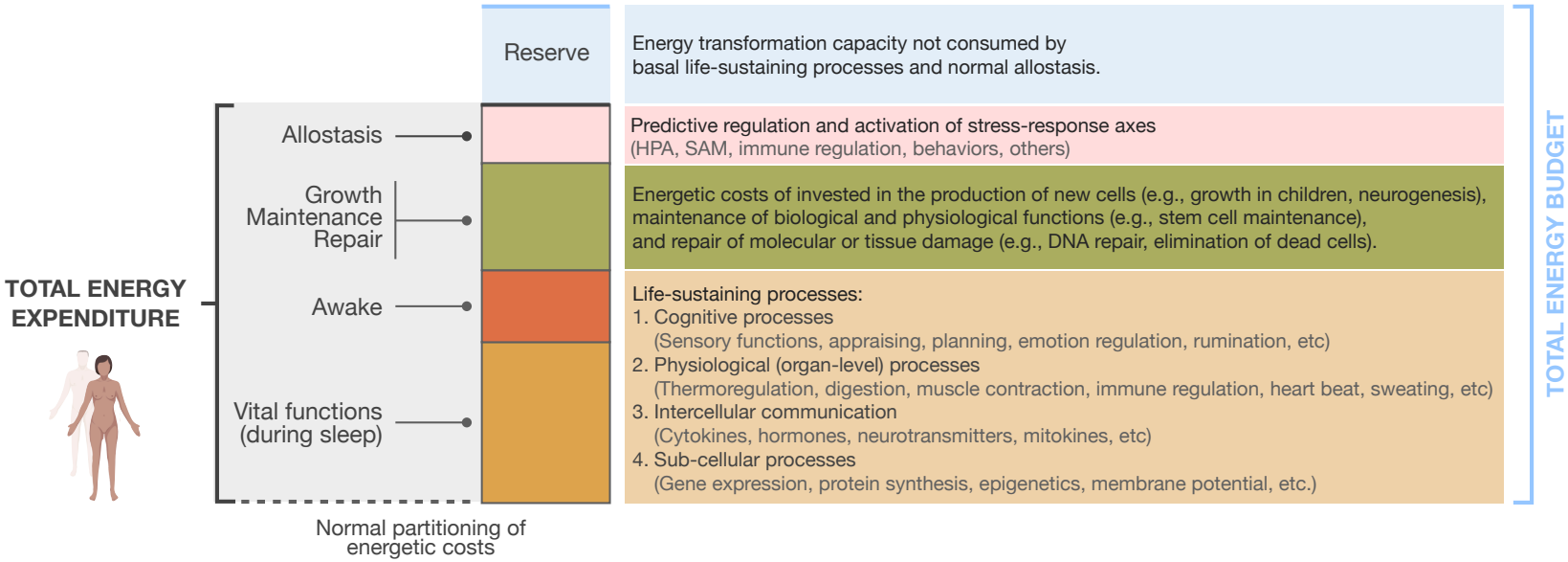
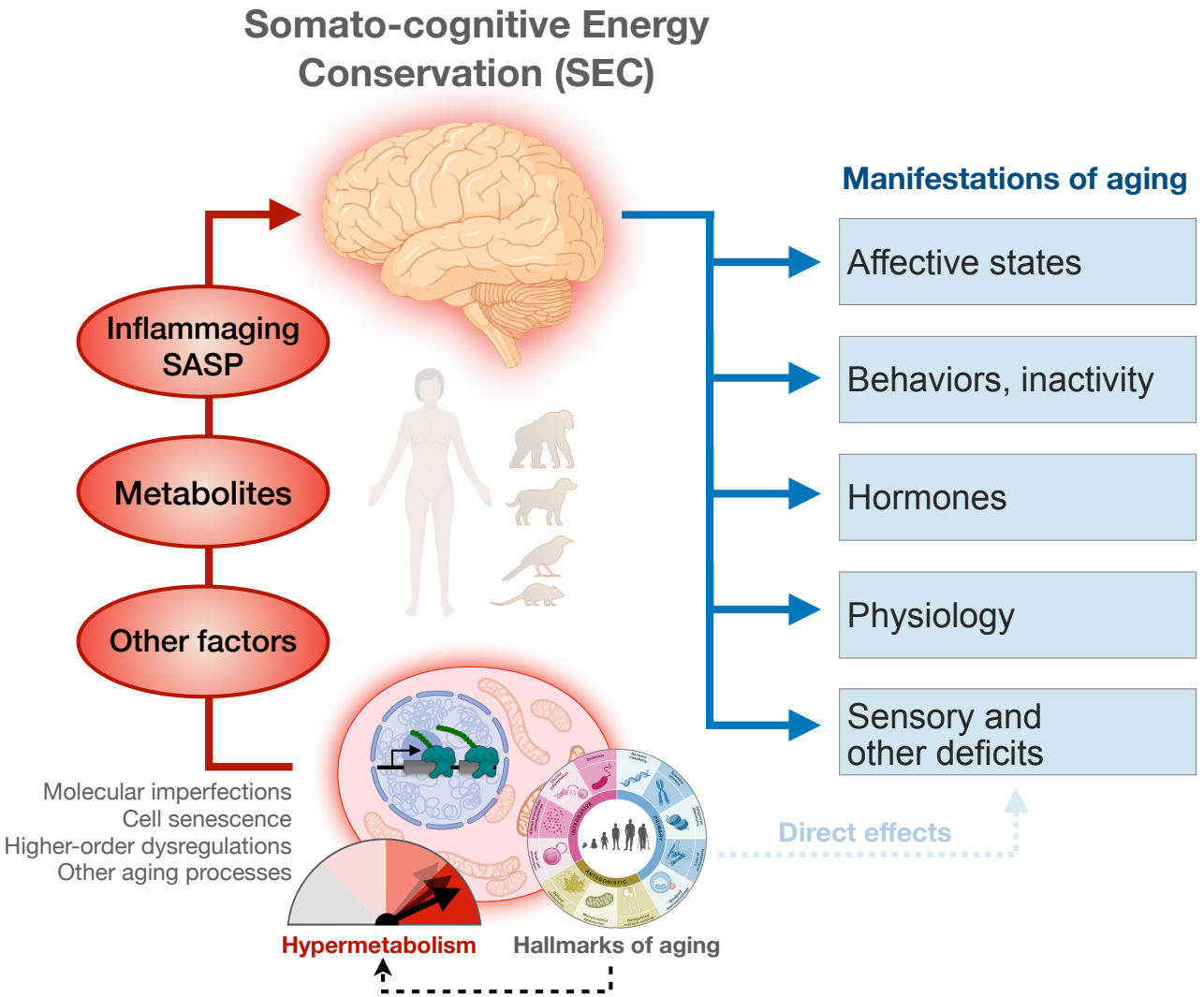
MITOCHONDRIA STRESS BRAIN EPIGENETICS
MiSBiE

Energetic Model of Allostatic Load (EMAL)



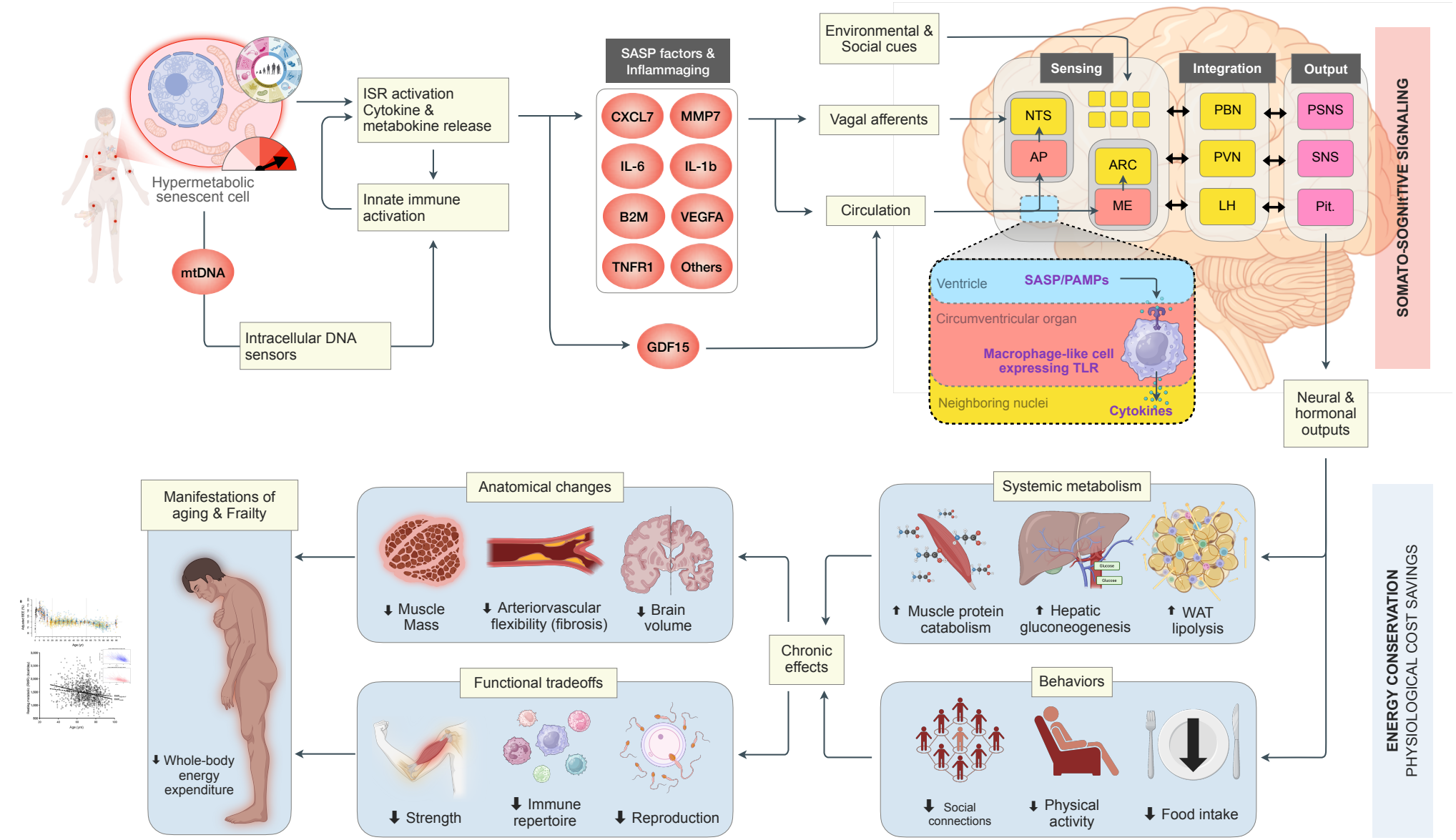
Bobba-Alves, Juster, Picard. *Psychoneuroendocrinol* 2022


TOTAL ENERGY EXPENDITURE
Reserve
Allostasis
Growth
Maintenance
Repair
Awake
Vital functions
(during sleep)
Normal partitioning of
energetic costs
Energy transformation capacity not consumed by
basal life-sustaining processes and normal allostasis.
Predictive regulation and activation of stress-response axes
(HPA, SAM, immune regulation, behaviors, others)
Energetic costs of invested in the production of new cells (e.g., growth in children, neurogenesis),
maintenance of biological and physiological functions (e.g., stem cell maintenance),
and repair of molecular or tissue damage (e.g., DNA repair, elimination of dead cells).
Life-sustaining processes:
1. Cognitive processes
(Sensory functions, appraising, planning, emotion regulation, rumination, etc)
2. Physiological (organ-level) processes
(Thermoregulation, digestion, muscle contraction, immune regulation, heart beat, sweating, etc)
3. Intercellular communication
(Cytokines, hormones, neurotransmitters, mitokines, etc)
4. Sub-cellular processes
(Gene expression, protein synthesis, epigenetics, membrane potential, etc.)
TOTAL ENERGY BUDGET



Shaulson, Cohen, Picard. *Preprint* (osf.io/zuey2)

A detailed view of somato-cognitive signaling



Shaulson, Cohen, Picard. *Preprint* (osf.io/zuey2)