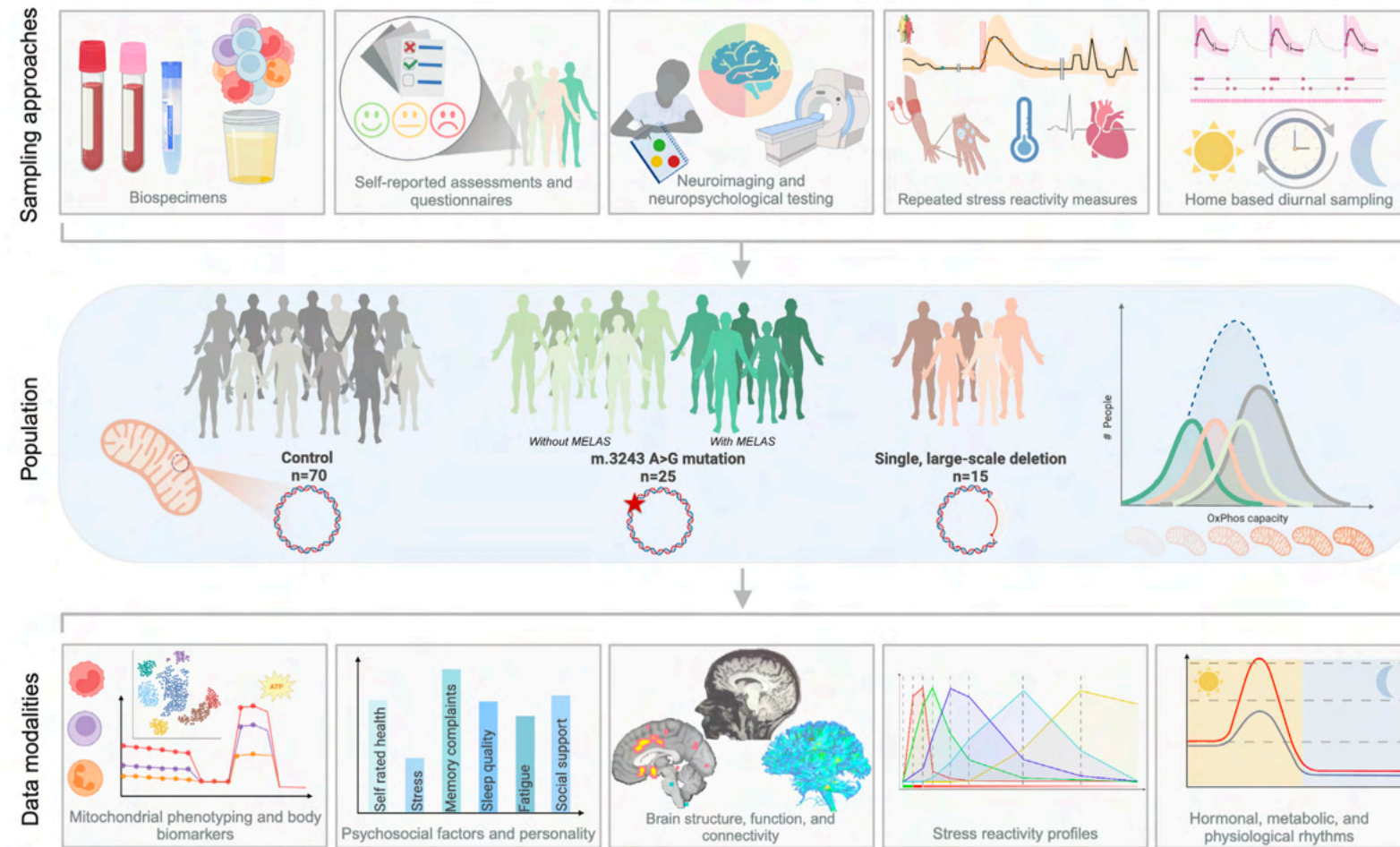
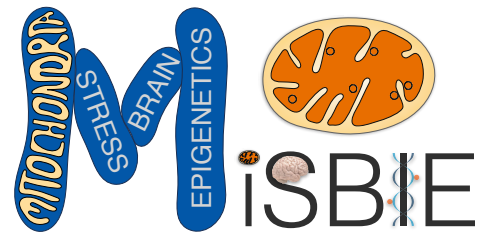


**Opinion**









A platform to map the mind–mitochondria connection and the hallmarks of psychobiology: the MiSBIE study



<https://doi.org/10.1038/s42003-022-04303-x>

OPEN

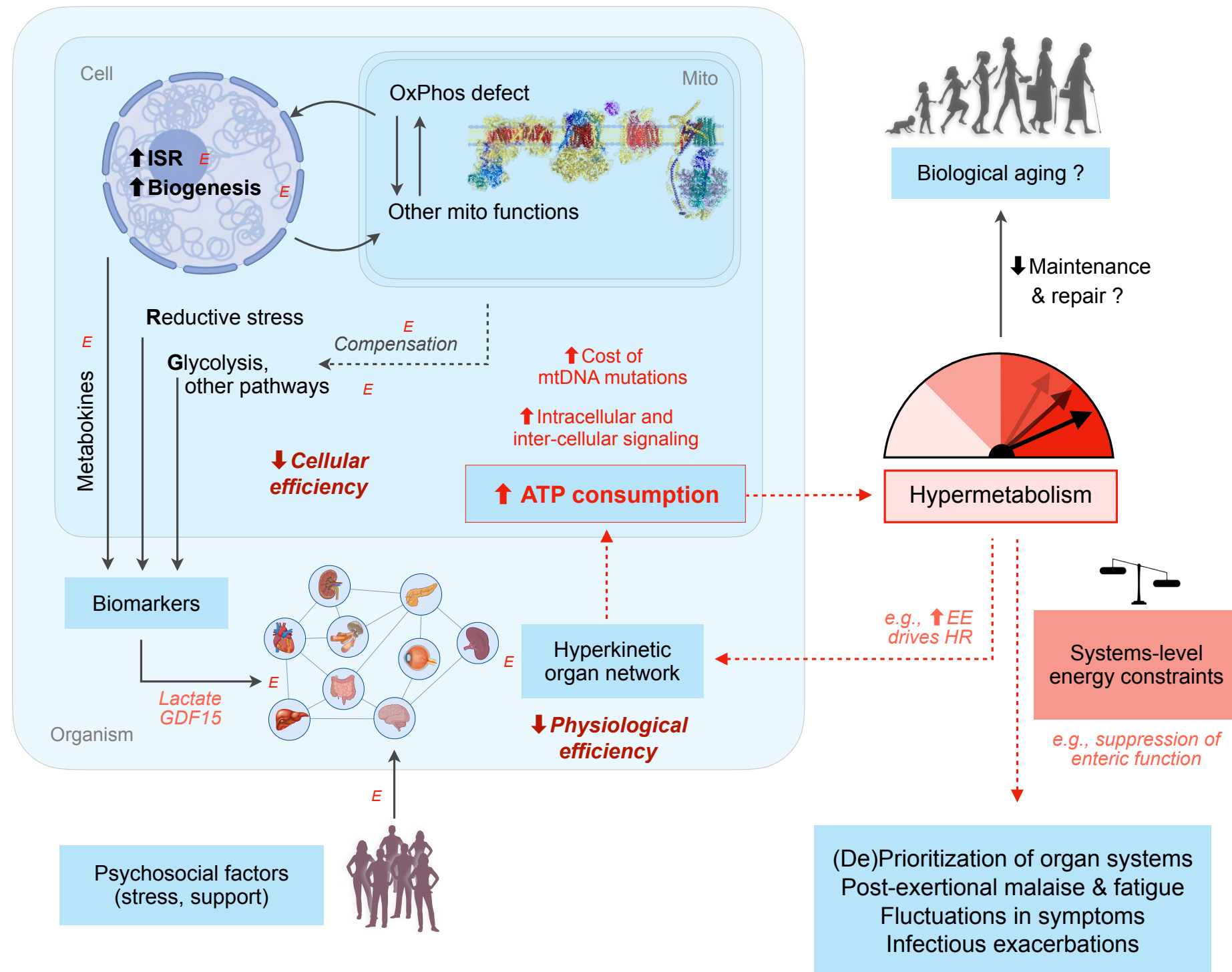
# OxPhos defects cause hypermetabolism and reduce lifespan in cells and in patients with mitochondrial diseases

Gabriel Sturm <sup>1,2</sup>, Kalpita R. Karan<sup>1</sup>, Anna S. Monzel<sup>1</sup>, Balaji Santhanam<sup>3</sup>, Tanja Taivassalo<sup>4</sup>, Céline Bris<sup>5,6</sup>, Sarah A. Ware<sup>7</sup>, Marissa Cross<sup>1</sup>, Atif Towheed<sup>1,8</sup>, Albert Higgins-Chen <sup>9</sup>, Meagan J. McManus<sup>10,11</sup>, Andres Cardenas <sup>12</sup>, Jue Lin<sup>2</sup>, Elissa S. Epel<sup>13</sup>, Shamima Rahman <sup>14</sup>, John Vissing<sup>15</sup>, Bruno Grassi<sup>16</sup>, Morgan Levine <sup>17</sup>, Steve Horvath <sup>17</sup>, Ronald G. Haller<sup>18</sup>, Guy Lenaers<sup>5,6</sup>, Douglas C. Wallace <sup>11</sup>, Marie-Pierre St-Onge<sup>19</sup>, Saeed Tavazoie<sup>3</sup>, Vincent Procaccio<sup>5,6</sup>, Brett A. Kaufman<sup>7</sup>, Erin L. Seifert<sup>20</sup>, Michio Hirano<sup>21</sup> & Martin Picard <sup>1,21,22</sup>✉

**OxPhos-deficient fibroblasts** burn 90-110% more energy  
**Meta-analysis** of human data suggest 30% (!) hypermetabolism  
**MDEE data** shows ~10%

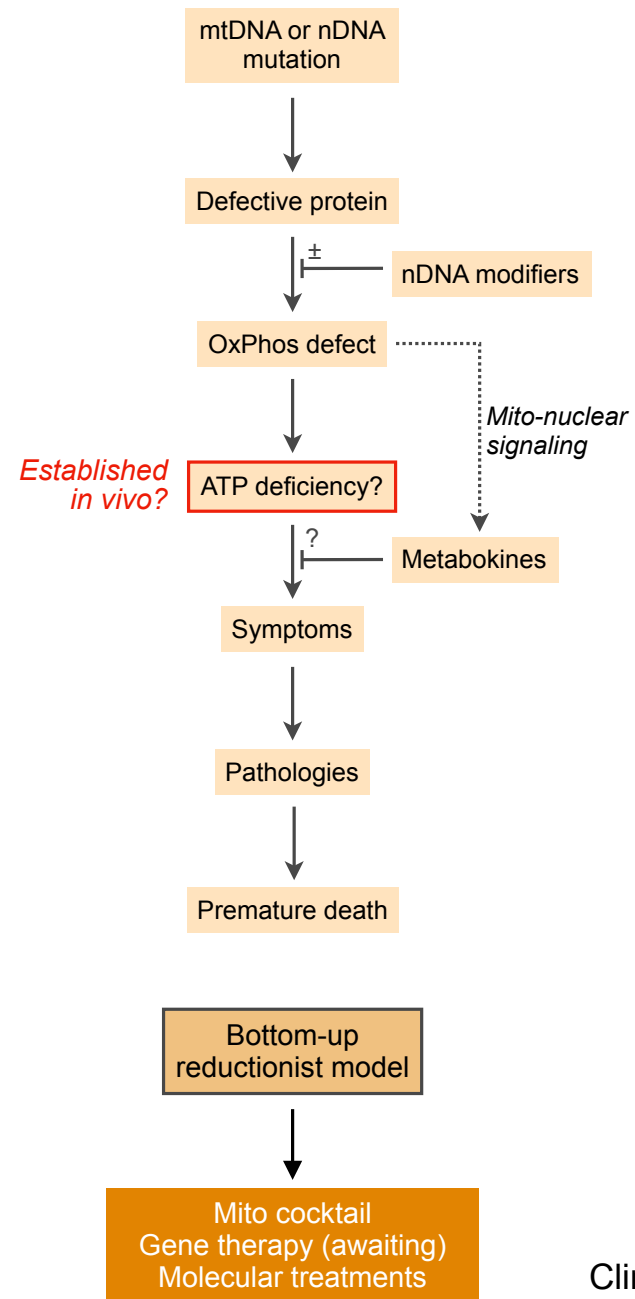
# Decreased energy efficiency in mitochondrial diseases

## From what?

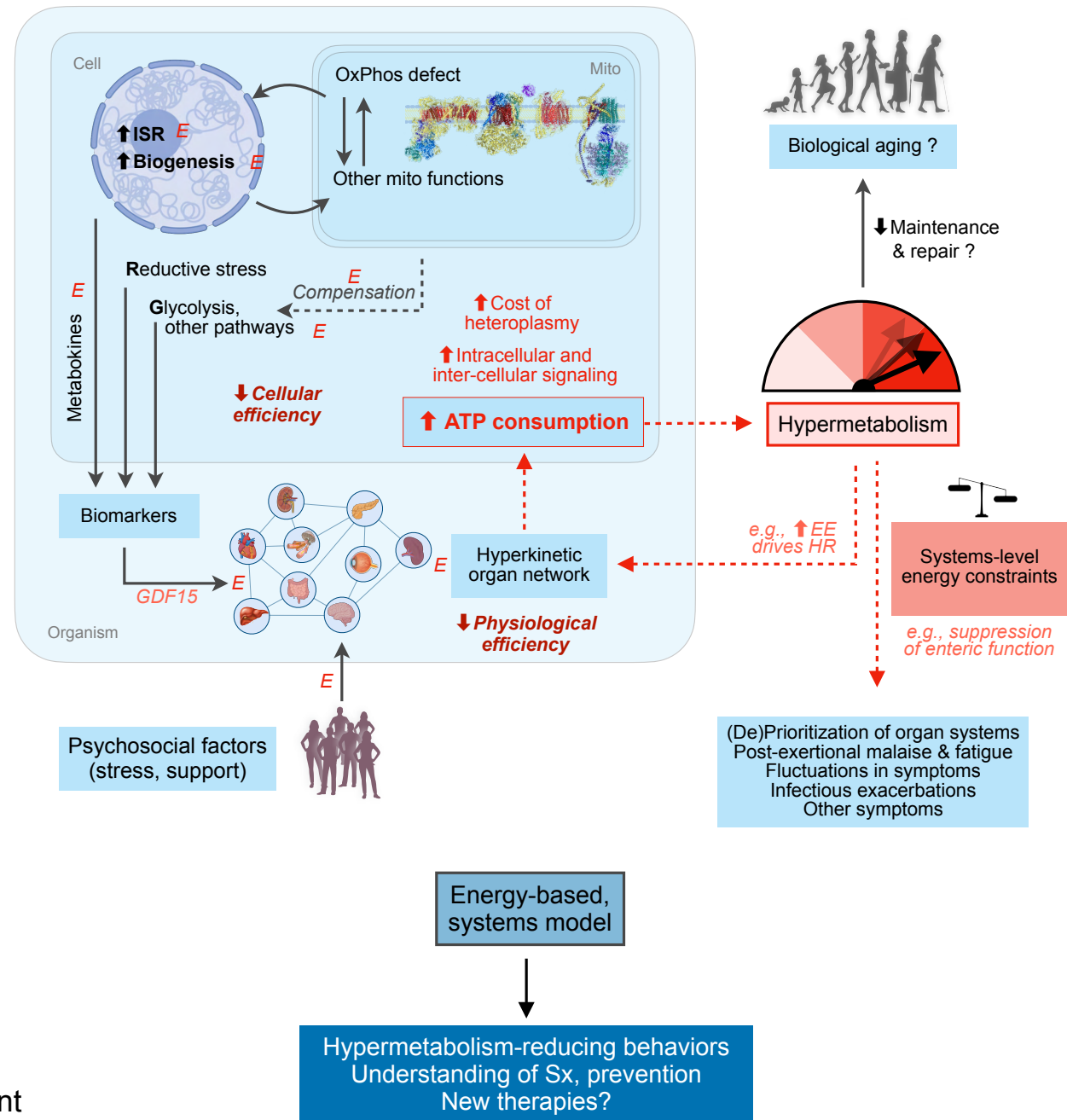


**Mitochondrial diseases**

**Central dogma model of mitochondrial diseases**



**Energy constraint model (Hypermetabolism)**

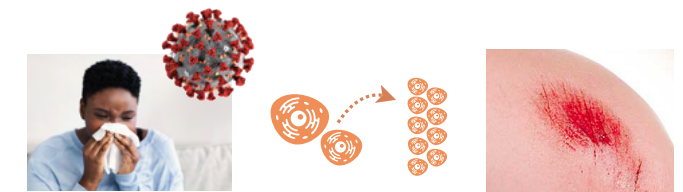
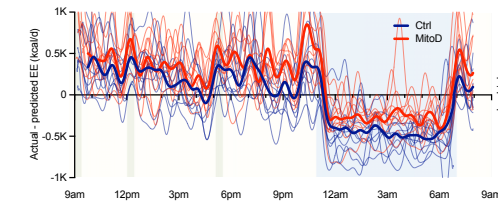
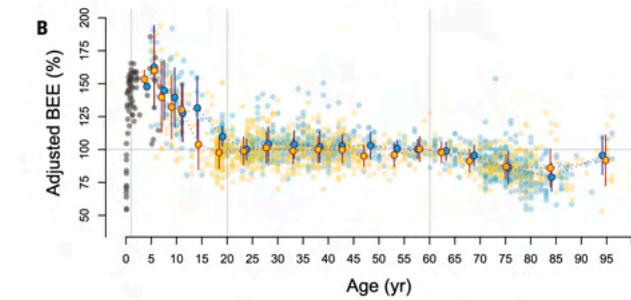


Interventions  
Clinical management

# What does is Mean for Mitochondrial Diseases & Human Health ?

## Hypermetabolism could explain why ...

- Many mitochondrial diseases are more **severe in childhood** (Pearson syndrome)  
Basal EE is highest in childhood, added costs to OxPhos defect-induced hypermetabolism
- Patients experience **fatigue, sleep** more, and **nap** frequently  
Sleep decreases basal EE (hypometabolism), countermeasure to hypermetabolism?
- In some patients **alcohol** triggers fatigue and decompensation (alcohol intolerance)  
Alcohol consumption increases basal EE (+16%), exacerbating hypermetabolism
- **Infectious conditions** can trigger clinical exacerbations, symptoms onset, death  
Immune activation costs energy, increasing basal EE, exacerbating hypermetabolism
- **Psychological stress** may trigger or exaggerate some symptoms of mitochondrial diseases  
Activation of stress response costs energy, increases EE by 9-67%, exacerbating hypermetabolism



# Outcome variables

Mitochondrial	Stress reactivity & Allostatic load	Multi-omics	Neuroimaging	Clinical and Psychosocial
<b>Genetic diagnosis</b> [ <i>categorical</i> ] - m.3243A>G - Single deletion (size, position, genes affected) - Heteroplasmy (sequencing) in blood, buccal, urine - mtDNA haplogroups	<b>Allostatic load</b> - Blood chemistry - Immune and inflammatory - Metabolic/neuroendocrine - Diurnal Cortisol - Hair Cortisol	<b>Epigenetic and genomic</b> - Genome-wide (EPIC 850K) - Epigenetic age clocks - Telomere length - Multiple tissues (blood, buccal, urine)	<b>Activation</b> - Task-elicited - Speech prep - Cold pressor - Positive control task - Checkerboard + sound	<b>Disease severity</b> - Columbia Neurological Score - NMDAS - NAMDC CRF - Functional capacity - Autonomic symptoms - Data-driven clinical phenotypes
<b>Mitochondrial bioenergetic phenotyping</b> [ <i>continuous</i> ] - OCR - ECAR - Metabolic flexibility (+UK5099) - Biochemical activities (CI, CII, CIV, CS) - mtDNAcn	<b>Physiological Reactivity</b> - Affect and mood - Heart rate, HRV, BP, EDA - HPA axis reactivity - Epi/Norepi - Cytokines - Proteomics - Metabolomics	<b>Gene expression</b> - RNA-Seq (monocytes, lymphocytes) - Pre and post-stress - scRNAseq PBMCs <b>Fecal sample</b> - Microbiome composition and complexity	<b>Functional connectivity</b> - Resting state - Task-evoked - Speech prep - Cold pressor - N-back - Brain-wide signatures of mitochondrial defects	<b>Neuropsychological testing</b> - Working memory - Cognitive function - Cognitive impairment - Psychiatric symptoms  <b>Psychosocial factors</b>
<b>Mitochondrial molecular phenotyping</b> - PMPC single-cell RNAseq - Single mitochondrial or nuclear genes - MitoPathways - Mitotype signatures	<b>Metabokines/Mitokines</b> - FGF21, GDF15 - cf-mtDNA (plasma, serum, saliva, urine)  <b>Immune cytokine production</b> - LPS challenge ± DEX - LPS challenge ± Inhibitors	<b>Metabolomics</b> - Plasma - Baseline and stress reactivity  <b>Proteomics</b> - Plasma and saliva - Baseline and stress reactivity	<b>Structural</b> - Voxel-based morphometry - Cortical surface area - Diffusion imaging & tractography	<b>Age of onset</b> <b>Demographic</b> <b>Psychosocial factors</b>  <b>Progression</b> (score/yr change)

# Biomarker analyses

- **Some Completed**
- **Several In Progress**
- **Planned** (metabolomics, proteomics)  
*Human Stress Metabolome*  
*Human Stress Proteome*
- **Biobank available** for emerging markers

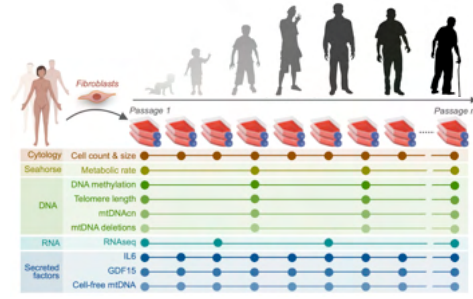
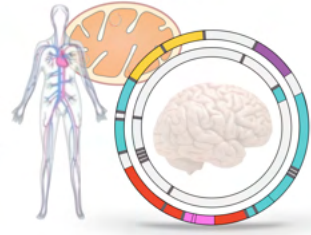
Biomarker	Sample type	Description	Units	Stage
Cortisol	Hair	Fasting	pg/mg	In progress
Cortisone	Hair	Fasting	pg/mg	In progress
Corticosterone	Hair	Fasting	pg/mg	In progress
Testosterone	Hair	Fasting	pg/mg	In progress
Progesterone	Hair	Fasting	pg/mg	In progress
DHEA	Hair	Fasting	pg/mg	In progress
Cortisol	Saliva	Fasting, TSST, MRI, diurni	ng/mL	In progress
Cortisone	Saliva	Fasting, TSST, MRI, diurni	ng/mL	In progress
Corticosterone	Saliva	Fasting, TSST, MRI, diurni	ng/mL	In progress
Testosterone	Saliva	Fasting, TSST, MRI, diurni	ng/mL	In progress
Progesterone	Saliva	Fasting, TSST, MRI, diurni	ng/mL	In progress
DHEA	Saliva	Fasting, TSST, MRI, diurni	ng/mL	In progress
FGF21	Plasma	Fasting, TSST	pg/mL	Done
GDF15	Plasma	Fasting, TSST	pg/mL	Done
GDF15	Saliva	Fasting, TSST	pg/mL	Done
Epinephrine	Urine	Overnight	mcg/24 hours	Done
Norepinephrine	Urine	Overnight	mcg/24 hours	Done
IL-6	EDTA whole blood	Fasting		Not started
TNF-a	EDTA whole blood	Fasting		Not started
CRP	Serum	Fasting	mg/dL	Done
Fibrinogen	Bluetop tube	Fasting	mg/dL	Done
Glucose	Serum	Fasting	mg/dL	Done
HgbA1c	EDTA whole blood	Fasting	%	Done
Insulin	Serum	Fasting	uIU/mL	Done
Peptide C	Serum	Fasting	ng/mL	Done
Triglycerides	Serum	Fasting	mg/dL	Done
Total cholesterol	Serum	Fasting	mg/dL	Done
HDL	Serum	Fasting	mg/dL	Done
Creatinine	Serum	Fasting	mg/dL	Done
Albumin	Serum	Fasting	g/dL	Done
cf-mtDNA	Plasma	Fasting, TSST		In progress
cf-mtDNA	Serum	Fasting, TSST		In progress
cf-mtDNA	Saliva	Fasting, TSST, MRI, diurnal		Done
cf-mtDNA	Urine	Overnight		Done
MCHC	EDTA whole blood	Fasting	g/dL	Done
MPV	EDTA whole blood	Fasting		Done
pct_Neutrophils	EDTA whole blood	Fasting	%	Done
pct_Lymphs	EDTA whole blood	Fasting	%	Done
pct_Monos	EDTA whole blood	Fasting	%	Done
pct_Eos	EDTA whole blood	Fasting	%	Done
pct_Basos	EDTA whole blood	Fasting	%	Done
WBC	EDTA whole blood	Fasting	cells/L	Done
RBC	EDTA whole blood	Fasting	cells/mcL	Done
PLT	EDTA whole blood	Fasting	cells/L	Done
Hemoglobin	EDTA whole blood	Fasting	g/dL	Done
Hematocrit	EDTA whole blood	Fasting	%	Done
MCV	EDTA whole blood	Fasting	fl	Done
MCH	EDTA whole blood	Fasting	pg	Done
RDW	EDTA whole blood	Fasting	%	Done
IG%	EDTA whole blood	Fasting	%	Done
NeutroAbsolute	EDTA whole blood	Fasting	%	Done
LymphAbsolute	EDTA whole blood	Fasting	%	Done
MonoAbsolute	EDTA whole blood	Fasting	%	Done
EosAbsolute	EDTA whole blood	Fasting	%	Done
BasoAbsolute	EDTA whole blood	Fasting	%	Done
LDL	Serum	Fasting	mg/dL	Done
Sodium	Serum	Fasting	mEq/L	Done
Potassium	Serum	Fasting	mEq/L	Done
Chloride	Serum	Fasting	mEq/L	Done
CO2	Serum	Fasting	mEq/L	Done

# Using MiSBIE Data and Samples

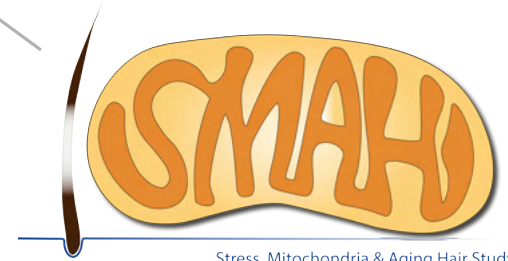
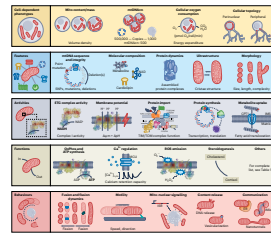
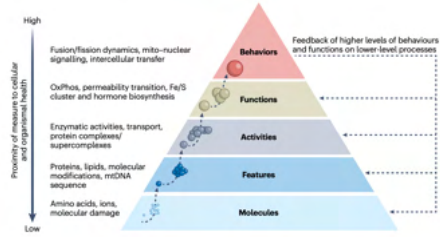
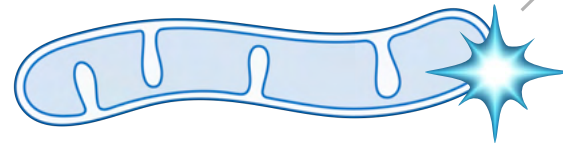
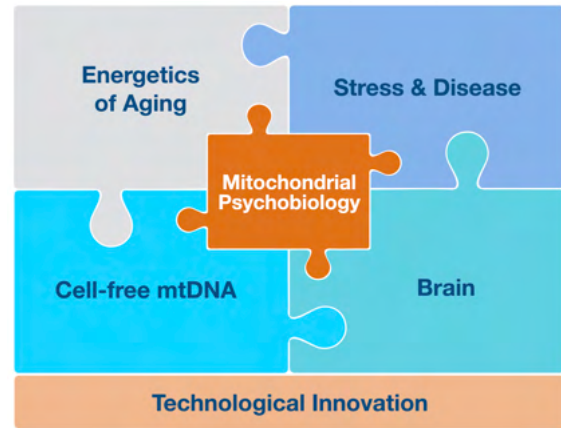
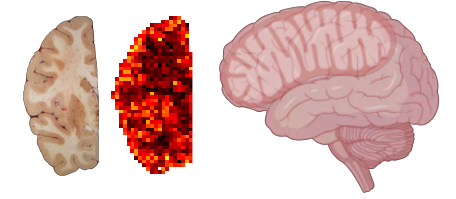
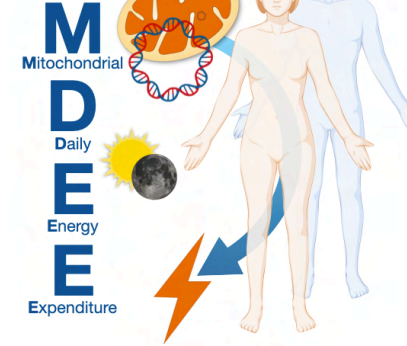
# Using MiSBIE Data and Samples

- Parent MiSBIE R01MH122706 data in **NIMH Data Archive** (NDA)
- Future OMICS data deposited in **GEO**
- All other data harmonized in sharable form in **RedCap**
- (In development) Data Request Form — online portal, early 2026
- *Lead: Caroline Trumpff*  
*Project Coordinator: Vanessa Giardino*  
*Data manager: Grace Liu*

MaPS

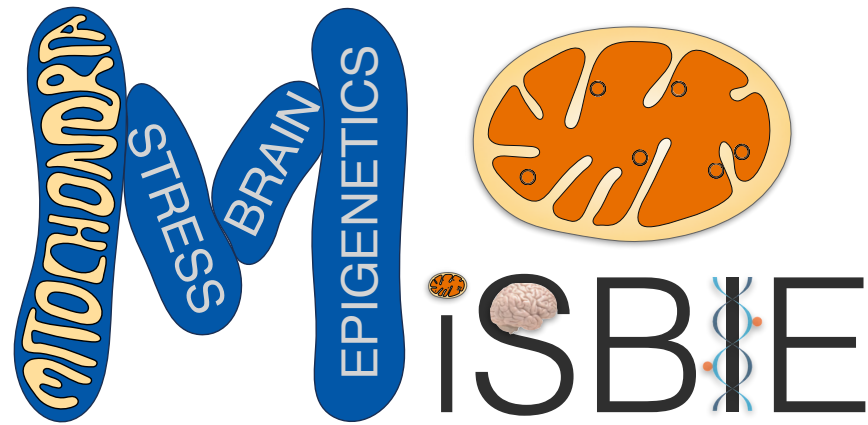


MITOCHONDRIA STRESS BRAIN EPIGENETICS ISBIE



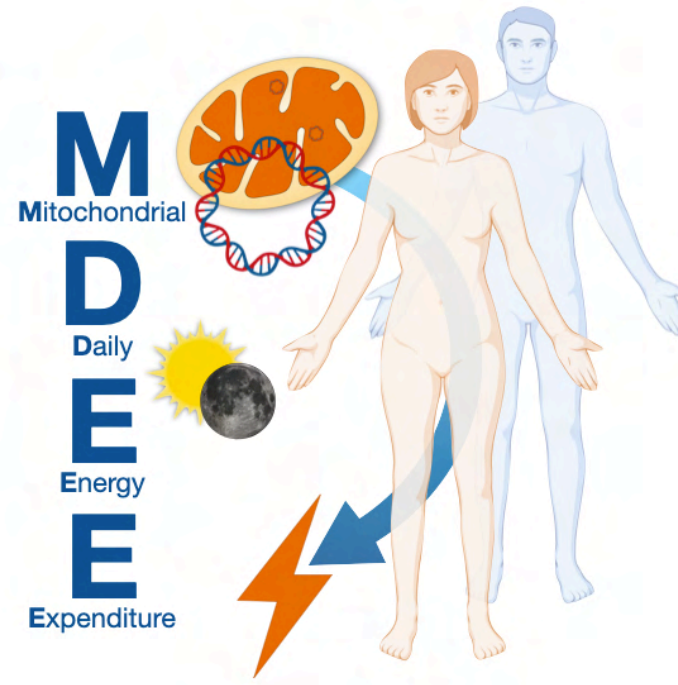
Stress, Mitochondria & Aging Hair Study





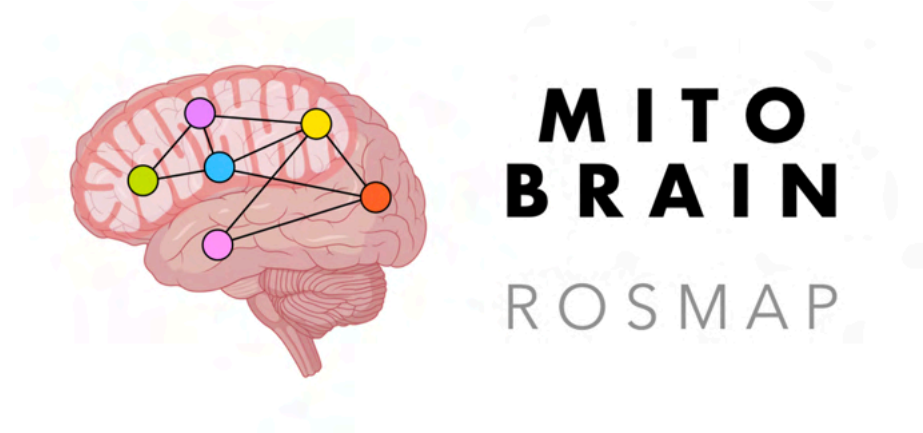
**Mitochondrial Stress, Brain Imaging,  
and Epigenetics — MiSBIE**

**2016-2023**



**Mitochondrial Daily Energy  
Expenditure — MDEE**

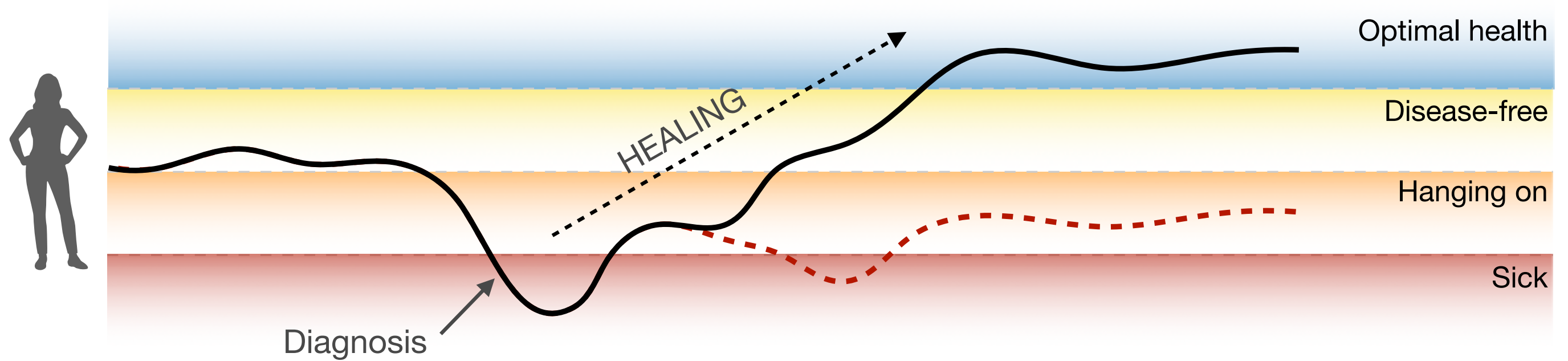
**2021-2025**



**MitoBrain ROSMAP**  
n=5,000 samples

**2023-2026**

# The Basis of Health is Healing



# What is **healing**?

**Healing** is a set of dynamic, energetic processes by which the organism moves towards **optimal function**

It can manifest as **growth** and **development**, **recovery** from injury and trauma, and **adaptation** that enhance the system's **coherence** as a whole

Healing can also extend to **social** or **communal** contexts

Thank you !