Misfolding of acid sphingomyelinase, associated with Niemann-Pick A/B, as a risk factor for the development of Parkinson disease

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George S. Wise Faculty of Life Sciences
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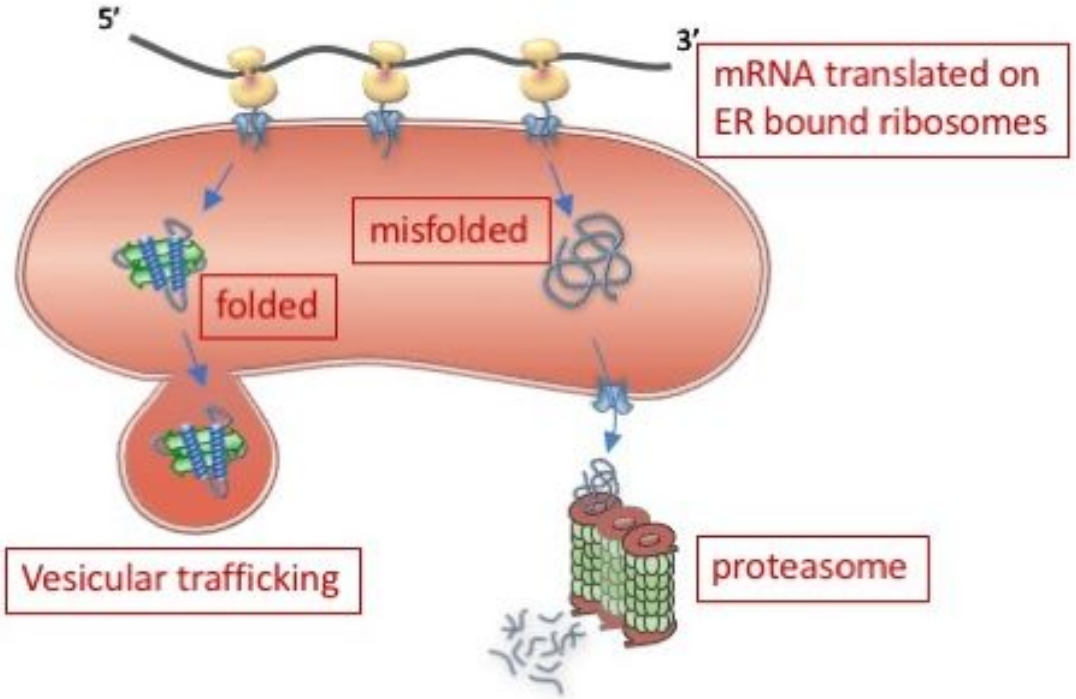
Protein misfolding and ER Associated degradation (ERAD)



ERAD: Misfolded proteins undergo retrotranslocation form the ER to the cytoplasm where they are ubiquitinated, reach the proteasome and undergo proteasomal degradation

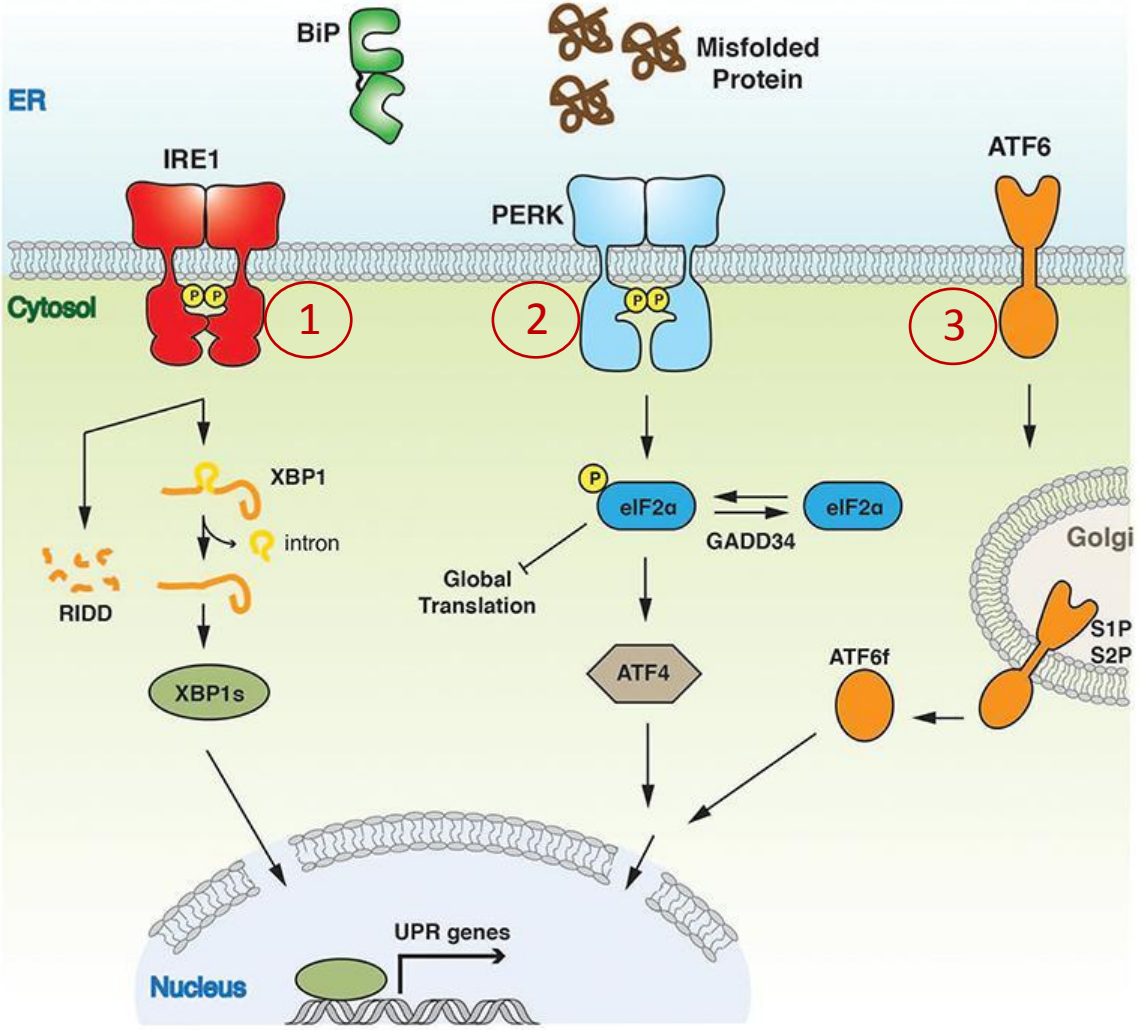
Unfolded Protein Response (UPR)

The three arms of UPR:

1. IRE1-Degradation,
XBP1 splicing

2. PERK-Attenuated protein synthesis
eIF2a phosphorylation
CHOP upregulation

3. ATF6- Upregulated folding capacity
BiP upregulation



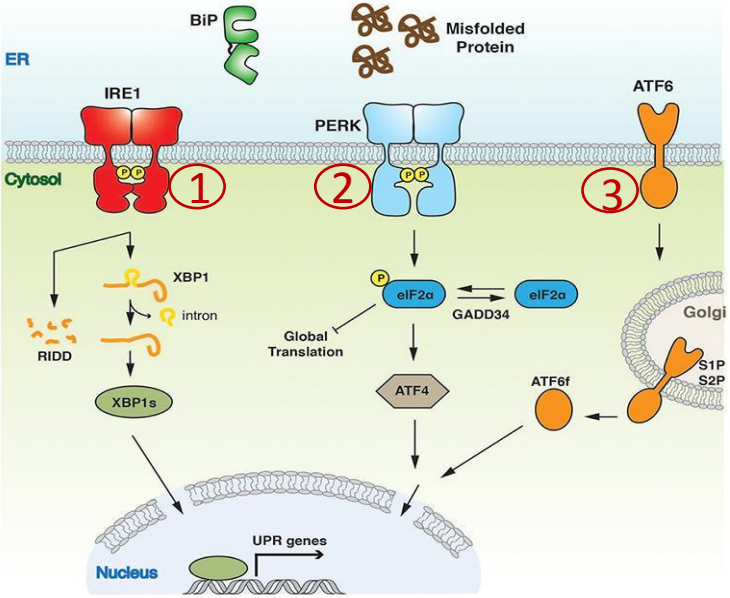
Structure and Molecular Mechanism of ER Stress Signaling by the Unfolded Protein Response Signal Activator IRE1
Adams et al, Front. Mol. Biosci., 2019, vol. 6.

UPR and Lysosomal Storage Diseases

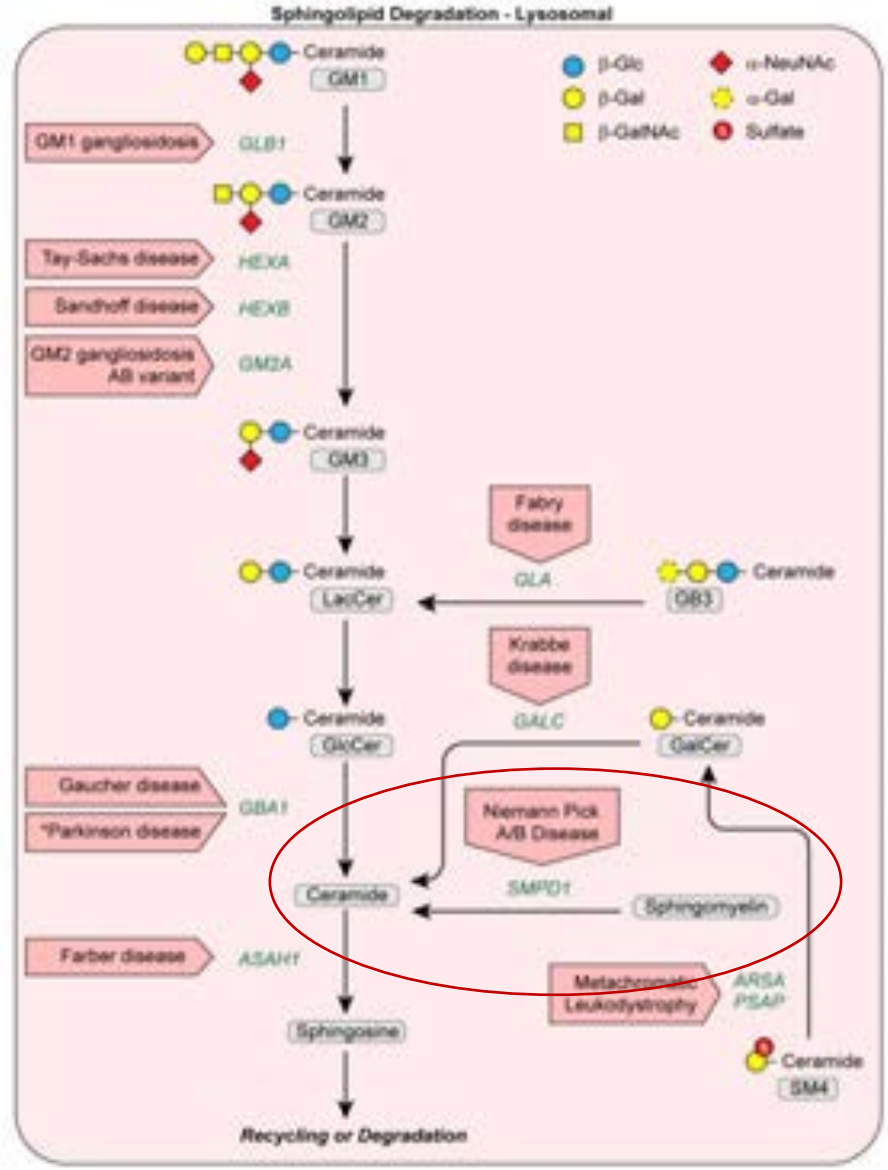
We have shown in the past that Stress and Stress Response (UPR) exist in:

- Gaucher disease-misfolding is a major determinant in development of Parkinson disease in a fly model
- Fabry disease

We wondered what happens in Niemann-Pick disease A/B

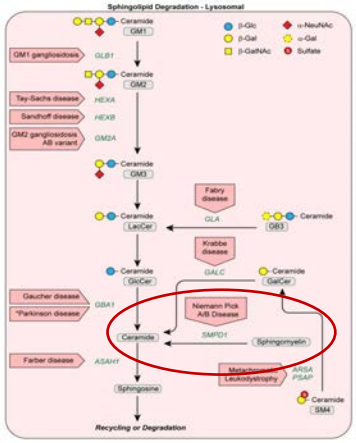


Niemann-Pick disease=mutant acid sphingomyelinase (ASM) encoded by *SMPD1*



Dunn et al: A Perilous Path: The Inborn Errors of Sphingolipid Metabolism
Journal of Lipid Research 60, 2019, 60(3):jlr.S091827

Niemann-Pick disease (NPD)=mutant acid sphingomyelinase (ASM) encoded by *SMPD1*



NPD *A* is a progressive neurological disorder leading to death within the first 3 years of life. It is characterized by hepatosplenomegaly and profound CNS involvement.
Prevalent among Ashkenazi Jews.
Combined carrier frequency for the three common *SMPD1* pathogenic variants (p.Arg498Leu, p.Leu304Pro, and p.Phe333SerfsTer52) is between 1:80 and 1:100

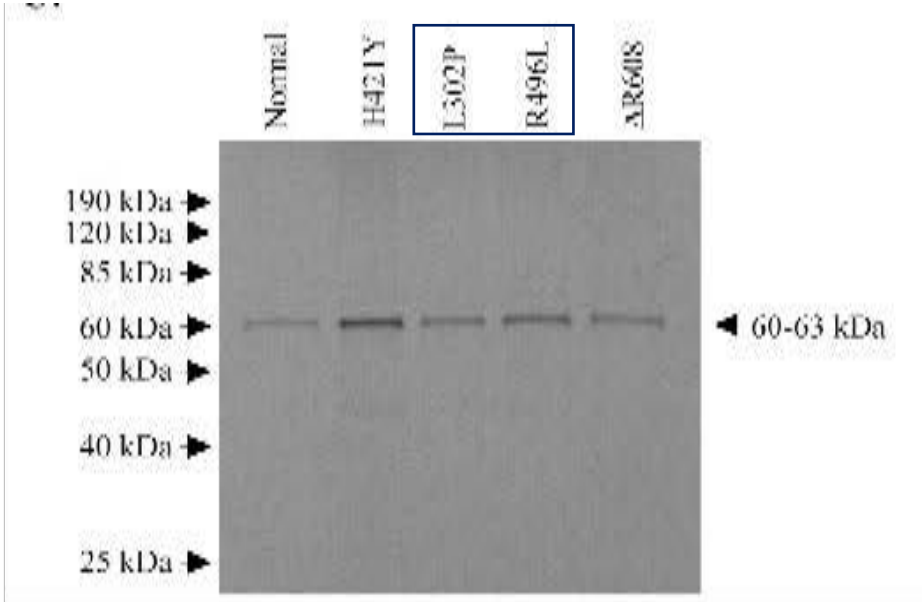
NPD B is a non-neuronopathic disorder characterized by progressive visceral organ abnormalities, including hepatosplenomegaly, pulmonary insufficiency, cardiovascular disease, and survival into adulthood

The estimated prevalence of NPD A/B is 1:250,000.

Niemann-Pick disease=mutant acid sphingomyelinase (encoded by *SMPD1*)

Jones et al: Characterization of Common *SMPD1* Mutations Causing Types A& B Niemann-Pick Disease and Generation of Mutation-Specific Mouse Models. Mol Genet Metab. 2008 November ; 95(3): 152–162

"western blotting and fluorescent microscopy showed that the mutant ASM polypeptides were expressed at normal levels and trafficked to lysosomes".



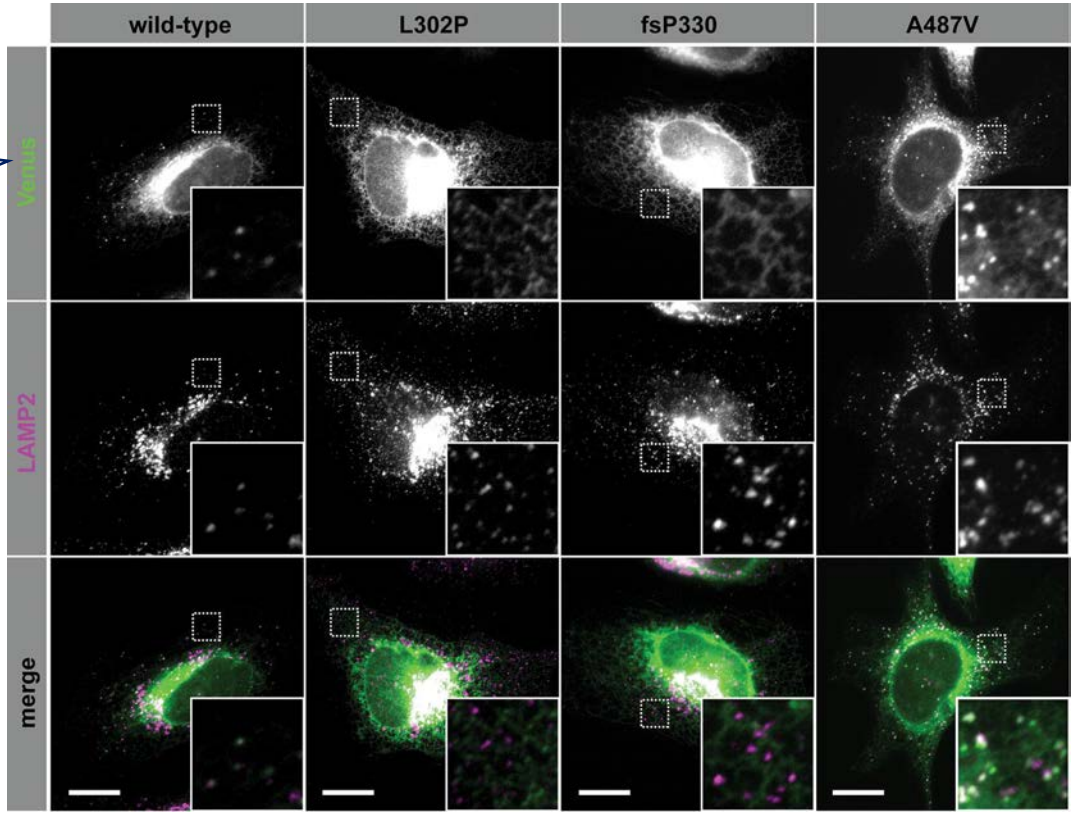
Niemann-Pick disease A/B and Parkinson Disease

Gan-Or et al :Neurology 80, 2013, 1606-1610.
"The p.L302P mutation in the lysosomal enzyme gene SMPD1 is a risk factor for Parkinson disease"

Gan-Or et al:Parkinsonism and Related Disorders 21, 2015, 1294-1295
"We reanalyzed the data from the recent and previous papers, and we show that the association between SMPD1 and PD is indeed not driven by only one mutation, but it is also not driven by all SMPD1 mutations. In the Ashkenazi-Jewish population, the p.fs330P (OR = 3.03, p = 0.0026) and p.L302P (OR = 9.62, p < 0.0001) are associated with PD, and the p.R496L mutation is not (OR = 0.84, p = 0.71), and similar observation was noted in the Chinese population. Thus, we conclude that similar to the GBA1 gene where different mutations have differential effects, SMPD1 mutations also have a differential effects on the risk for PD".

Niemann-Pick disease A/B and Parkinson Disease

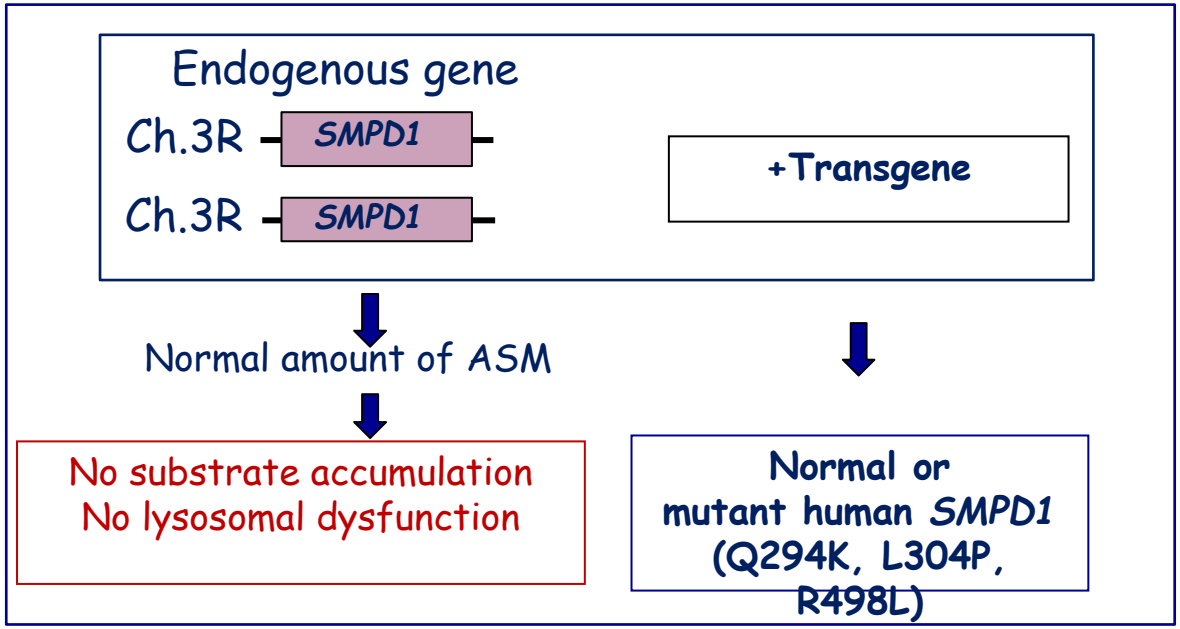
ER localization



Lysosomal local.

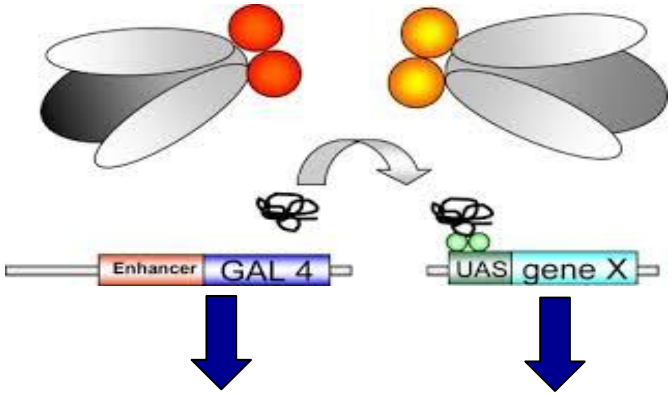
Alcalay et al: Mov Disord. 2019, 34(4): 526-535
Hela cells transfected with plasmids encoding variants of ASMase fused to a C-terminal Venus tag.
ASMase with the p.L302P or p.P330fs mutations failed to reach lysosomes, and was almost exclusively localized in the ER.
Trafficking of ASMase with the p.A487V variant seemed unaffected.

Flies transgenic for human mutant *SMPD1* (acid sphingomyeninase) variants



The transgenic fly contains one endogenous gene and an UAS-derived human *SMPD1* cDNA

Drosophila UAS-GAL4



Any *Drosophila* enhancer
For dopaminergic cells:
Dopamine decarboxylase-Ddc
or Tyrosine hydroxylase-TH

Normal or
mutant human *SMPD1*
(Q294K, L304P,
R498L)

Parkinson disease (PD)

Test in the flies:

UPR

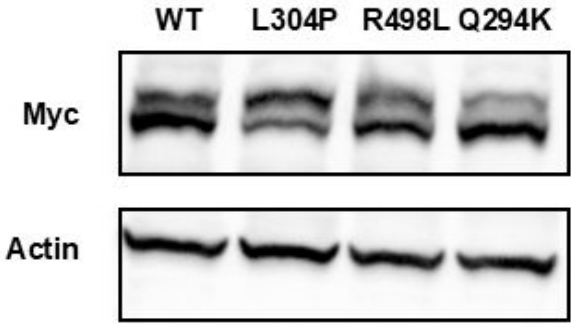
The hallmarks of PD:

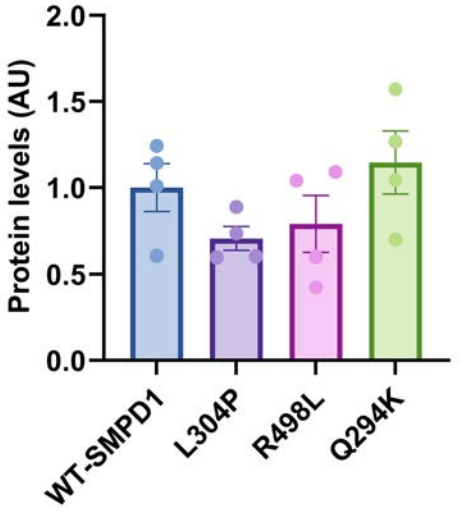
★Death of dopaminergic cells in the brain

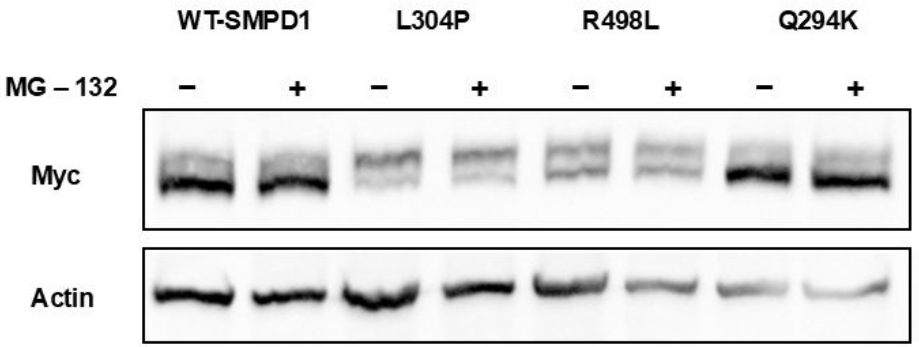
★Motor disabilities

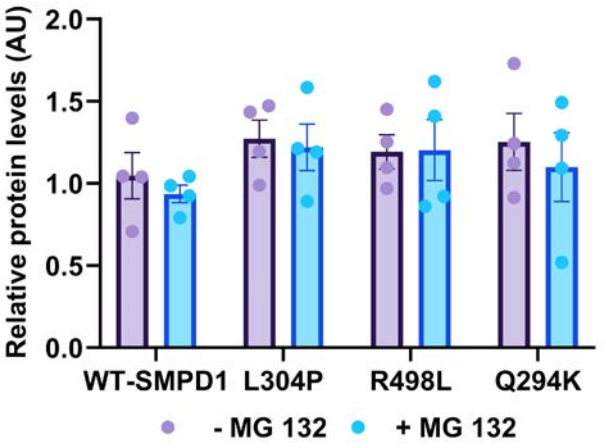
★Shorter survival

SMPD1 expression in flies



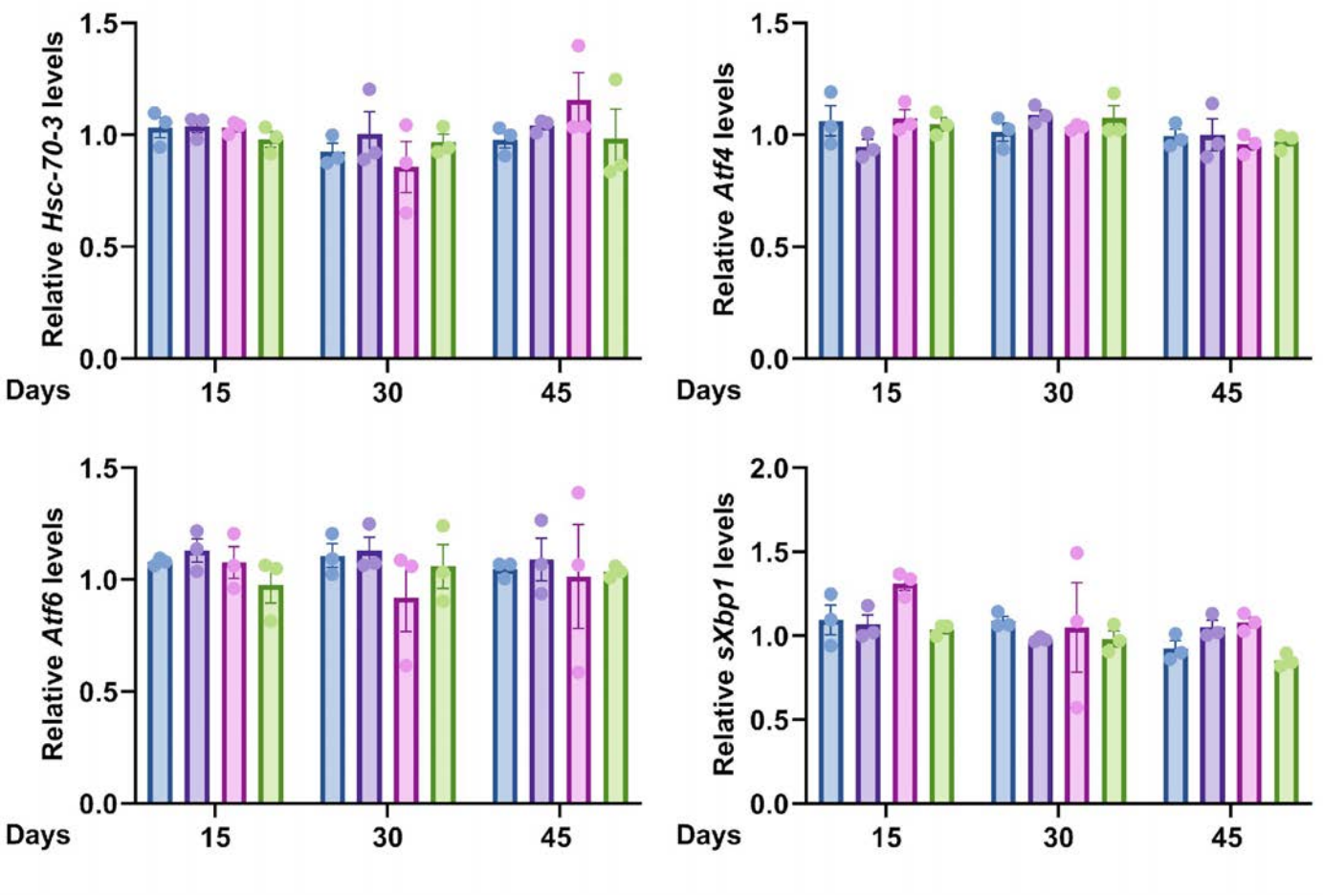






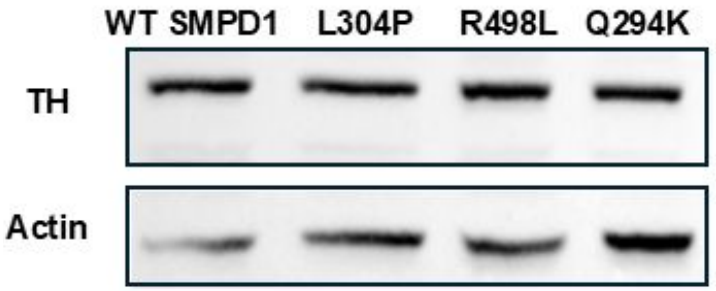
No change in levels of the different tested variants and no effect of proteasome inhibition-no ERAD

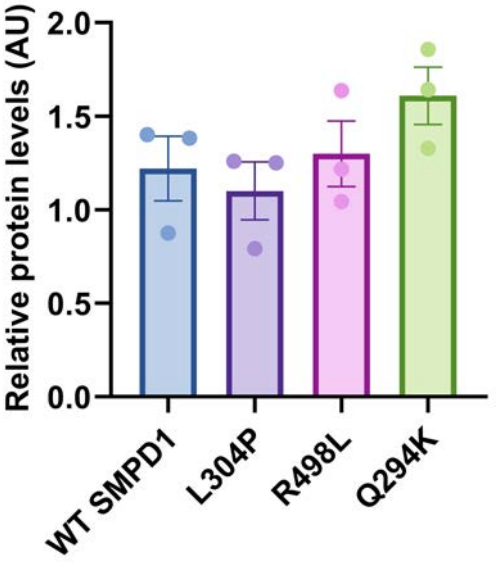
UPR in *SMPD1* flies



The mutant *SMPD1* variants do not activate UPR in adult flies (grown at 25°C)

TH expression levels in the flies

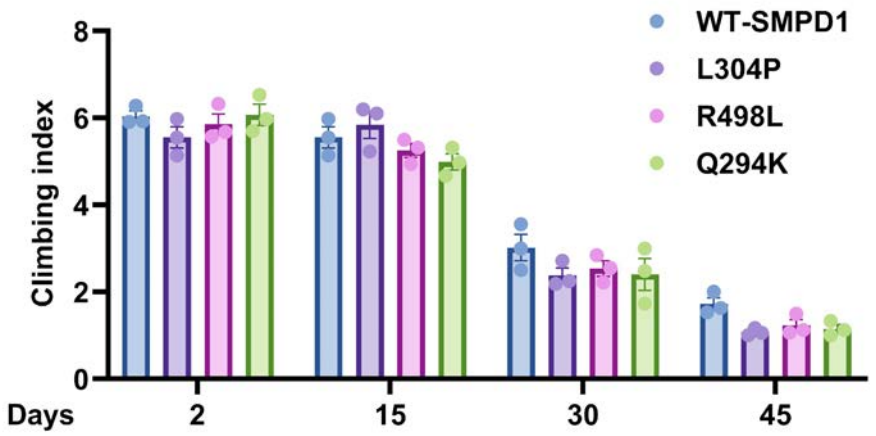




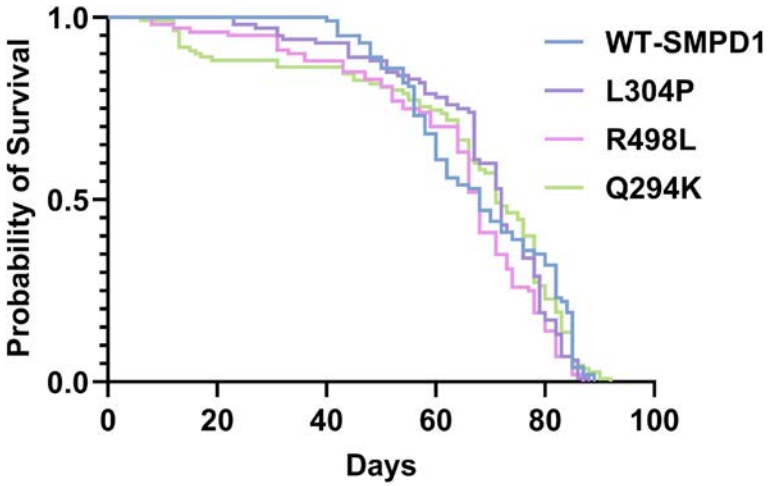
No changes in TH levels between the different flies (grown at 25°C) at day 35

Climbing and survival of the *SMPD1* flies

Climbing ability

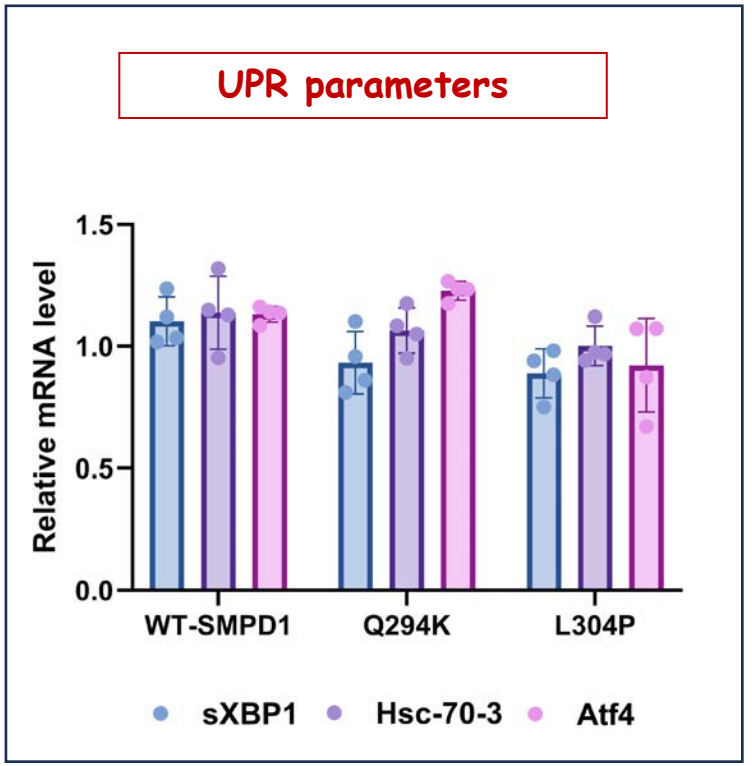


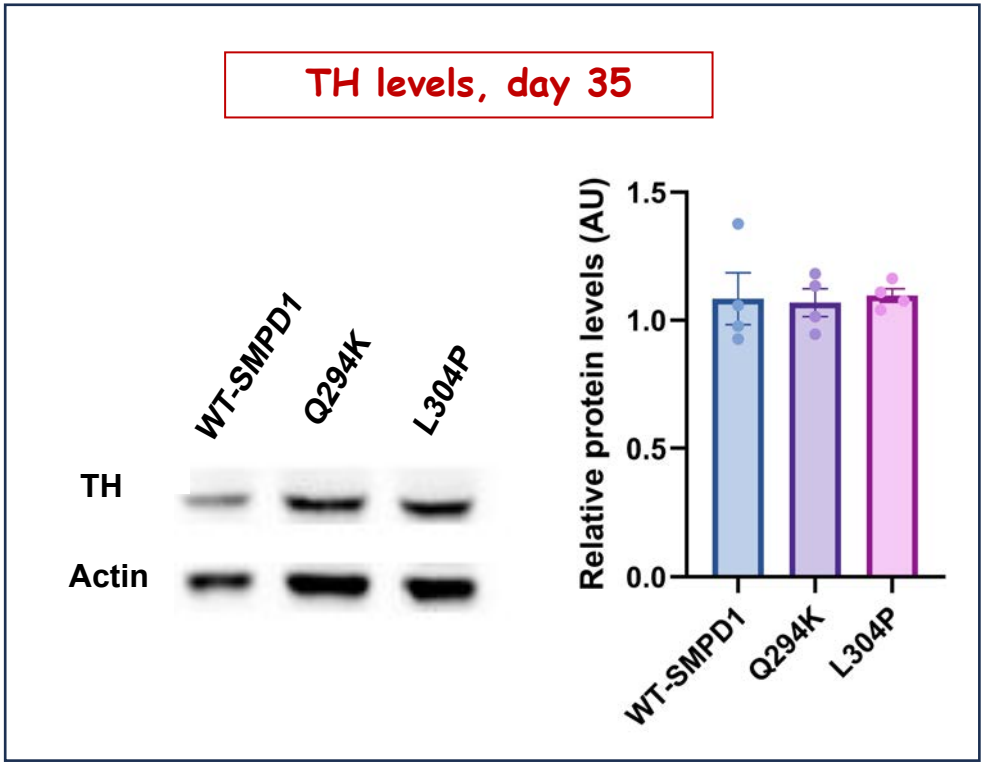
Survival



The mutant SMPD1 variants do not present change in motor ability nor in survival compared to flies expressing the WT *SMPD1* variant

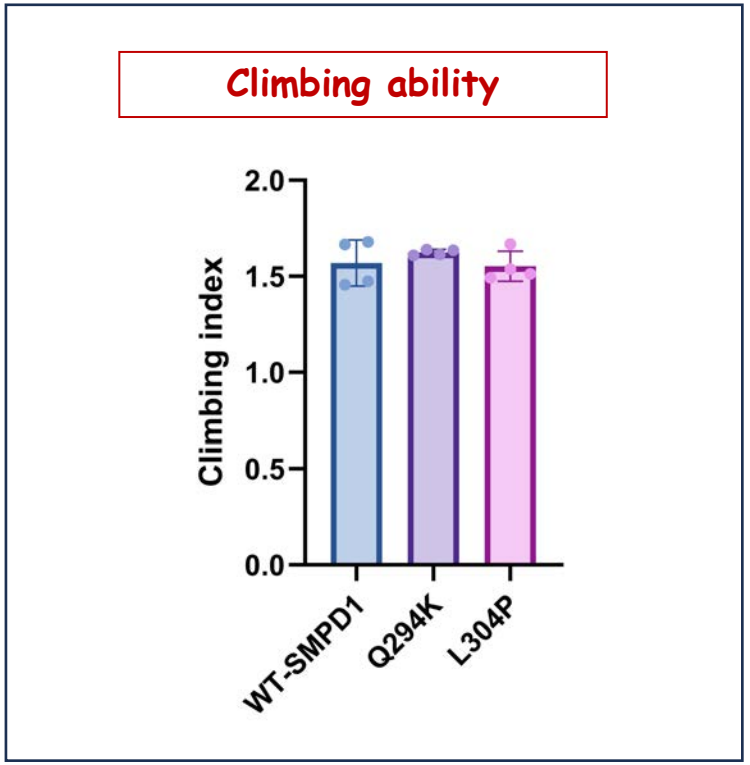
UPR, TH levels and climbing in *SMPD1* flies

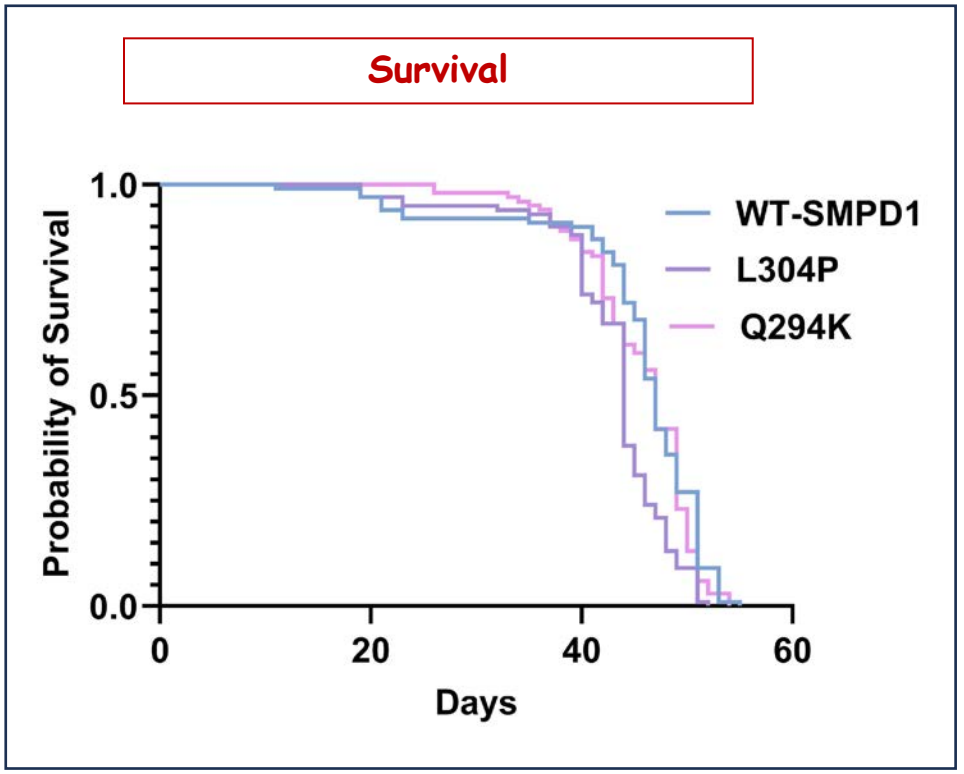




Mutant SMPD1 variants, grown at 29°C, do not activate UPR and do not present decreased TH levels

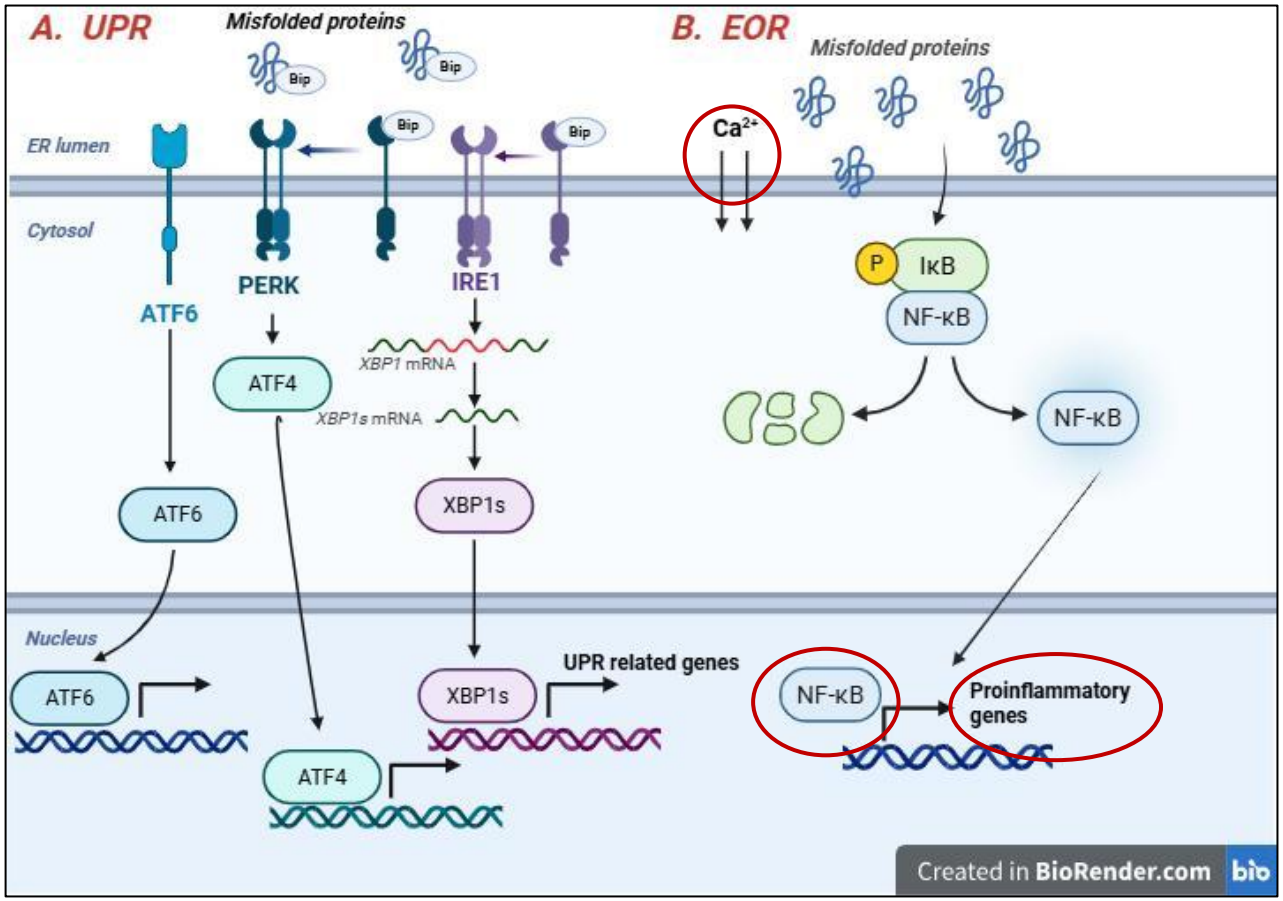
SMPD1 expression in the flies





The mutant variants do not present change in motor ability nor in survival compared to flies expressing the WT *SMPD1* variant at 29°C

ER Stress responses: UPR versus ER Overload Response (EOR)



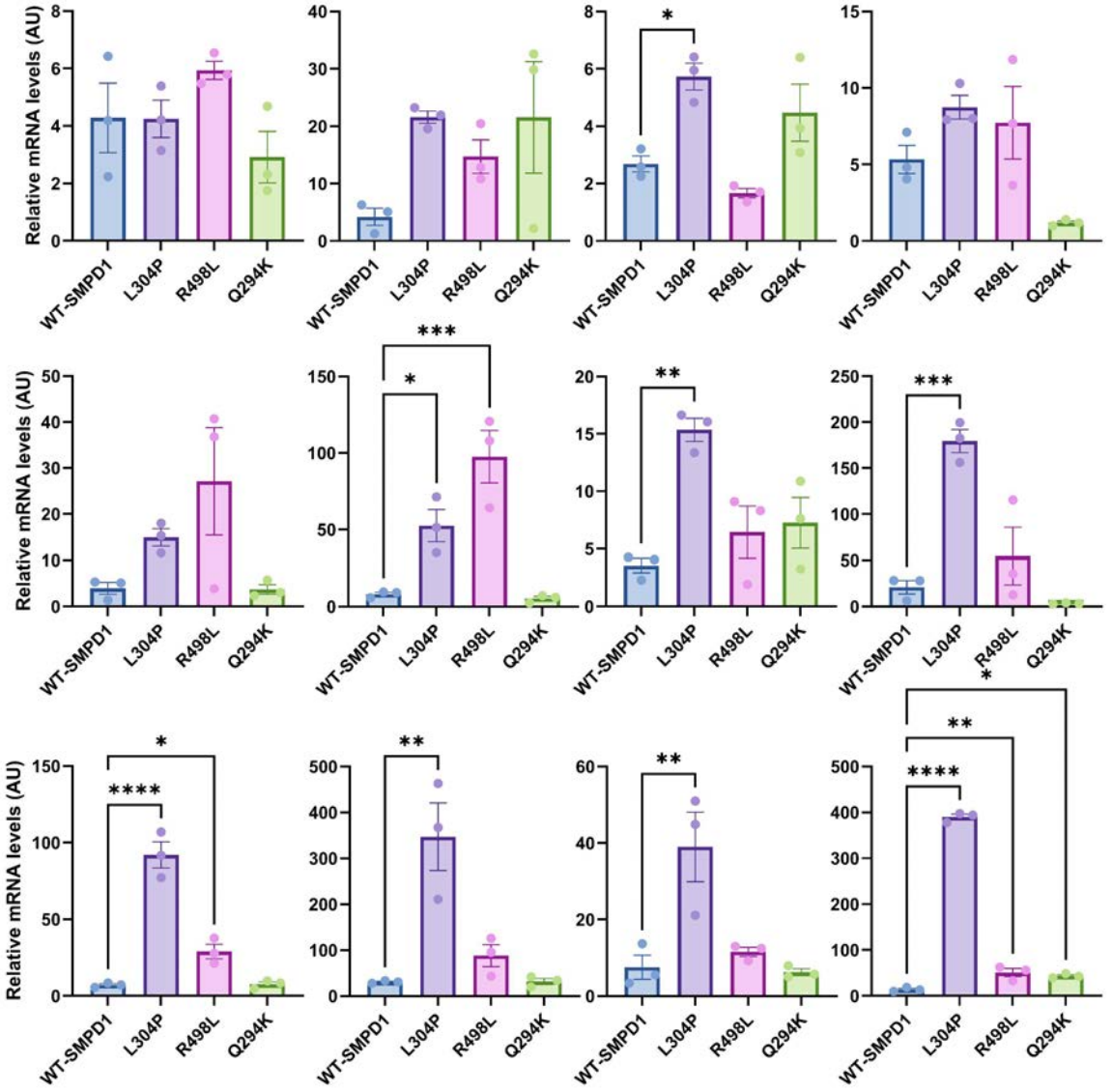
A. Retention of misfolded proteins activates the canonical UPR machinery, leading to the transcription of UPR-related genes. **B.** Misfolded proteins activate the non-canonical EOR, resulting in calcium release, nuclear translocation of NF-κB and induction of inflammatory gene expression

SMPD1 expression in flies

Day 15

Day 30

Day 45



Activation of neuroinflammation in the mutant *SMPD1* flies

Conclusions

Our results indicate ER localization of the L304P mutant *SMPD1* variant, strongly implying misfolding

This misfolding does not activate UPR. It seems to activate the ER Overload Response (EOR)

This misfolding and EOR activation may explain the association between the L304P mutant *SMPD1* and Parkinson disease

Thanks

Past students:

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Dr. Or Cabasso
Maria Papazian
Hila Braunstein

Present students:

Vera Serebryany
Aparna Kuppuramalingam

Leiden, 2022

ISRAEL SCIENCE FOUNDATION

Pfizer

Shire

Takeda

Moscow, 2017

Synthetic heart models for the study of human cardiac development and disease

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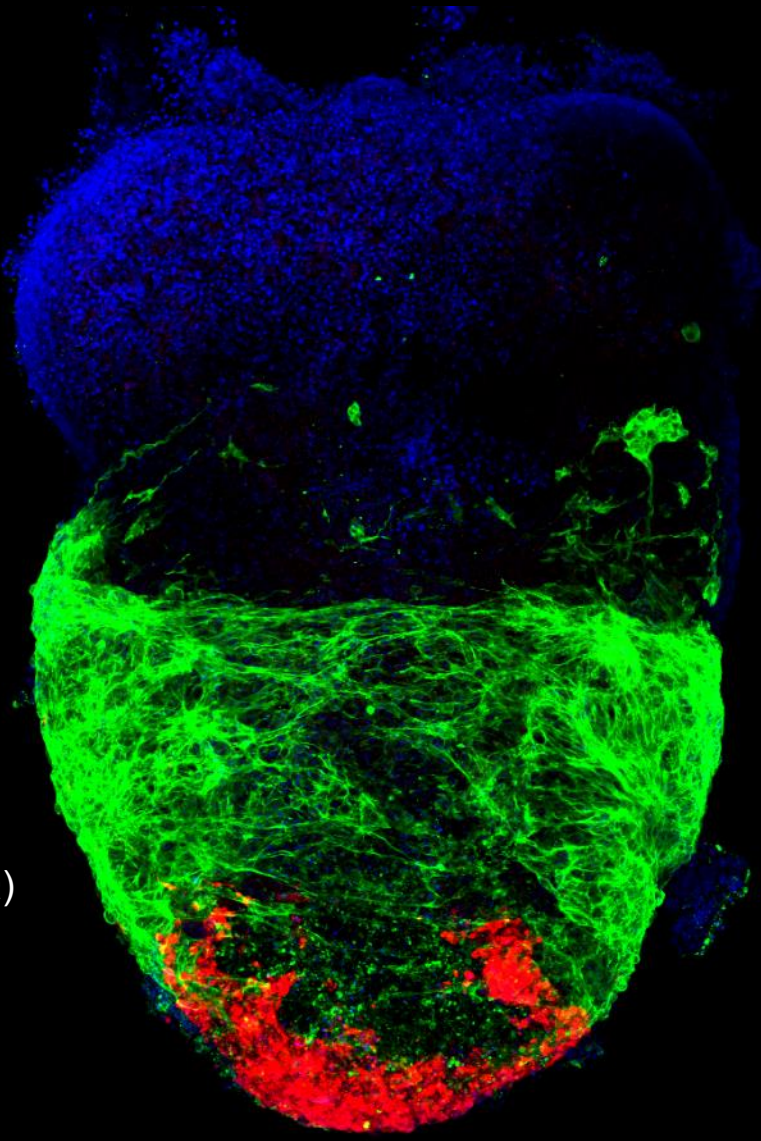
Associate Professor of Biomedical Engineering
Institute for Quantitative Health Science and Engineering
Chief, Division of Developmental and Stem Cell Biology (IQ)
Director, MSU Stem Cell Core
Michigan State University



Disclosures

Dr. Aitor Aguirre has no relevant financial relationships with ineligible companies to disclose.

Disclosure will be made when a product is discussed for an unapproved use.

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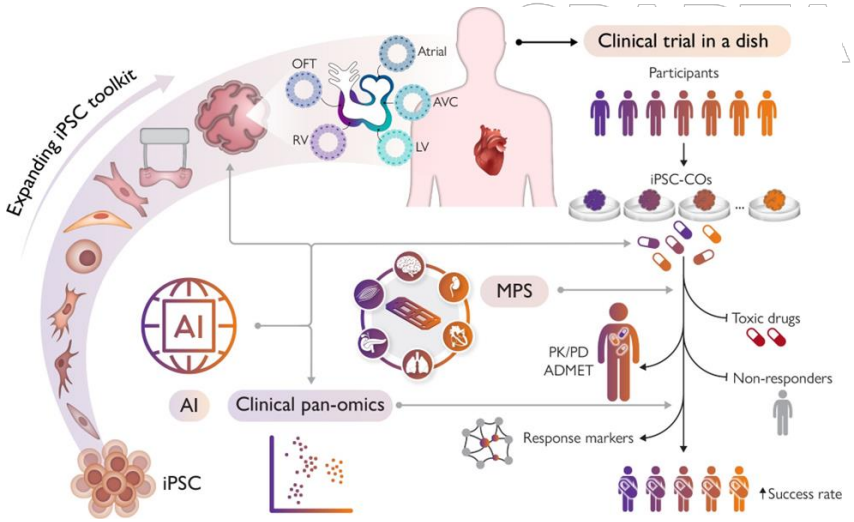
CytoHub

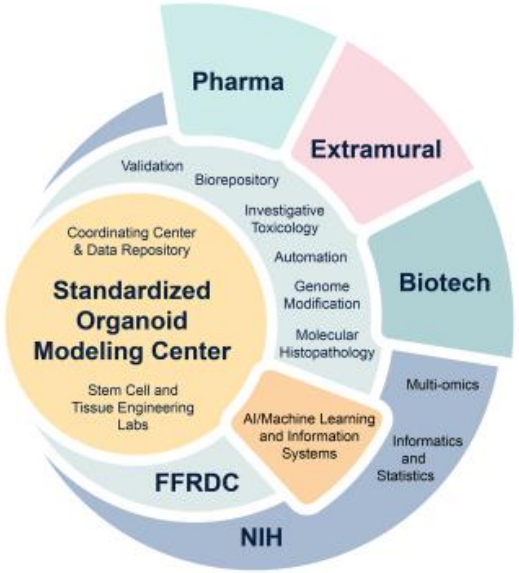
JAAN Biotherapeutics

Why heart organoids? Human-centric models and future steps in regulation



Wu et al., European Heart Journal, 2024

NIH Standardized Organoid Modeling Center



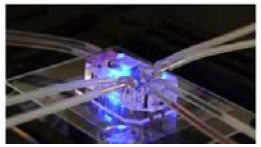
The SOM Center connects resources across the NIH with other federal agencies and industry partners to foster collaboration and accelerate NAMs technologies for the greater scientific community.

Tuesday, April 29, 2025

NIH to prioritize human-based research technologies

New initiative aims to reduce use of animals in NIH-funded research.

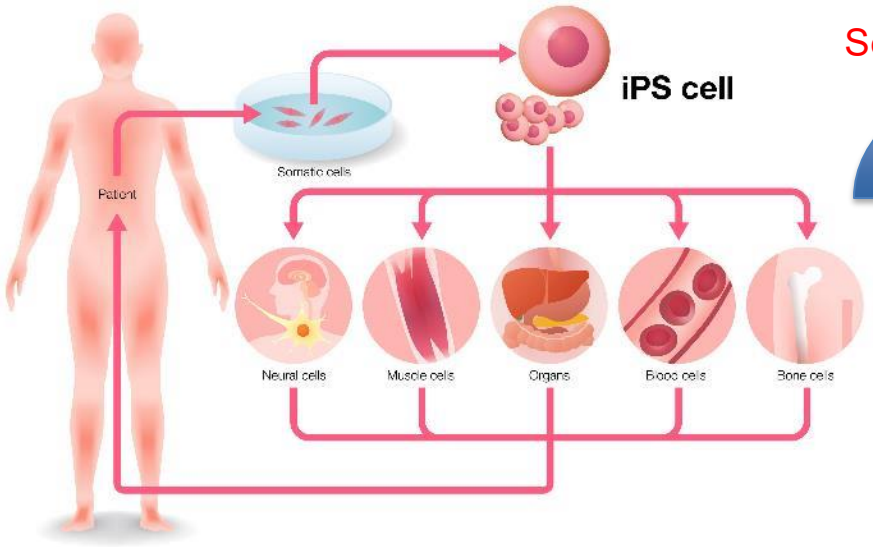
The National Institutes of Health (NIH) is adopting a new initiative to expand innovative, human-based science while reducing animal use in research. Developing and using cutting-edge alternative nonanimal research models aligns with the U.S. Food and Drug Administration's (FDA) recent initiative to reduce testing in animals. While traditional animal models continue to be vital to advancing scientific knowledge, using new and emerging technologies can offer unique strengths that, when utilized correctly or in combination, can expand the toolbox for researchers to answer previously difficult or unanswerable biomedical research questions.



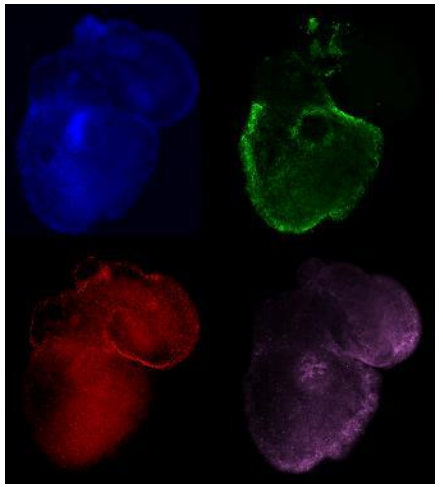
Pluripotent stem cells and lessons from development

PSCs

Organoids



Self-organization

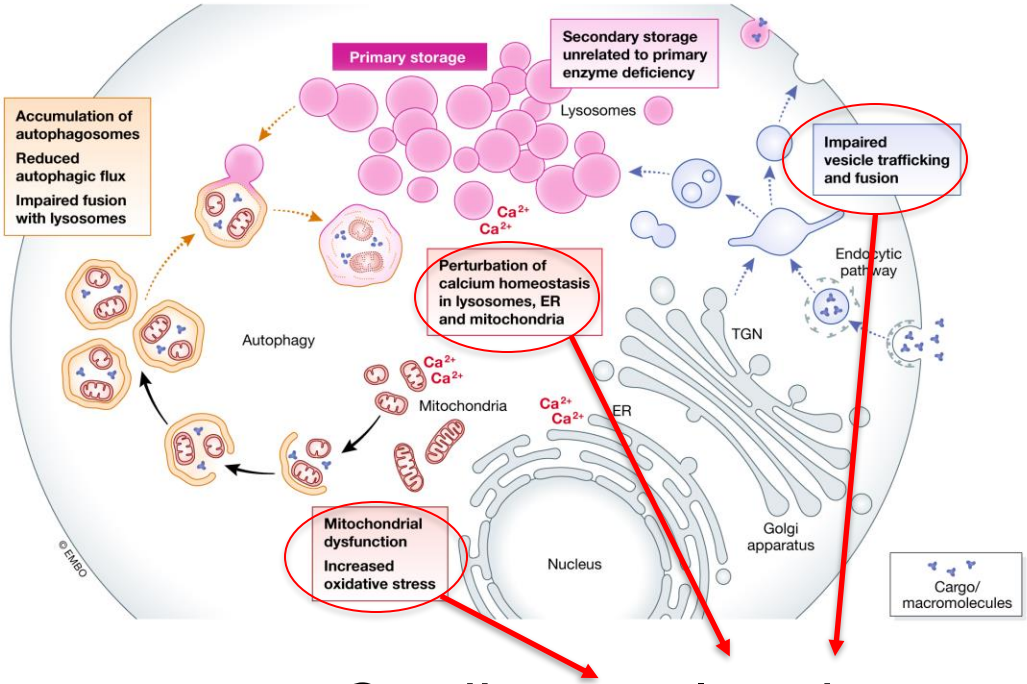


PSCs can make any tissue in the body
Unlimited source of human tissue-specific cells

Physiological relevance

Hofbauer et al., Cell, 2021
Lewis-Israeli et al., Nature Comms, 2021
Abilez et al., Science, 2025
Wu et al., European Heart Journal, 2024

Relevance to lysosomal disorders?



Fabry disease

Danon disease

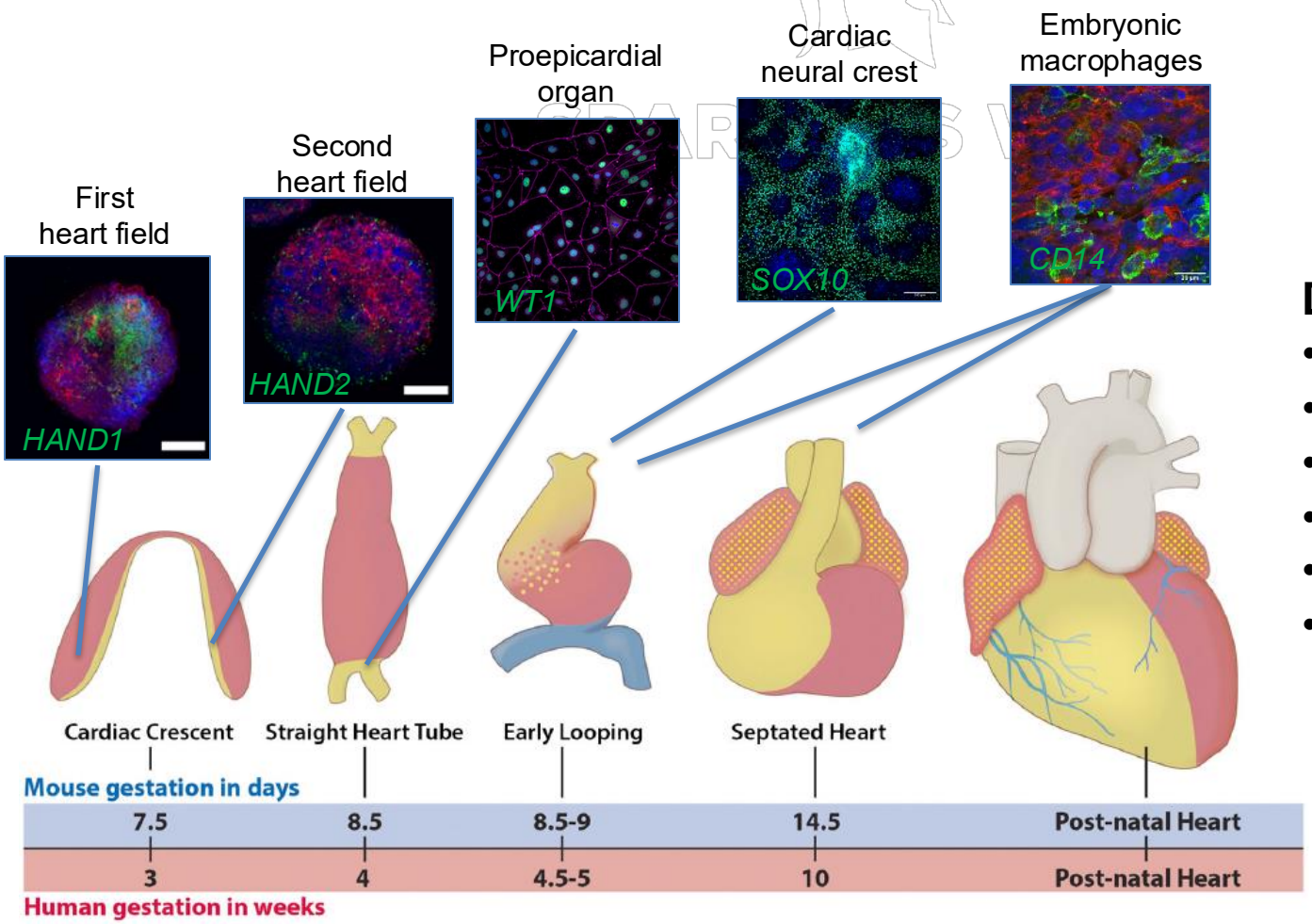
Others

Cardiovascular phenotypes

Synthetic heart models can help us understand the physiological mechanisms of lysosomal disorders in the human heart

Parenti et al., EMBO Molecular Medicine, 2021
Hashem et al., Stem Cells, 2015

Reverse engineering the human heart



Design directions

- Reproducibility
- Efficiency
- Relative simplicity
- Scalability
- High-throughput
- Modularity

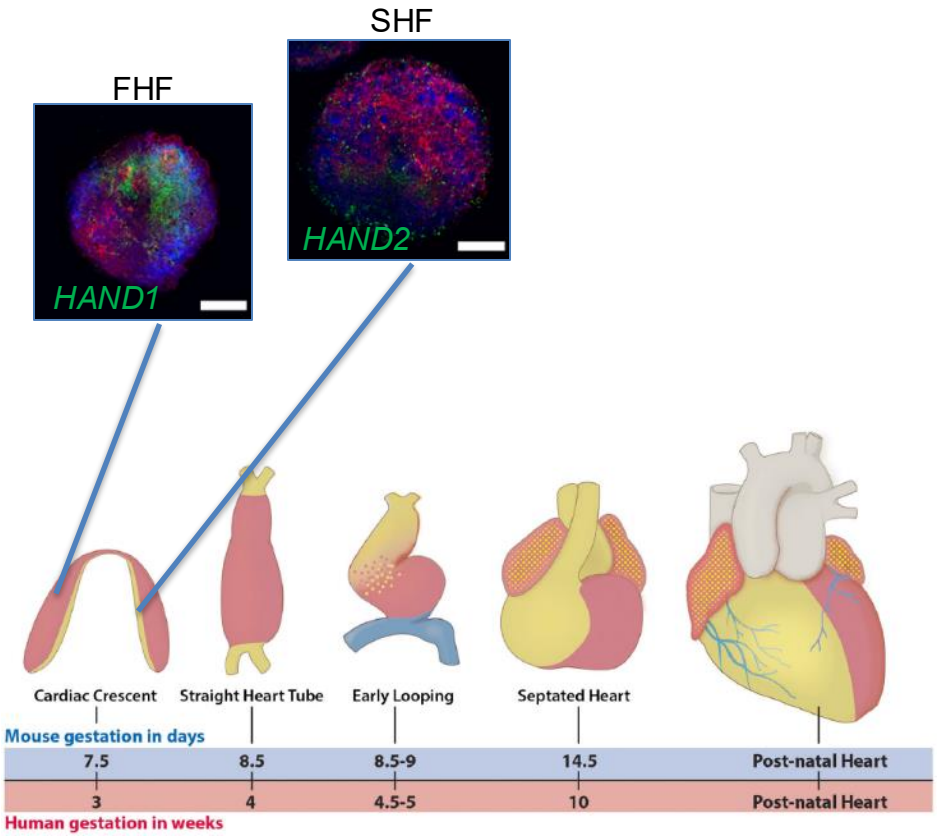
Oxygen availability
Neighboring tissue growth factors

Maternal growth factors
Maternal nutrients

Workload

Lewis-Israeli et al., Nature Comms., 2021
Volmert et al., Nature Comms., 2023
O'Hern et al., Cell Stem Cell, 2025
Kostina et al., biorxiv, 2024

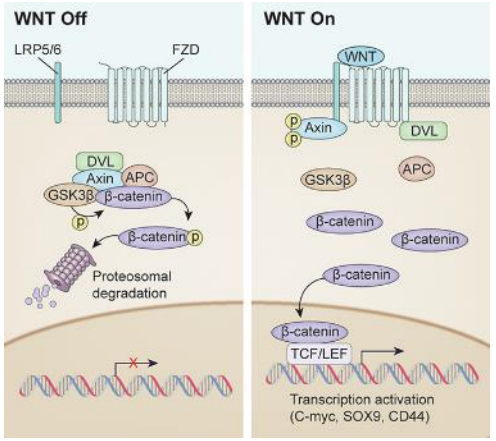
A self-organization approach to build a human heart



Lewis-Israeli et al., Nature Comms., 2021

Steps 1 and 2: Cardiogenic mesoderm induction (WNT ON/OFF)

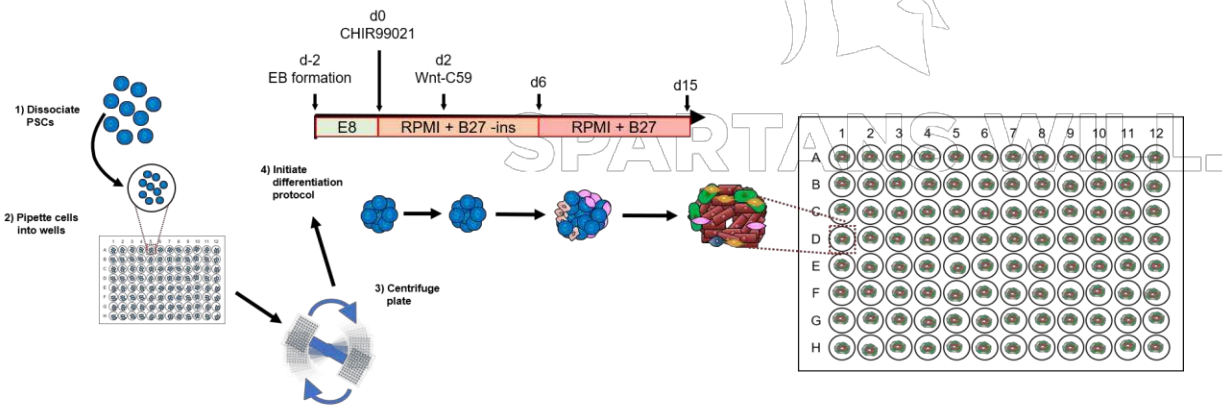
Ventricle, atria, parts of the OFT

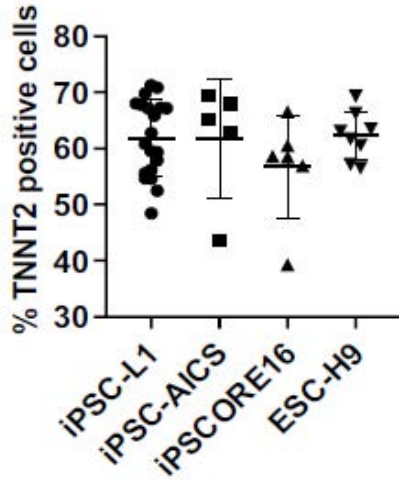


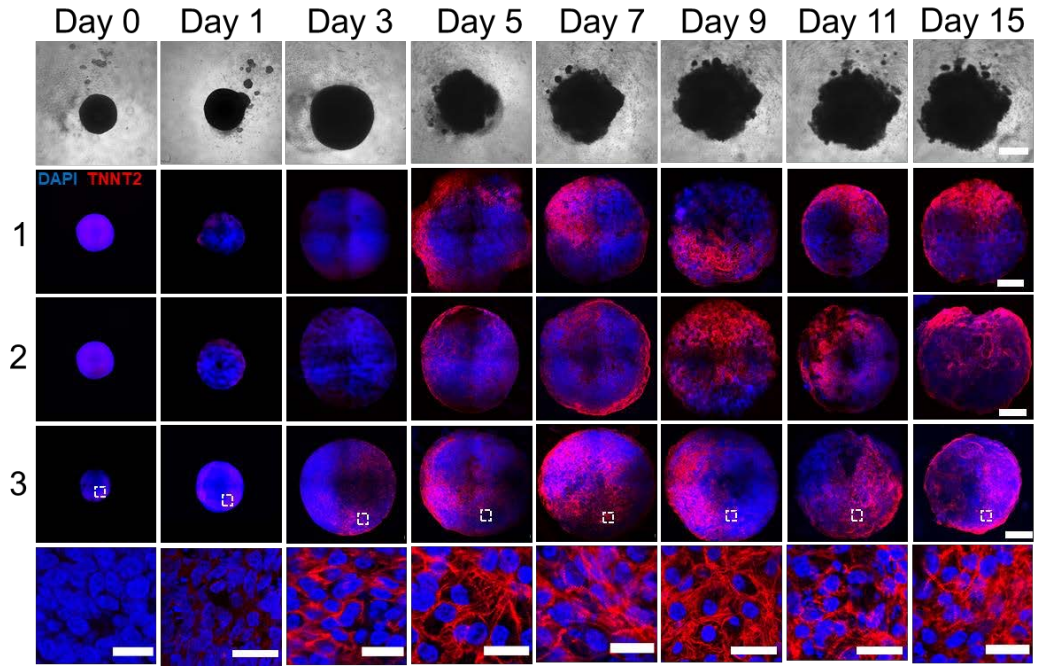
Temporal Wnt signaling modulation

Yonatan Lewis-Israeli, PhD student

Self-organizing cardiogenic mesoderm

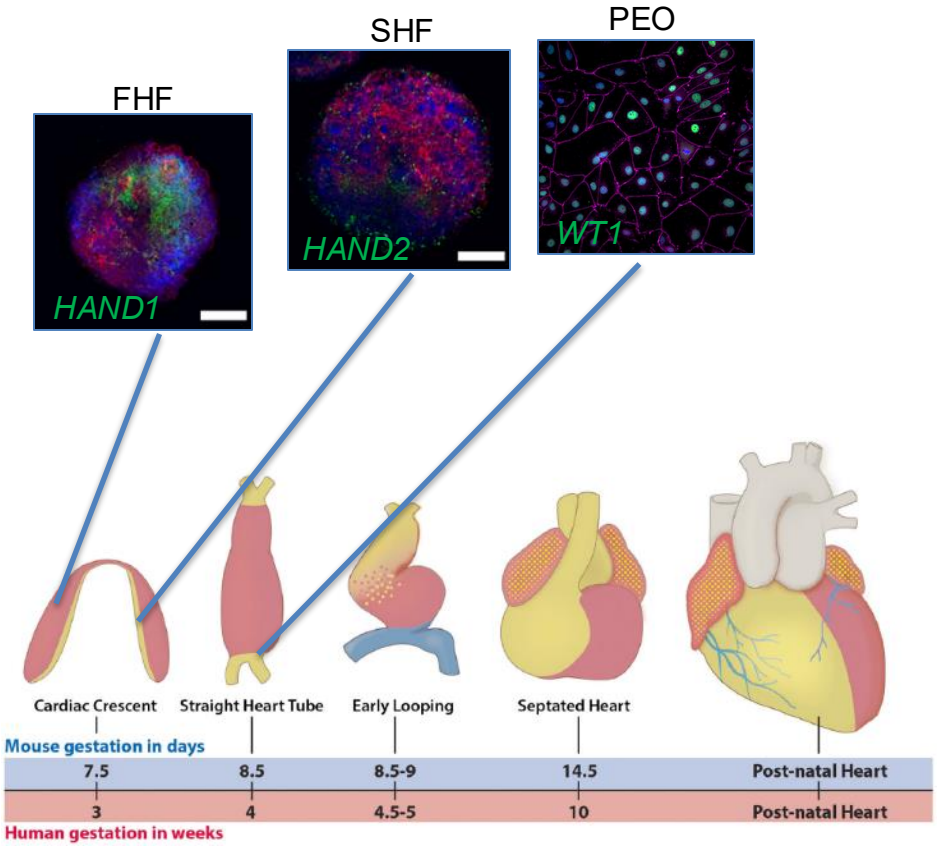






Lian et al, 2012, PNAS
Lewis-Israeli et al, 2021, Nature Comms

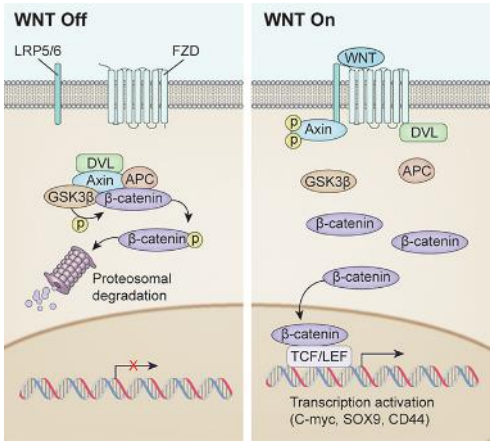
A self-organization approach to build a human heart



Lewis-Israeli et al., Nature Communications, 2021

Step 3: Proepicardial organ induction (WNT ON)

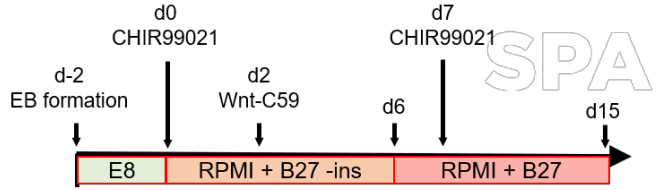
Epicardium formation, vascularization, valvular tissues, mesenchymal tissues, conductance?

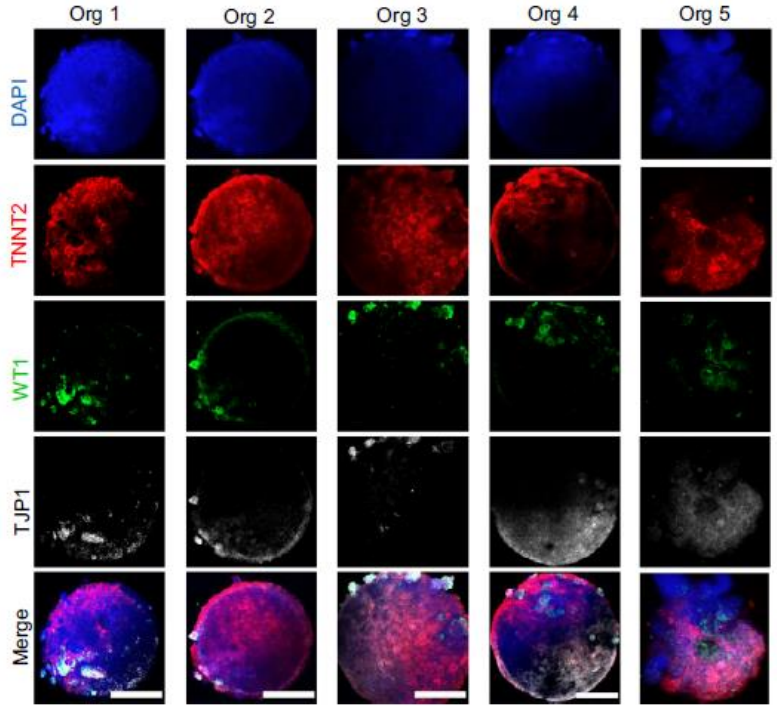


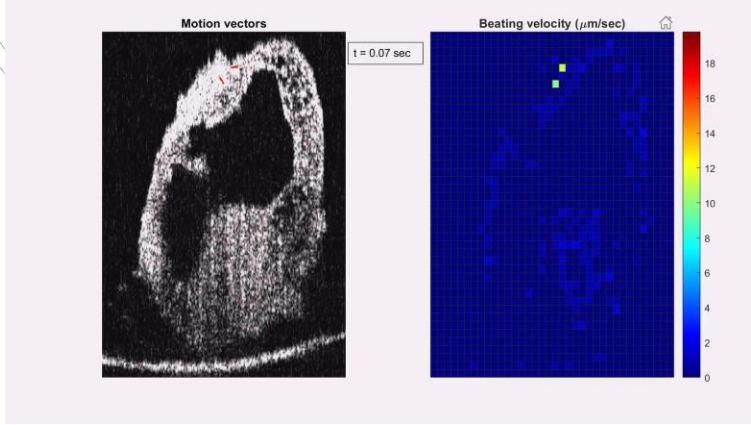
Temporal Wnt signaling modulation

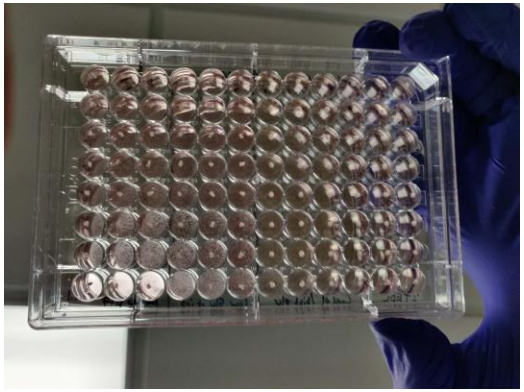
Yonatan Lewis-Israeli, PhD

Self-organizing heart organoids after proepicardial induction







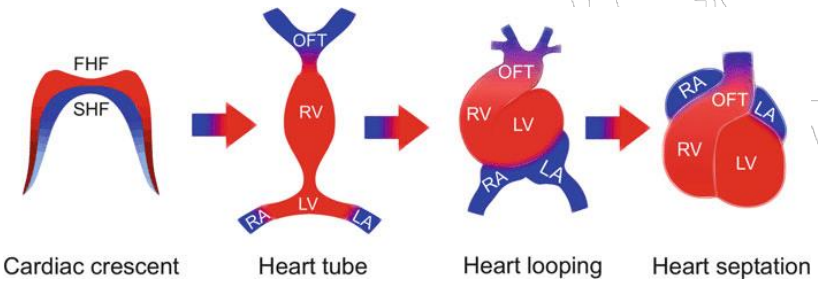


Chao Zhou, PhD
WUSTL

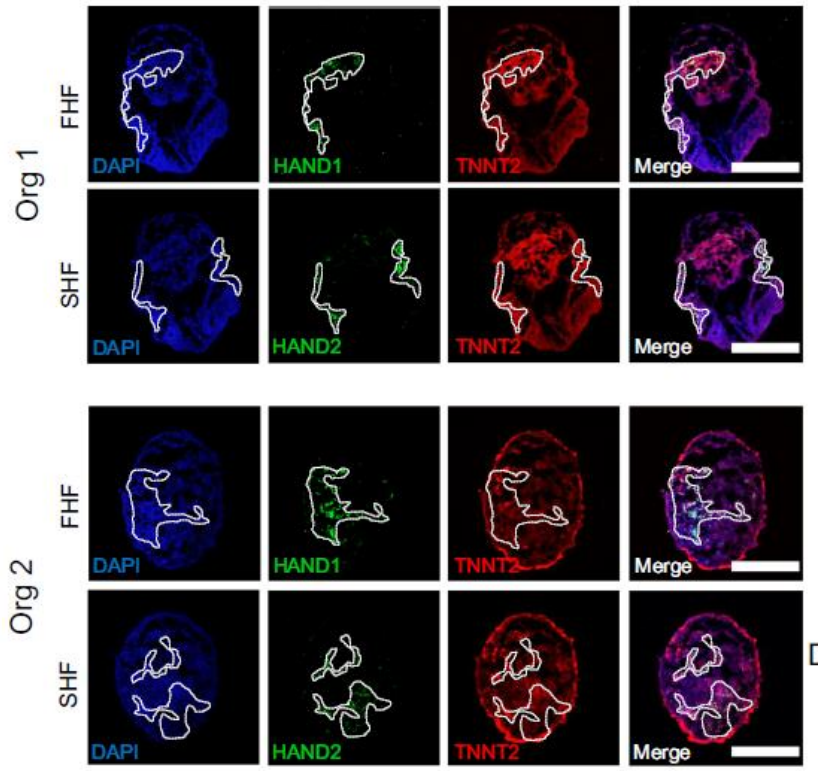
Bao et al., Nature BME, 2016
Lewis-Israeli et al., Nature Comms, 2021
Ming et al., Biosensors and Bioelectronics, 2022

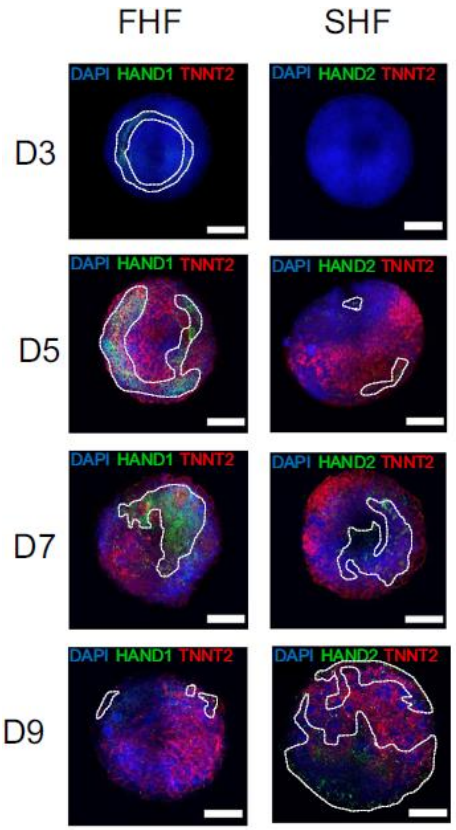
hHOs possess two chambers (atrium, ventricle) and all cardiac cell types derived from the cardiac mesoderm (ECs, fibroblasts, conductance cells, epicardium, etc)

Developmental fields in the heart

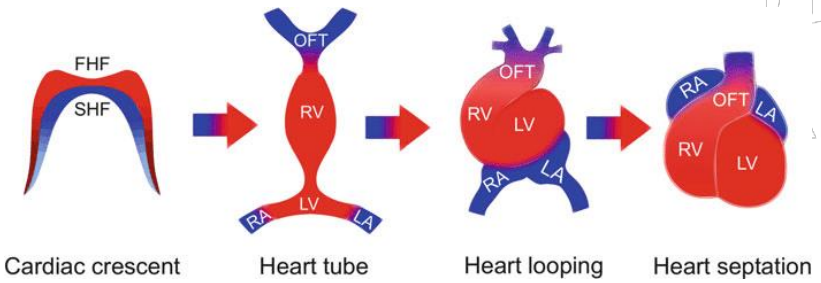


Red: first heart field
Blue: second heart field

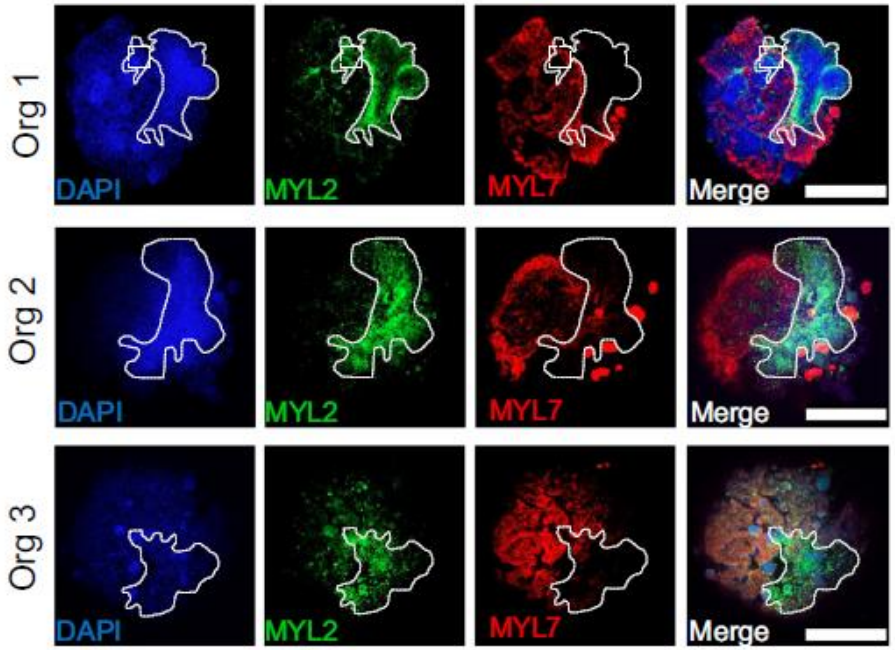


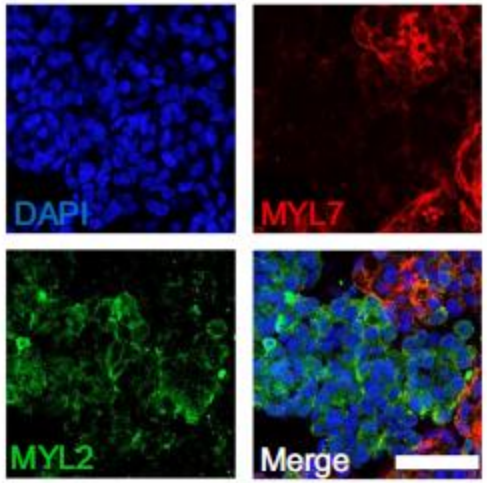


Atrioventricular specification

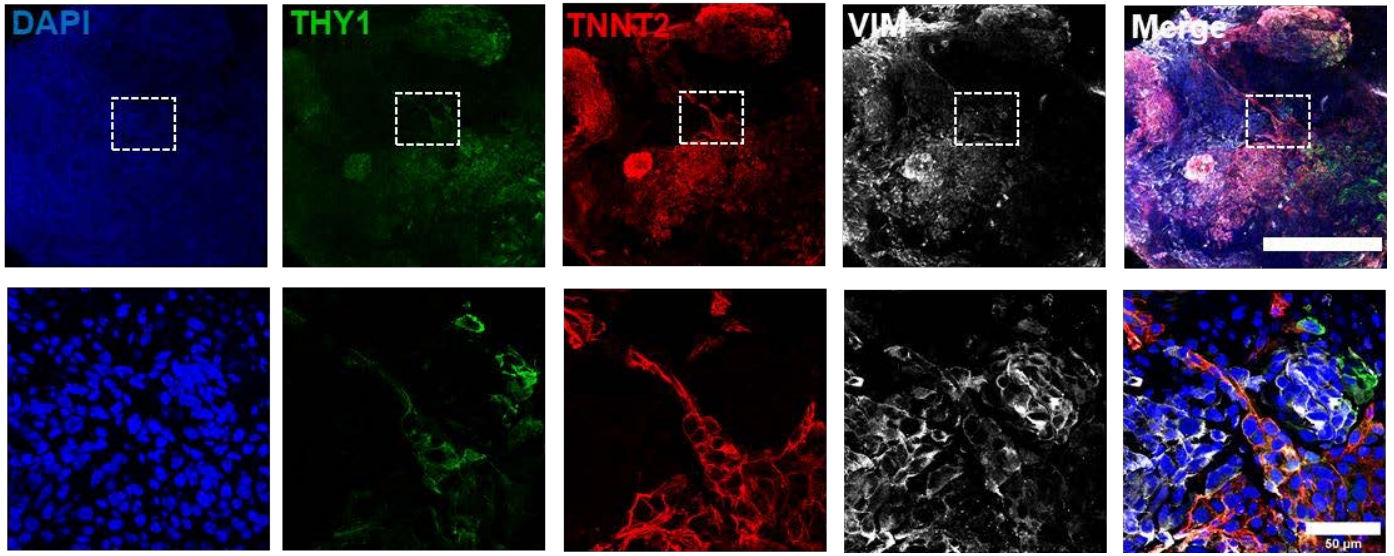


- All immature cardiomyocytes express MYL7
- As they differentiate some persist expressing MYL7 (atrial)
- Some start expressing MYL2 (ventricular)



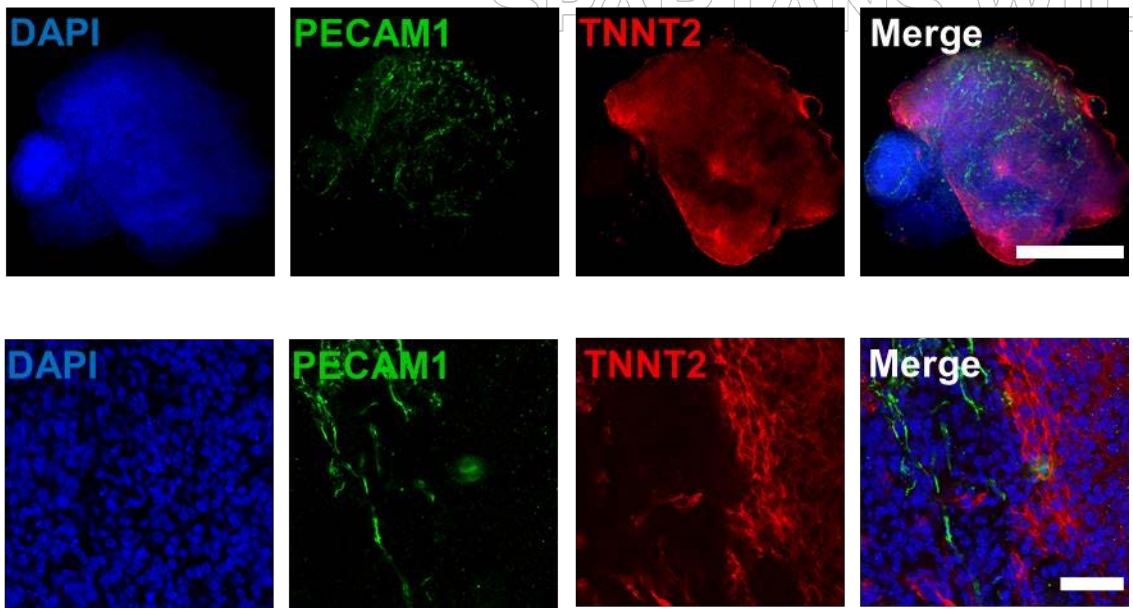


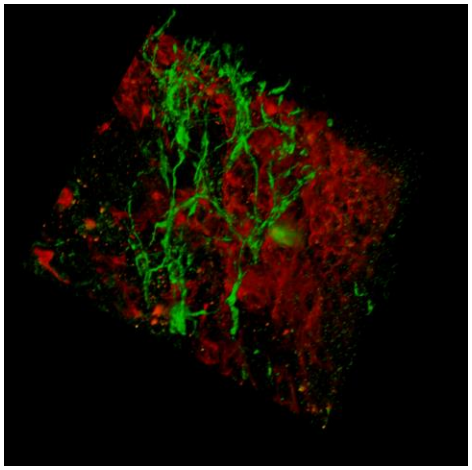
Heart organoid cell composition: cardiac fibroblasts



Cardiac fibroblasts contribute to cardiac ECM synthesis and possibly other mesenchymal cell types (e.g. smooth muscle cells)

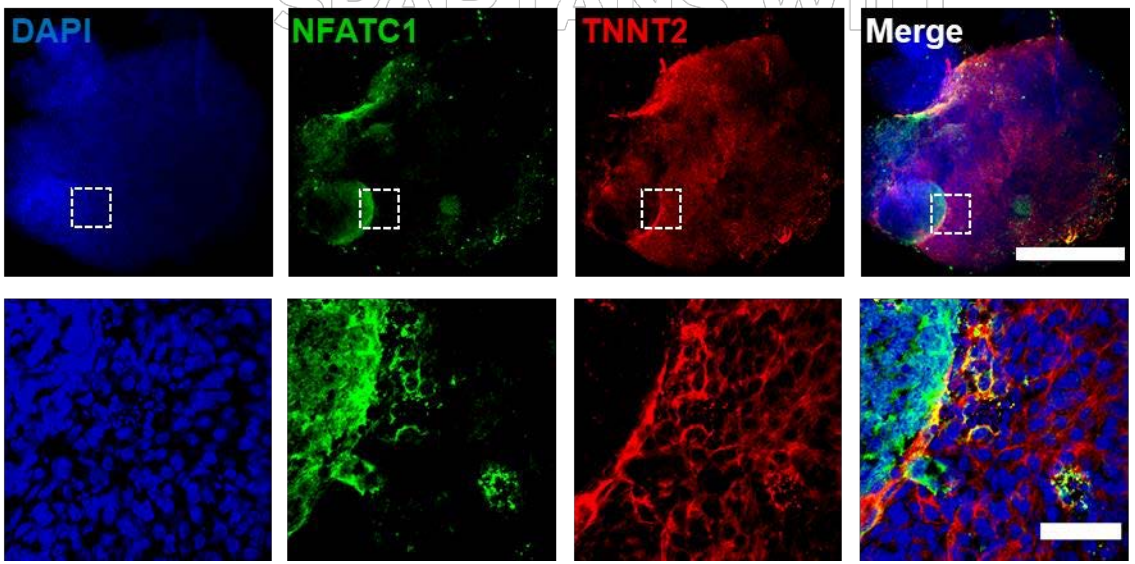
Heart organoid cell composition: Endothelial cells





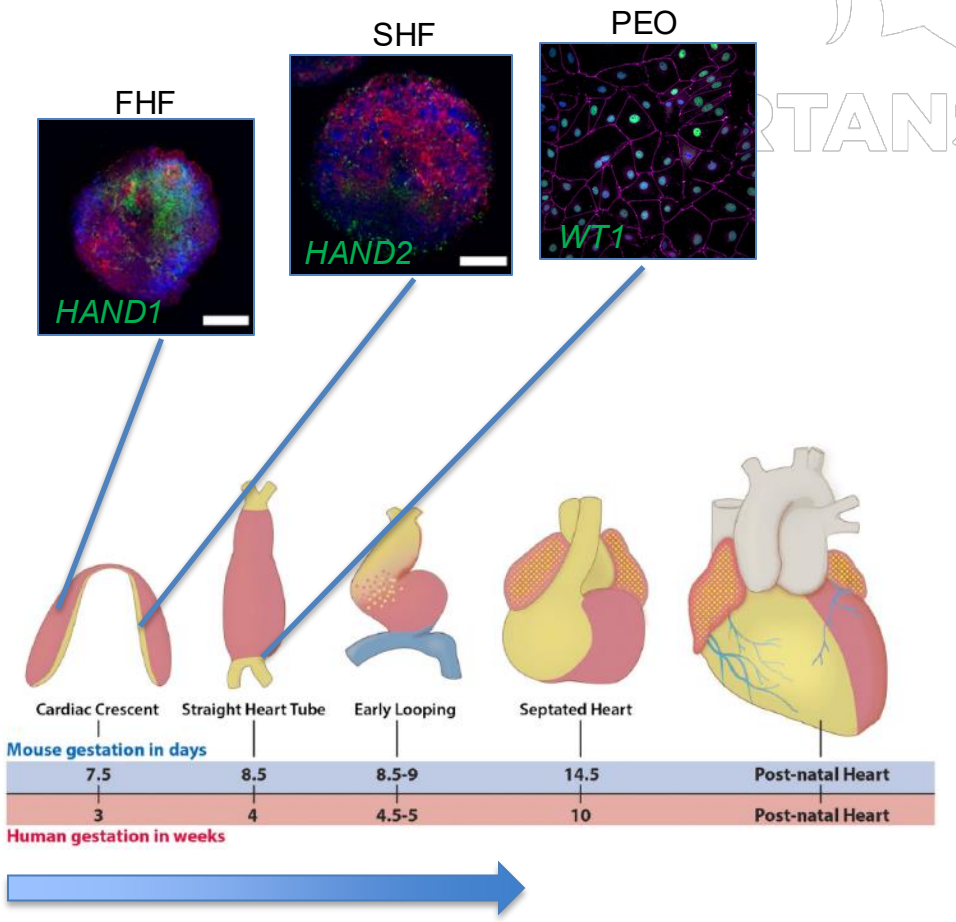
Endothelial cells contribute to coronary vasculature (arteries? veins?)

Heart organoid cell composition: endocardial cells



Endocardial cells line the lumen of cardiac chambers

Heart organoids 2.0

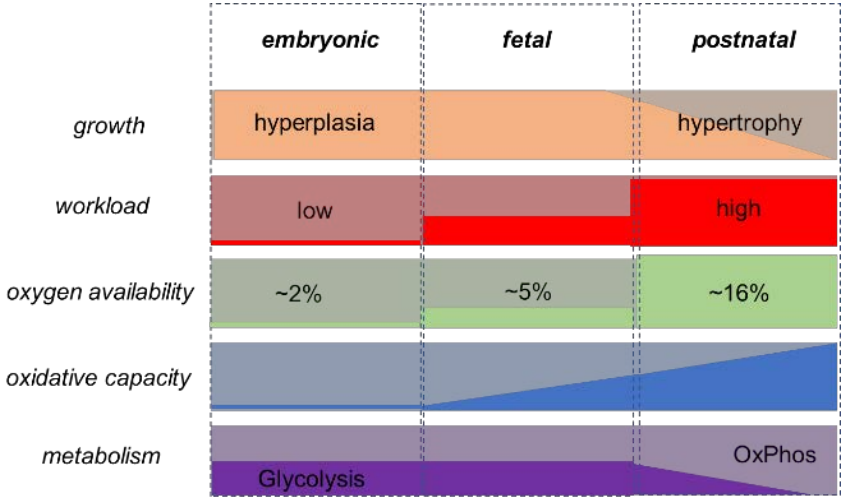


Maternal growth factors
Maternal nutrients

Oxygen availability
Neighboring tissue growth factors

Step 3: metabolism and maternal/fetal environment (developmental induction strategy)

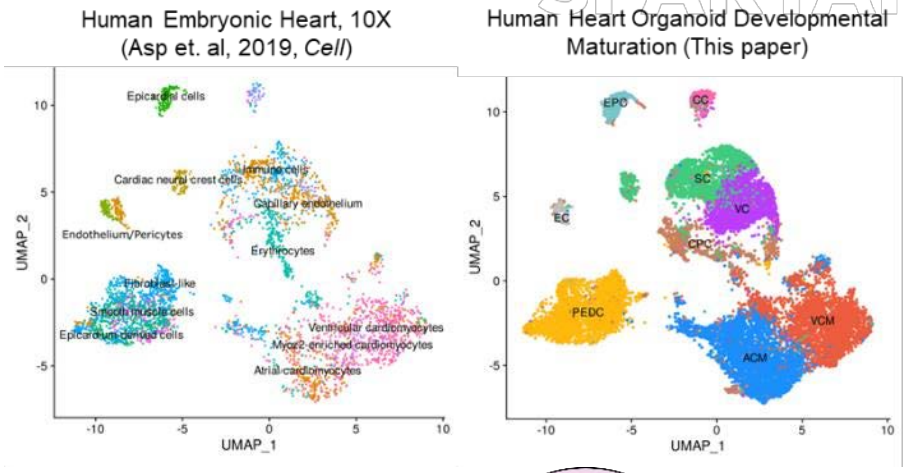
Glycolysis vs. OXPHOS
Gradual growth
Gradual hormone-induced maturation

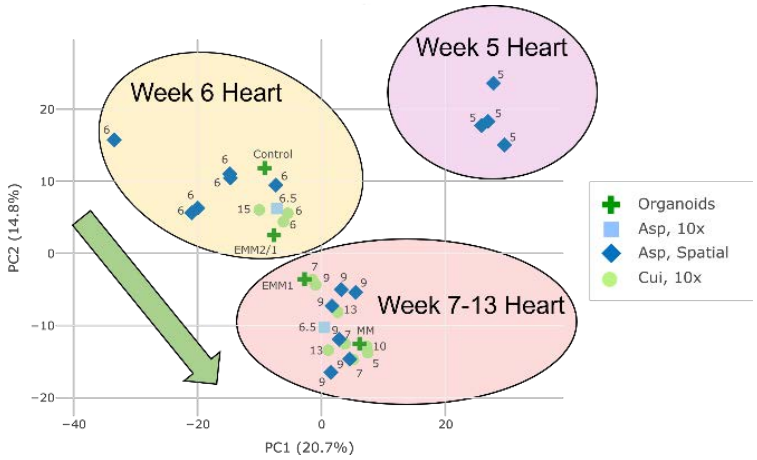


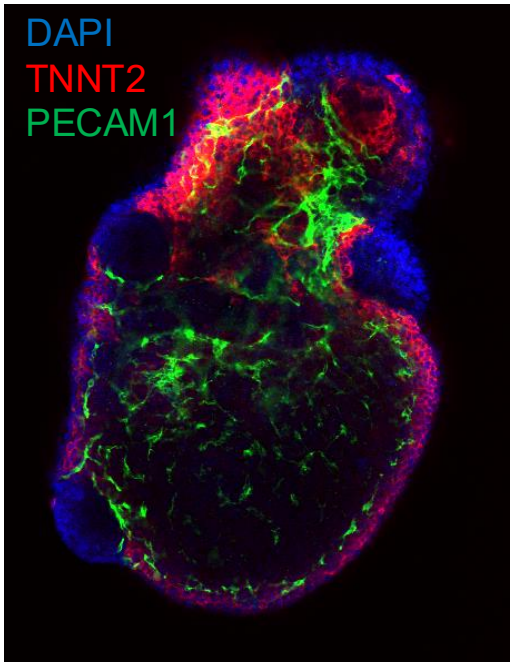
Volmert et al., Nature Comms, 2023

Brett Volmert, PhD student

Developmental induction produces hHOs similar to age-matched human hearts



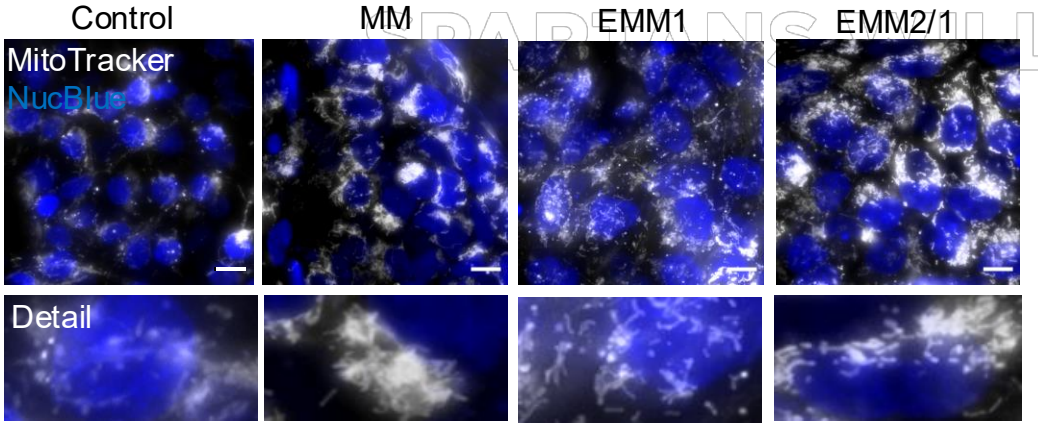


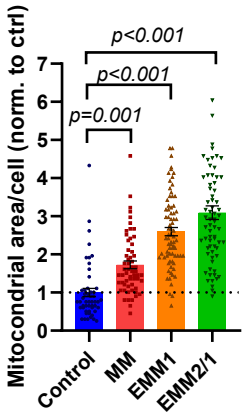


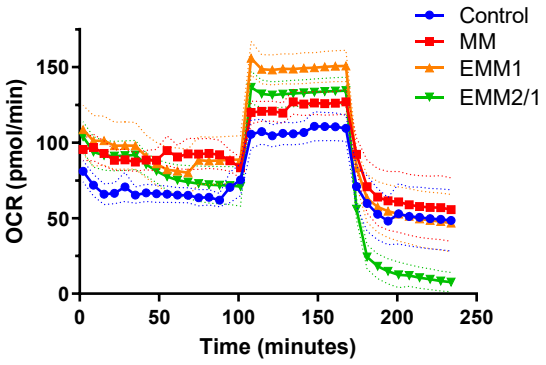
All cardiac mesoderm-derived heart-specific cell types present, improved anatomy and vascularization

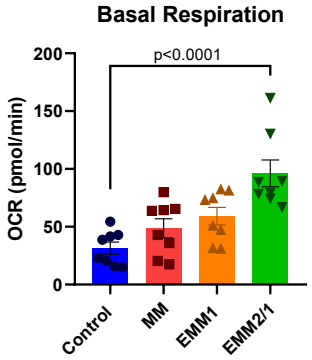
Volmert et al., Nature Comms, 2023

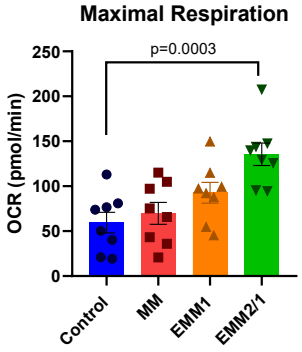
Developmental induction conditions promote progressive metabolic maturation

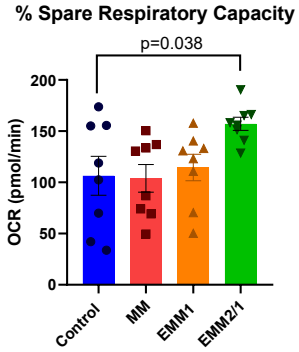






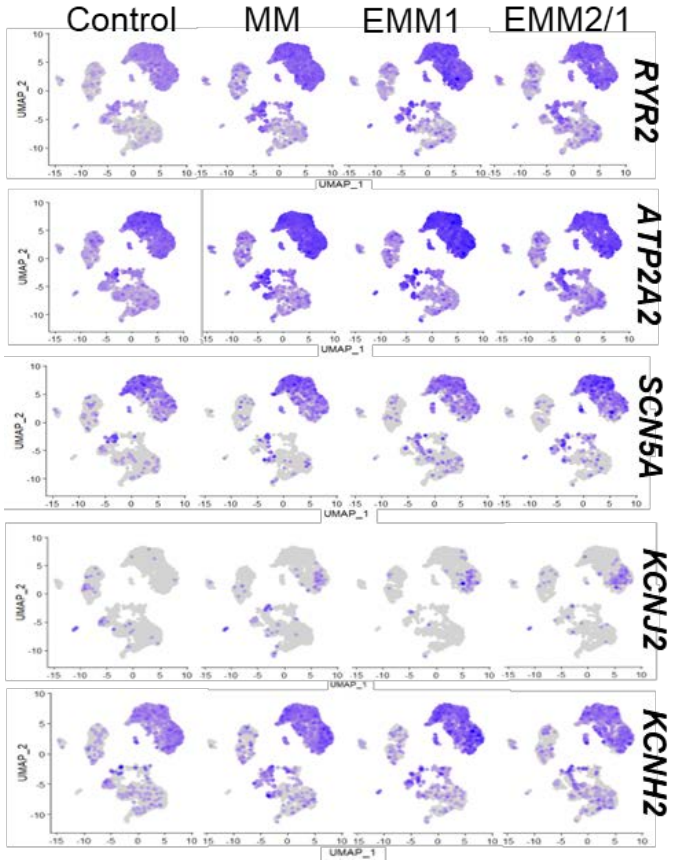


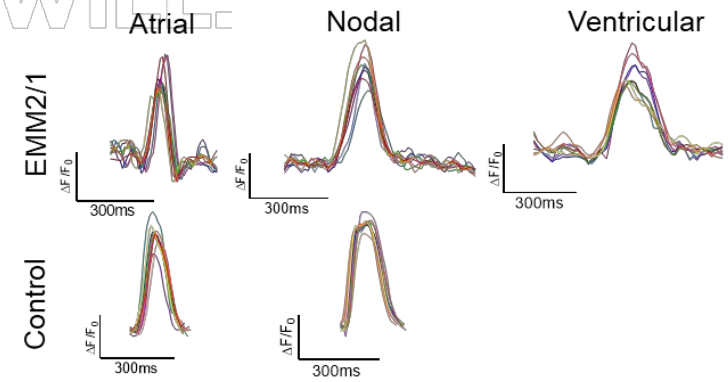


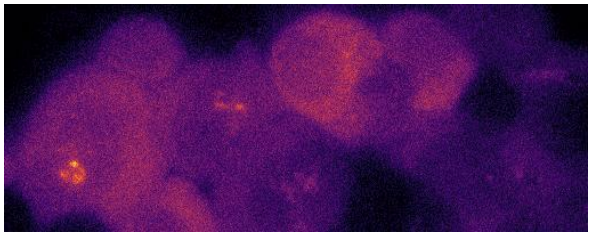


Accompanied by transcriptional changes consistent with progressive maturation

Developmental induction conditions promote progressive electrophysiological maturity



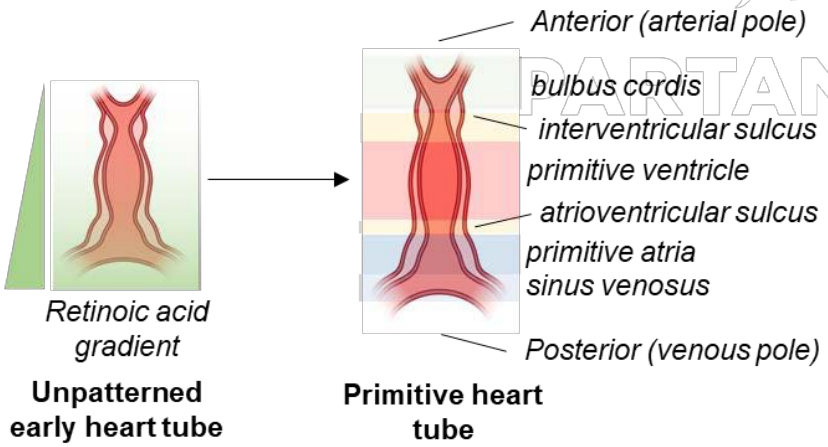


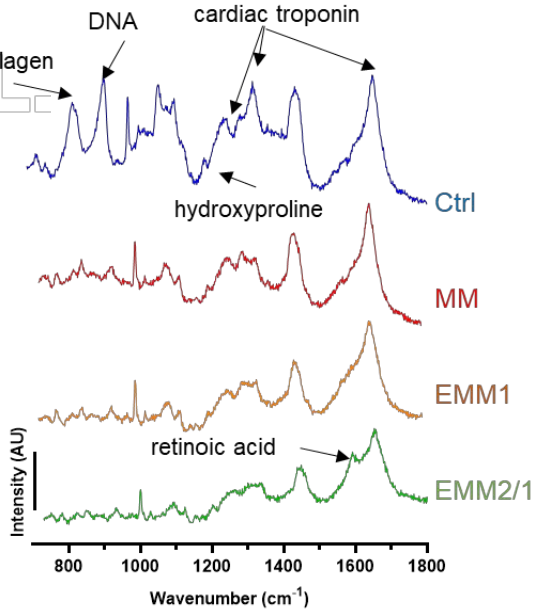


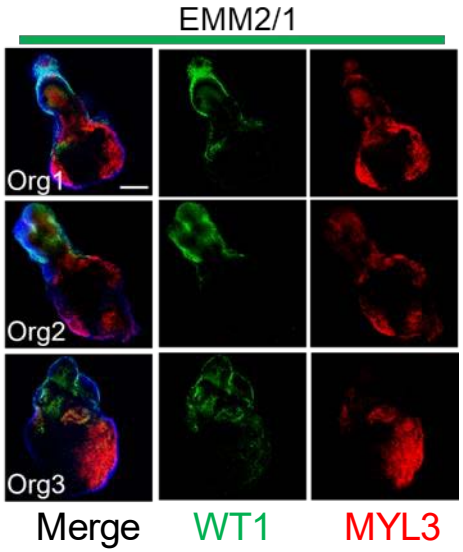
Jonathan Silva, PhD
WUSTL

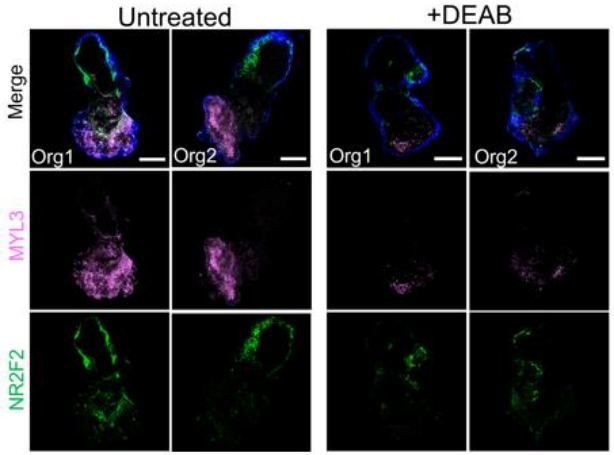
Volmert et al., Nature Comms, 2023

Spontaneous antero-posterior patterning









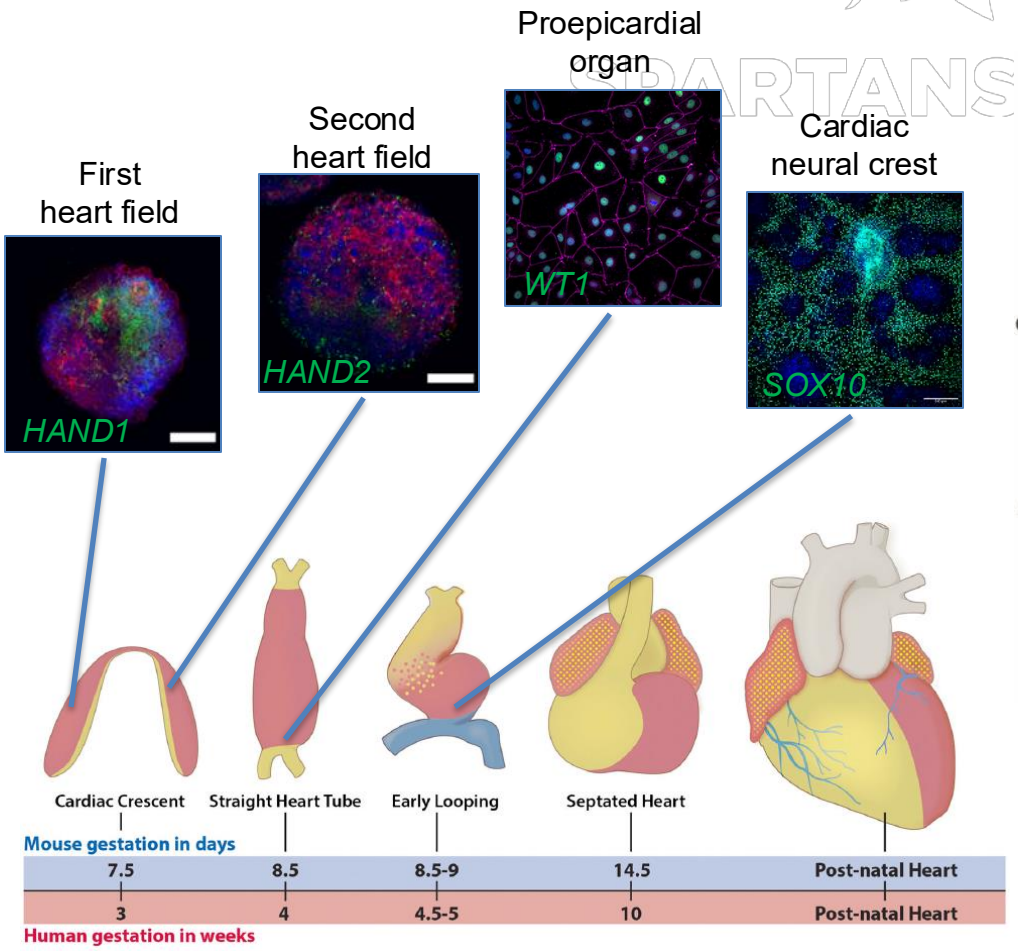
Conchi Estaras, PhD
Temple University

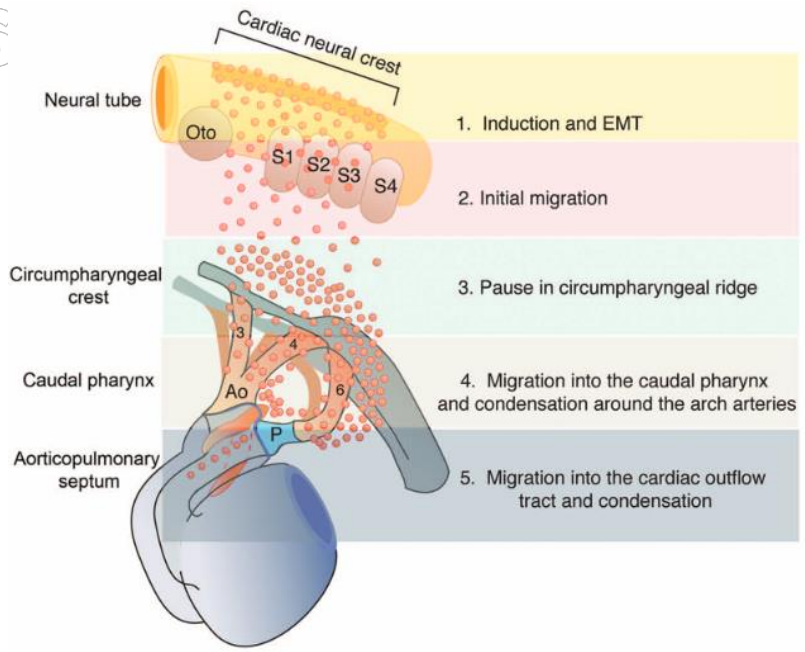
Zhen Qiu, PhD
MSU

Volmert et al., Nature Comms, 2023
Abraham et al., Cell Reports, 2025

Next-gen models: heart assembloids

Engineering heart assembloids with autologous cardiac neural crest (hNCHAs)



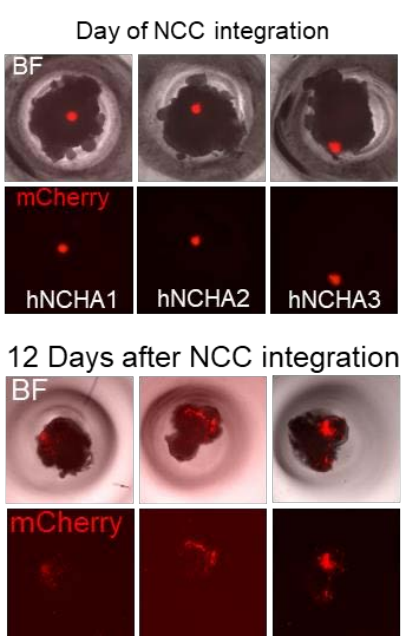


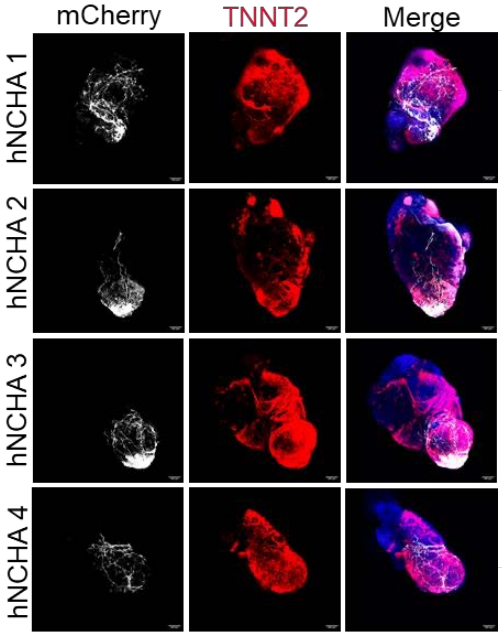
Kostina et al., bioRXiv, 2024 (in revision)

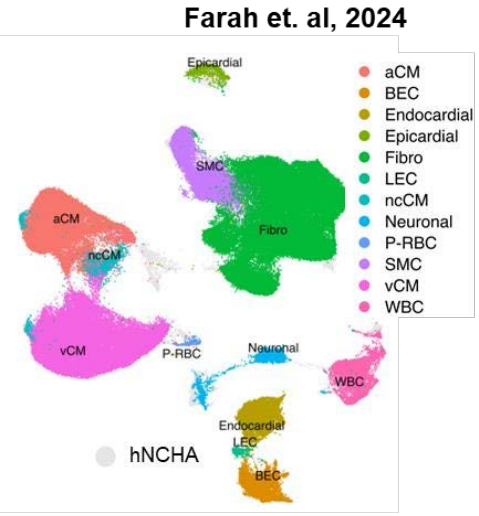
Kirby et al., 2010

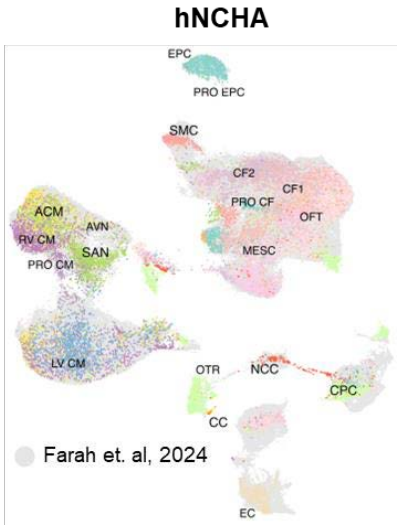
Aleksandra Kostina, PhD

hNCHAs develop relevant cardiac neural crest derived tissues







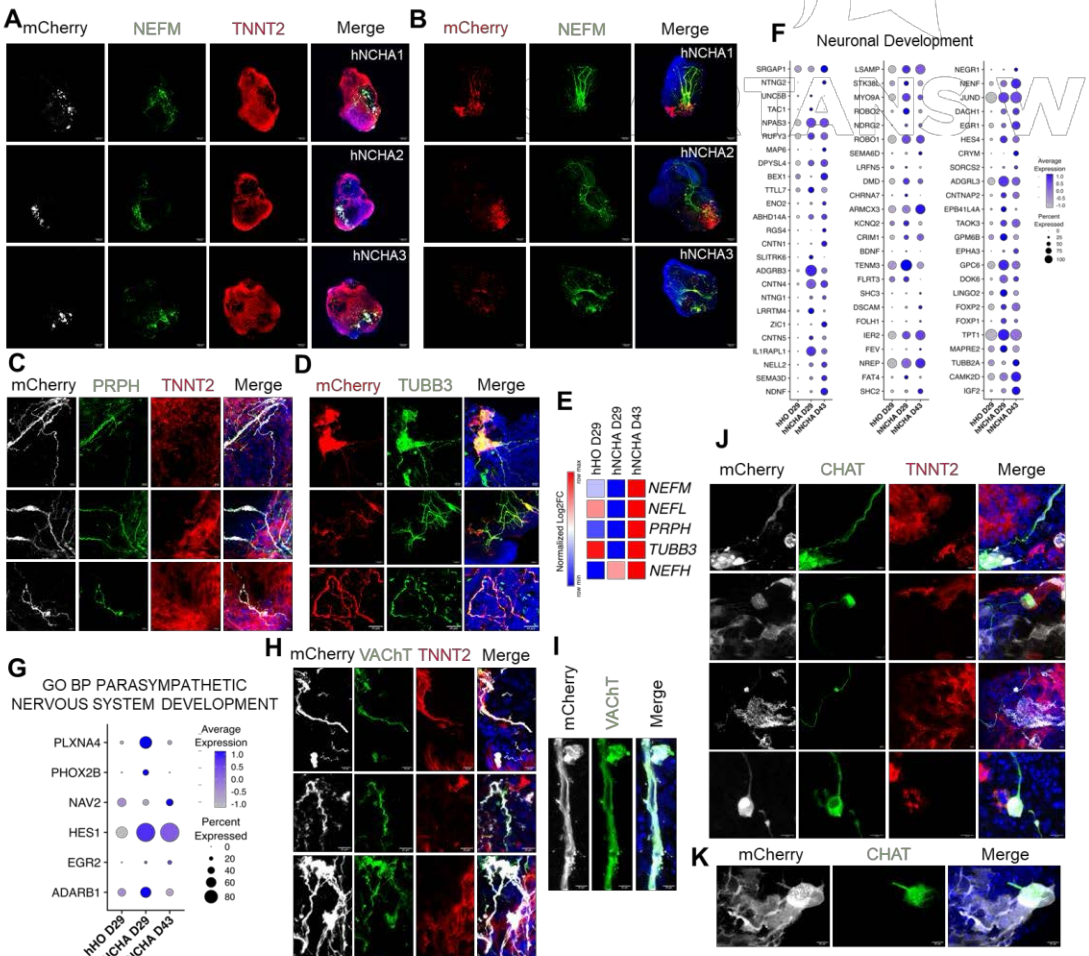


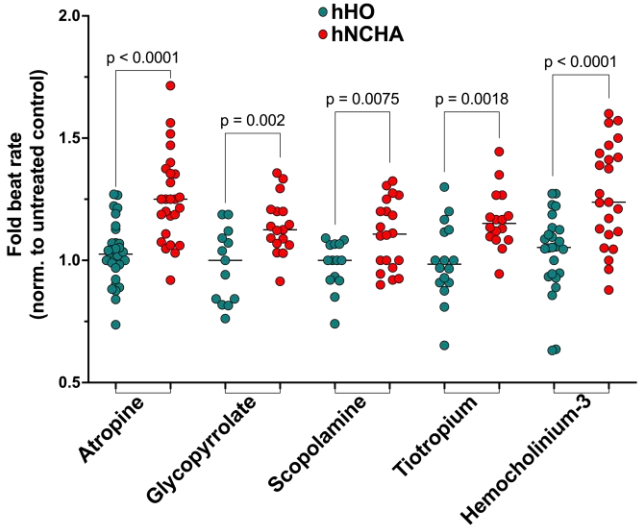
hNCHAs contain developmentally relevant cardiac NCCs and are highly similar to their embryonic counterparts

hNCHAs develop outflow tract, parasympathetic innervation, endocardial cushions, and rudiments of the septa

Kostina et al., bioRXiv, 2024 (in revision)

hNCHAs develop functional parasympathetic neurons



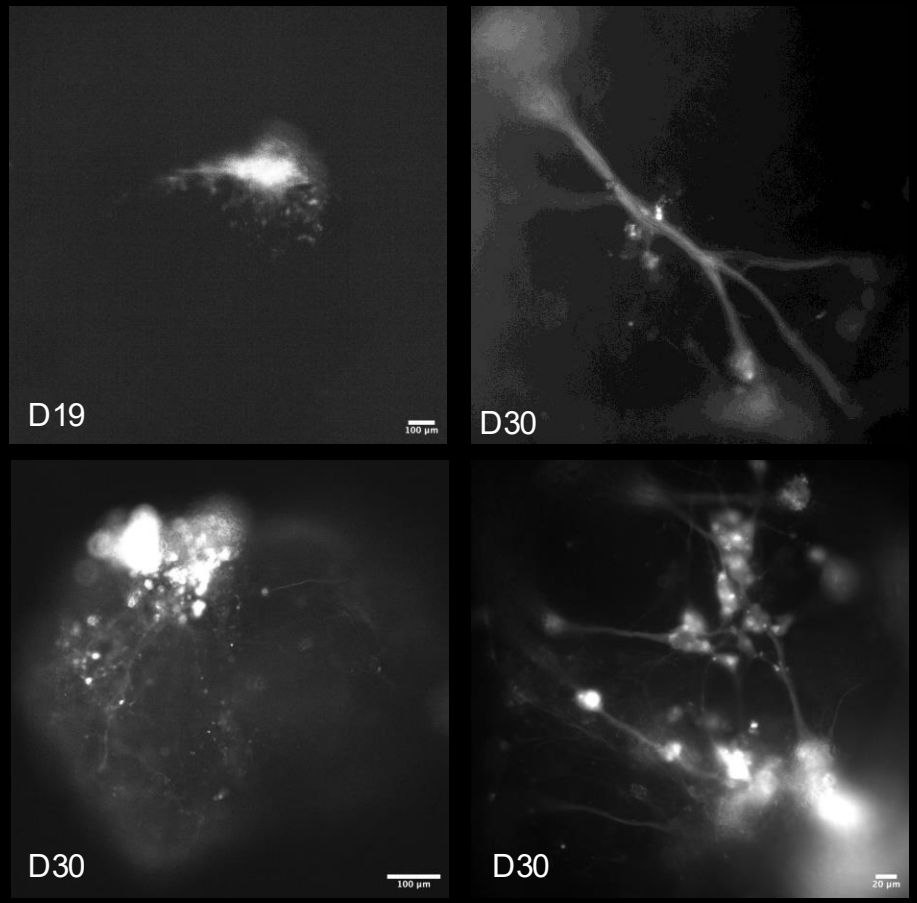


NEFM: neurofilament medium chain; PRPH: peripherin; TUBB3: beta tubulin III; VAChT: vesicular acetylcholine transporter; CHAT: choline O-acetyltransferase

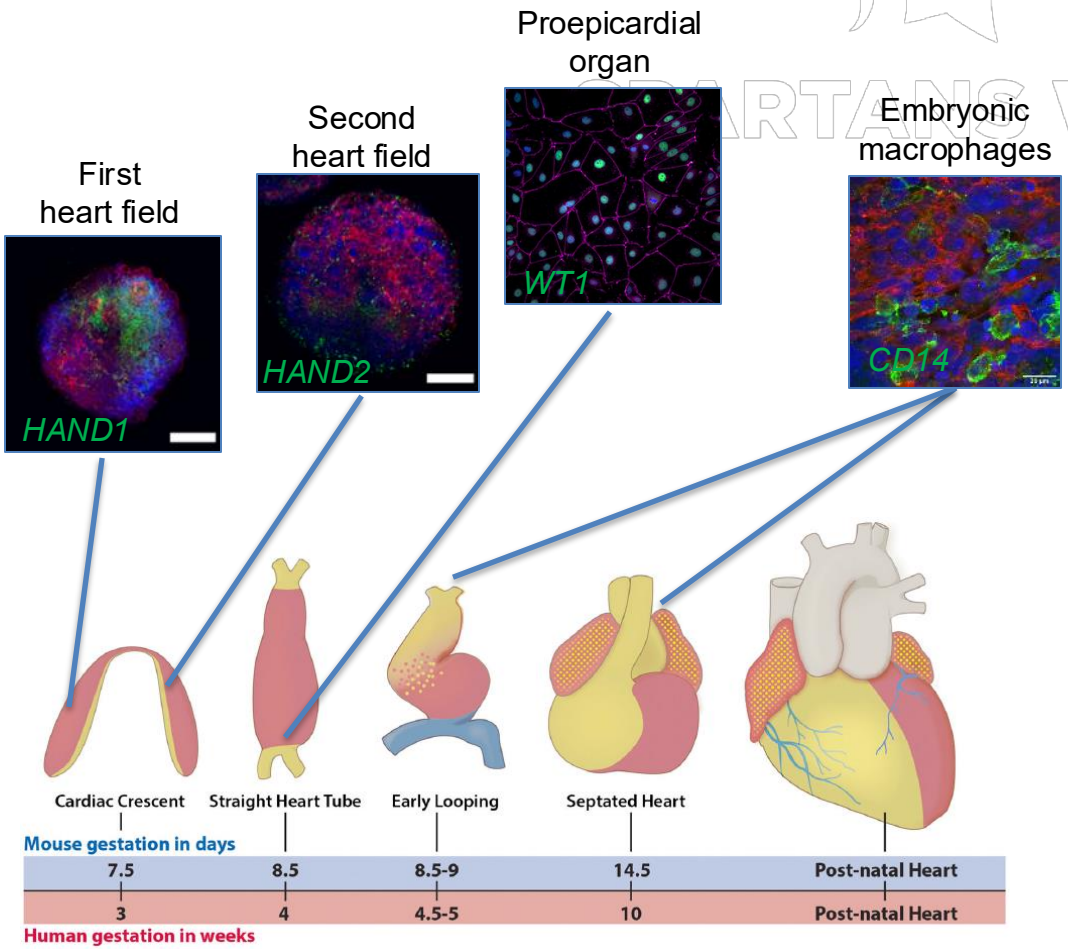
Kostina et al., bioRXiv, 2024 (in revision)

MICHIGAN STATE UNIVERSITY

hNCHAs develop functional parasympathetic neurons



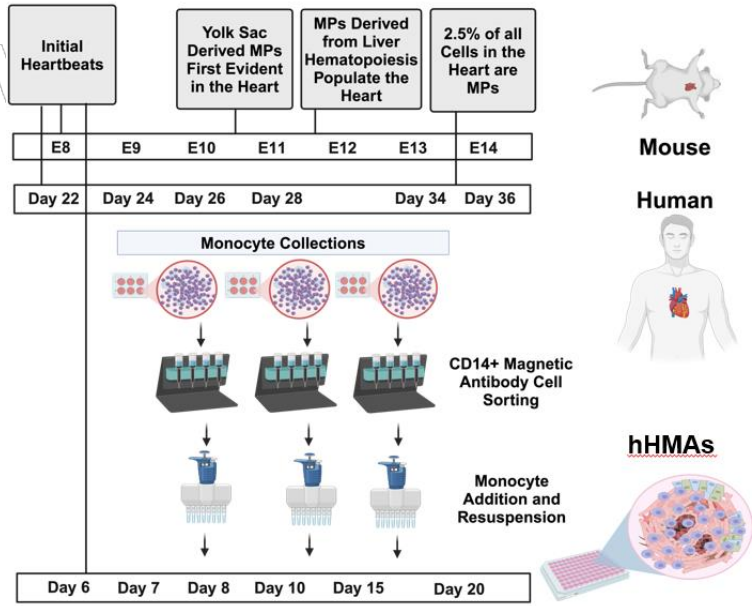
Engineering human heart-macrophage assembloids (hHMAs)



Oxygen availability
Neighboring tissue growth factors

Maternal growth factors
Maternal nutrients

Assembloid fabrication

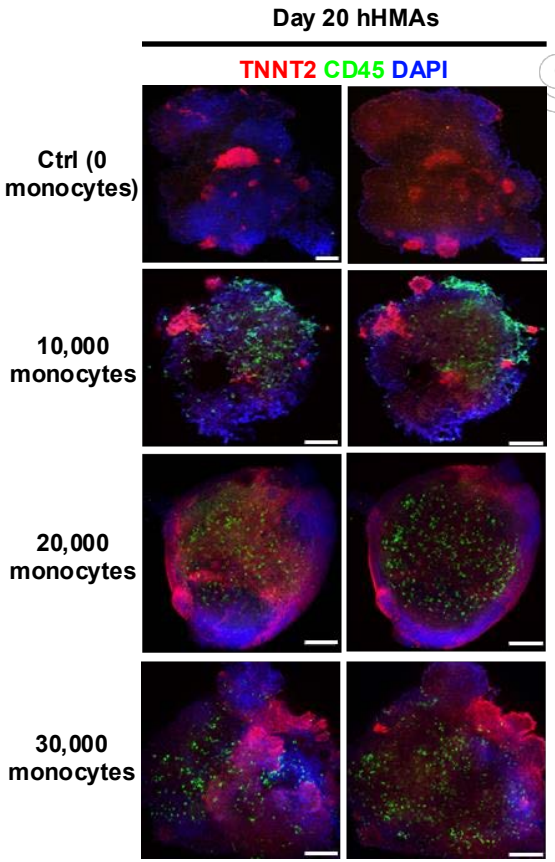


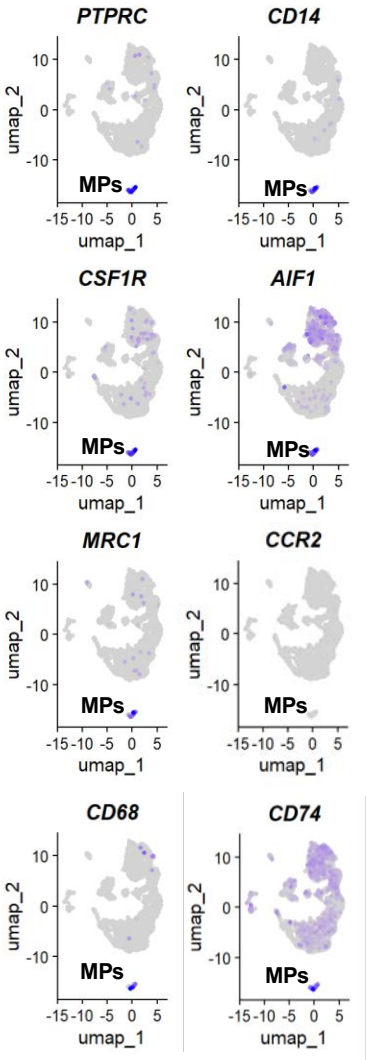
Myocardial maturation, ECM remodeling, coronary vasculature, conductance, epicardial and endocardial function

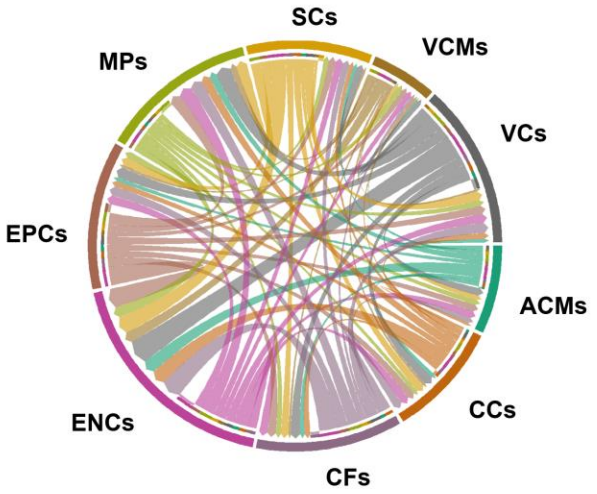
Colin O'Hern,
DO/PhD student

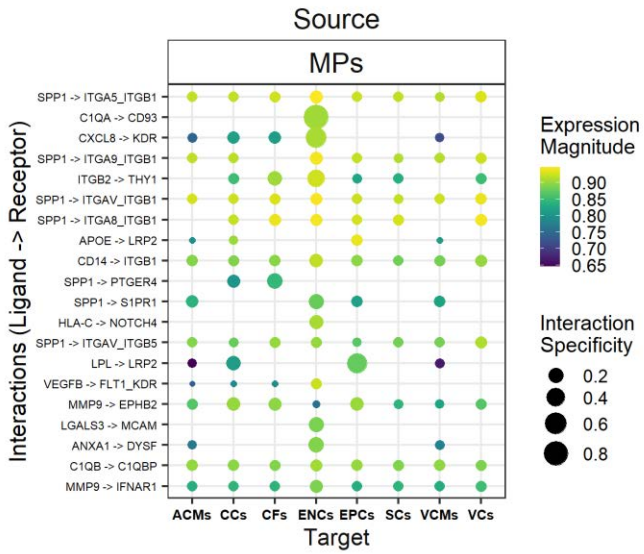
O'Hern et al., Cell Stem Cell, 2025 (in press)

Autologous embryonic monocytes integrate to become cardiac tissue-resident macrophages





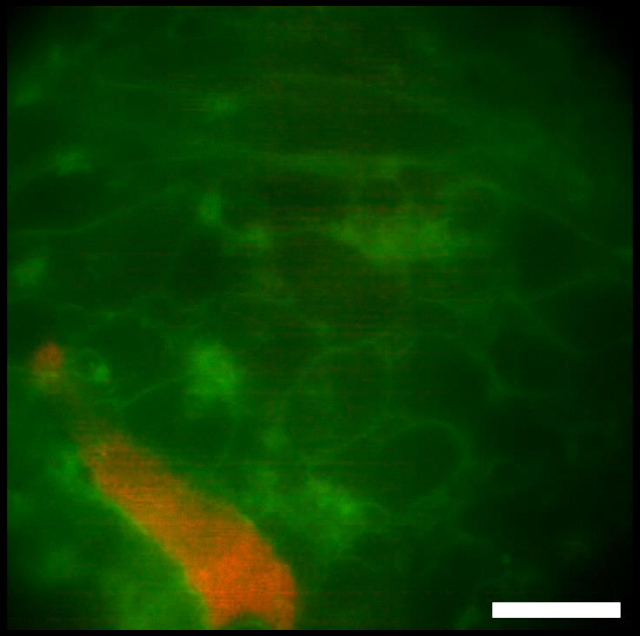




CTRMs are present at physiological levels, functional and persist long-term

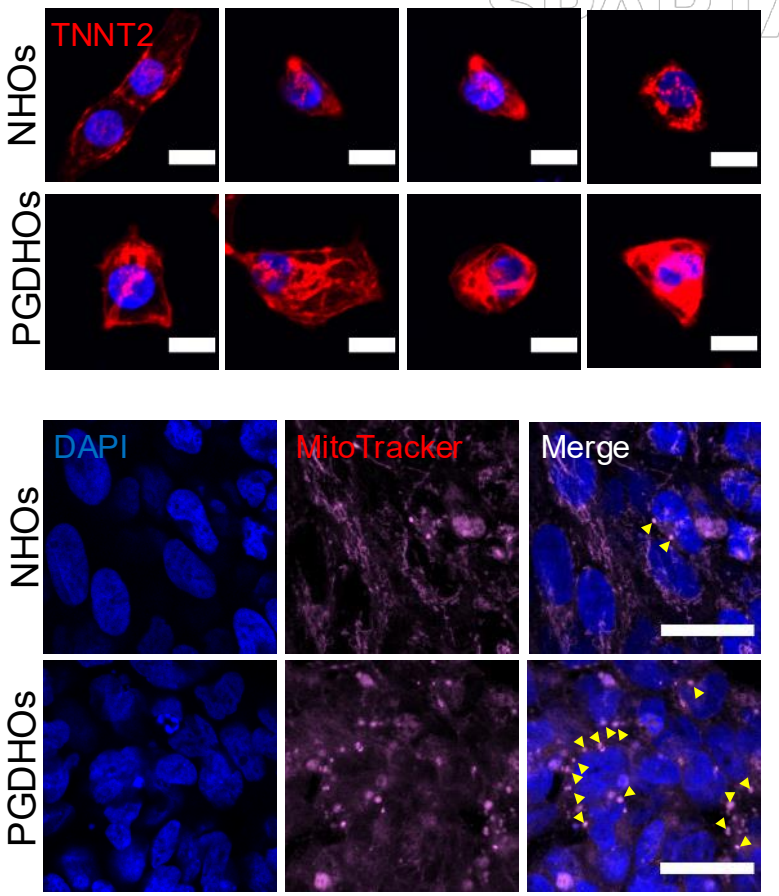
O'Hern et al., Cell Stem Cell, 2025 (in press)

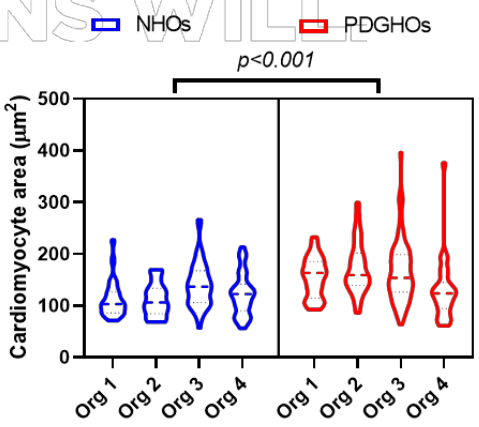
Autologous embryonic monocytes integrate to become cardiac tissue-resident macrophages

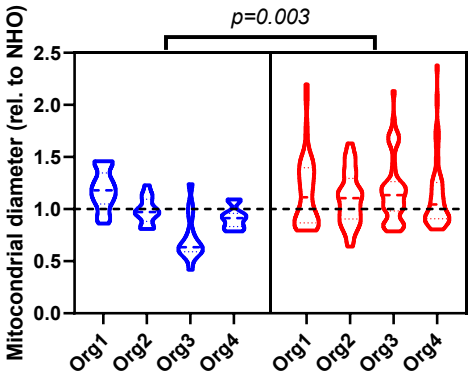


Translational applications

Pregestational diabetes induces hypertrophy and mitochondrial stress in heart organoids





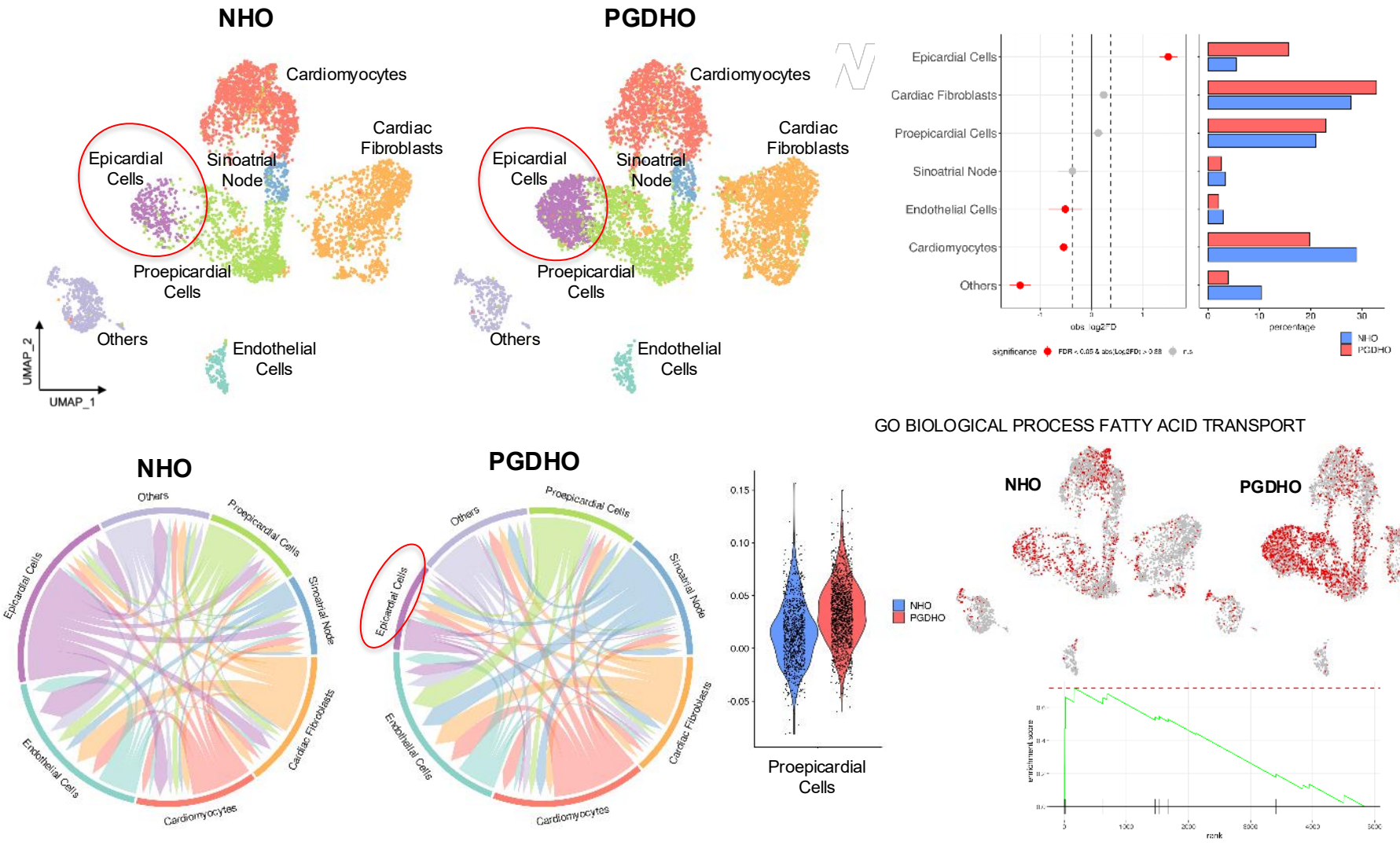


Yonatan Lewis-Israeli, PhD student

Aleksandra Kostina, PhD

Kostina et al., Stem Cell Reports, 2024

PGD induces cardiac lineage alterations a altered FA metabolism in developing hHOs



Kostina et al., Stem Cell Reports, 2024

Conclusions

- Synthetic heart models are powerful tools for disease mechanism studies in humans
- Further refinement is necessary to reach full potential (vascularization, improved anatomy, biomechanics)
- Disease modeling (clinical trial in a dish?): detailed molecular characterization in a fully controlled human system, offers unique advantages vs. animal models
  - Compound testing (efficacy)
  - Cardiotoxicity and safety studies

Acknowledgements

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Sammantha Caywood

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Artem Kiselev, Ph.D.

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Zhen Qiu, Ph.D. (MSU)
Erik Saphiro (MSU)
Christina Chan (MSU)
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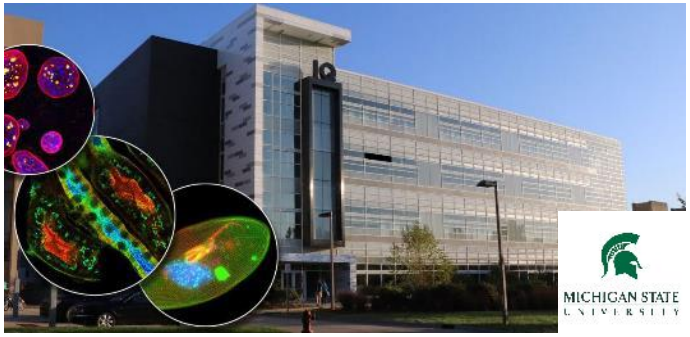

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Generation of Brain Organoid Platform to Investigate Neuronopathic Gaucher Disease and Therapeutic Strategies

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Cincinnati Children's Hospital Medical Center

University of Cincinnati

GRIDS2025 November 16 -17, 2025

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LEARNING OBJECTIVES

At the conclusion of this activity, participants will be able to

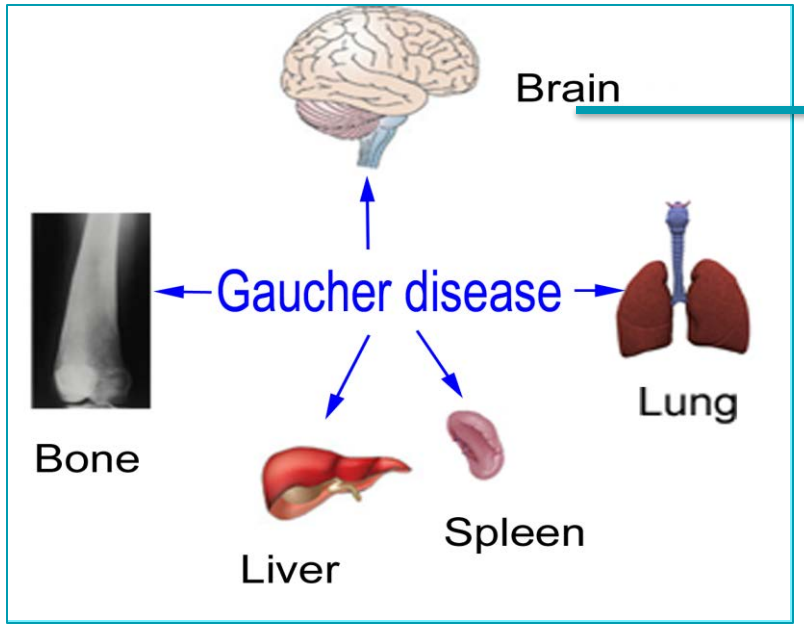
recognize the utility and application of brain organoid models in neuronopathic Gaucher disease research and drug development.

Neuronopathic Gaucher Disease (nGD)

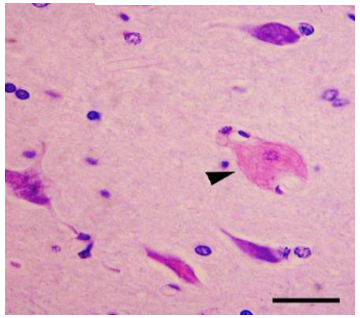
***GBA1* mutations** → **Acid-β-glucosidase (GCase)** → Ceramide

Glucosylceramide
Glucosylsphingosine

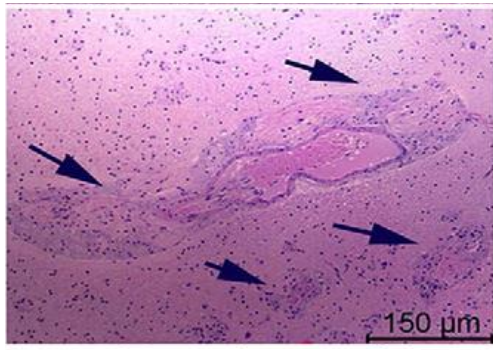
Gaucher disease { GD 1, GD 2, GD 3 } nGD



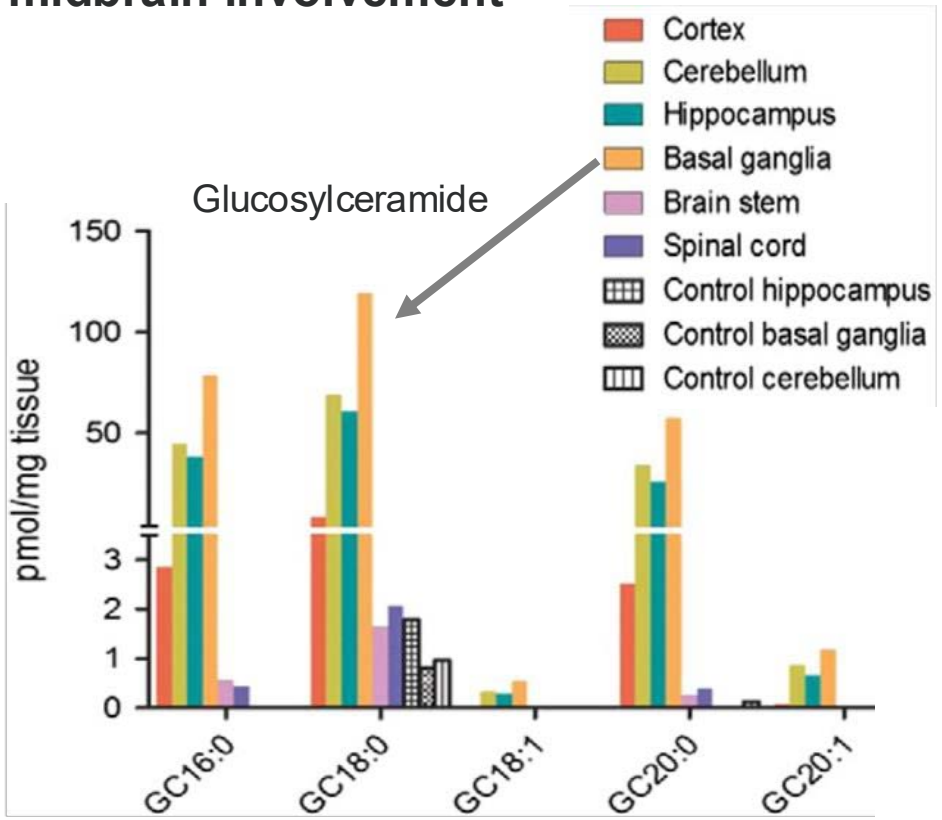
Pronounced midbrain involvement



GD 2



GD 3



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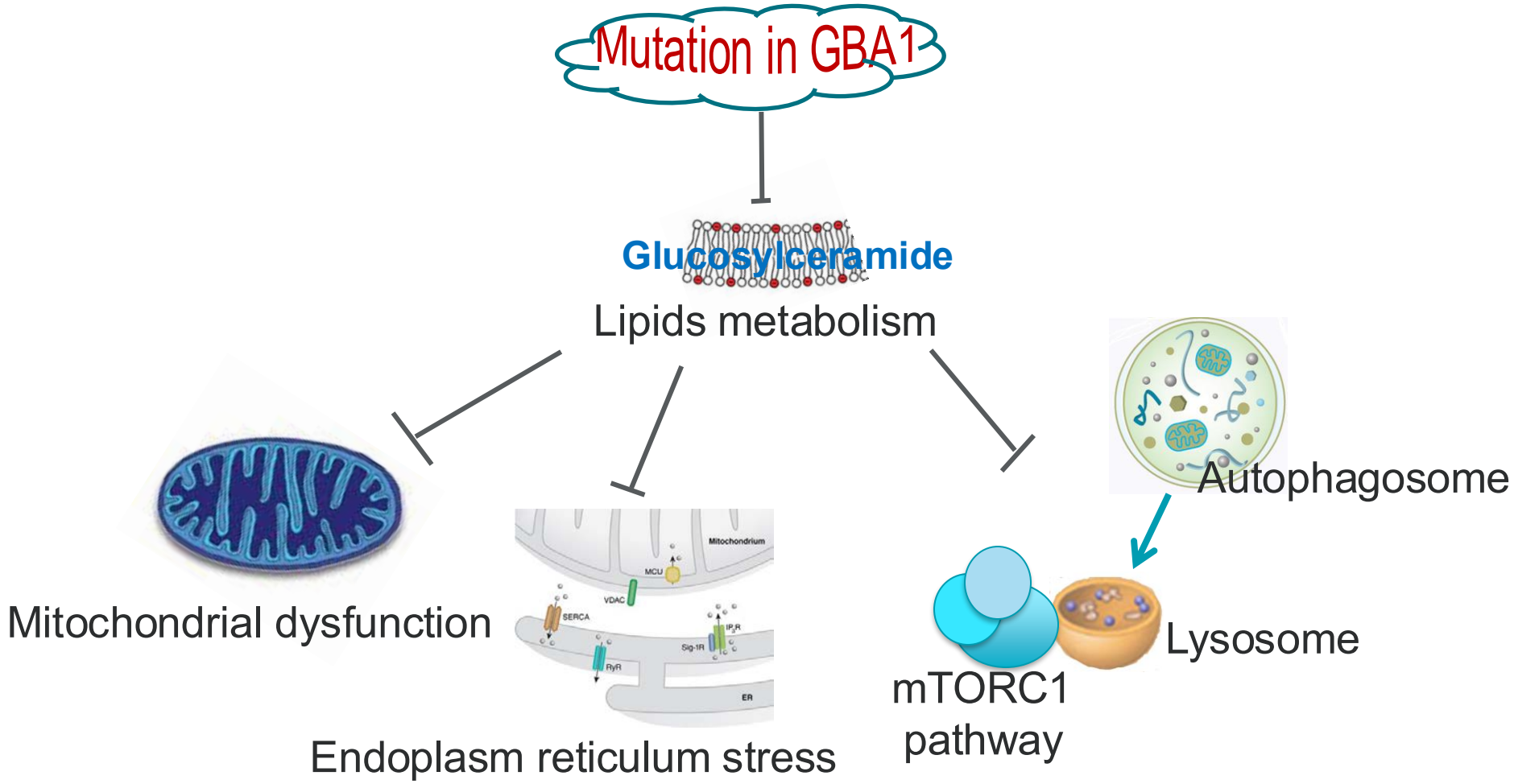
Disturbed cellular functions in nGD



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Models for nGD research and therapeutical evaluation

 Cell models (2D model)	Primary cell (Fibroblasts) Neural cell lines iPSC-derived brain cells
 Animal models (not human)	Knock-out Knock-in Transgenic Chemical-induced

Limitations of current models to study human nGD

- Only postmortem human brain tissues are available.
- Human cell models lacks complexity and functional capacity.
- Animal (mouse) brain is not identical to human brain.

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Models for nGD research

 Cell models (2D model)	Primary cell (Fibroblasts) Neural cell lines iPSC-derived cells
 Animal models (not human)	Knock-out Knock-in Transgenic Chemical-induced
Human organoids (3D model)	Human iPSC-derived Patient specific

3D brain organoid

- Miniature, simplified versions of the brain grown in vitro
- Derived from human patient's multipotent stem cells
- Multiple neural cell types and organization to resemble human brains
- Apply in modeling neurodegenerative diseases:
  - Parkinson's disease, Alzheimer's disease
  - Lysosomal diseases – nGD

Development of nGD patient iPSCs-derived midbrain like organoids (MLOs)

- Generation and characterization of MLO derived from iPSCs
  - **Heathy iPSC**: WT-75.1
  - **GD2 Patient iPSCs**: GD2-1260 (L444P/P415R), GD2-10-257 (L444P/RecNcil)
  - **Genome editing iPSC:** Iso-GD2-1260 (WT/P415R)

- Study disease phenotypes
  - GCase function
  - Cellular function
  - Transcriptome

- Evaluate therapies using nGD MLO model

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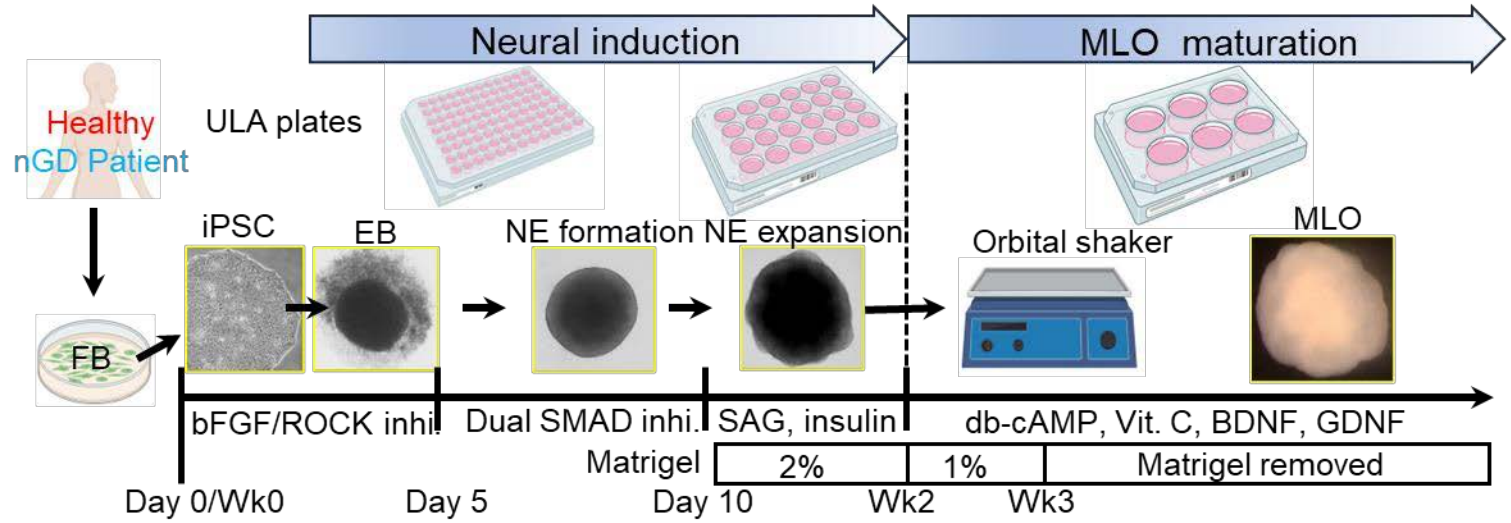
Generation and characterization of MLOs from healthy human iPSCs (WT-75.1)



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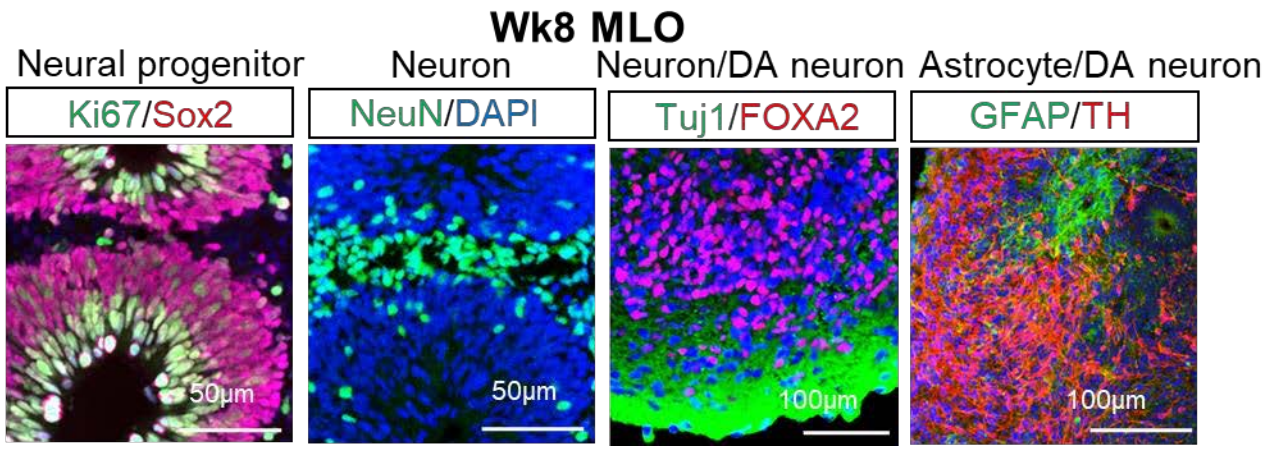
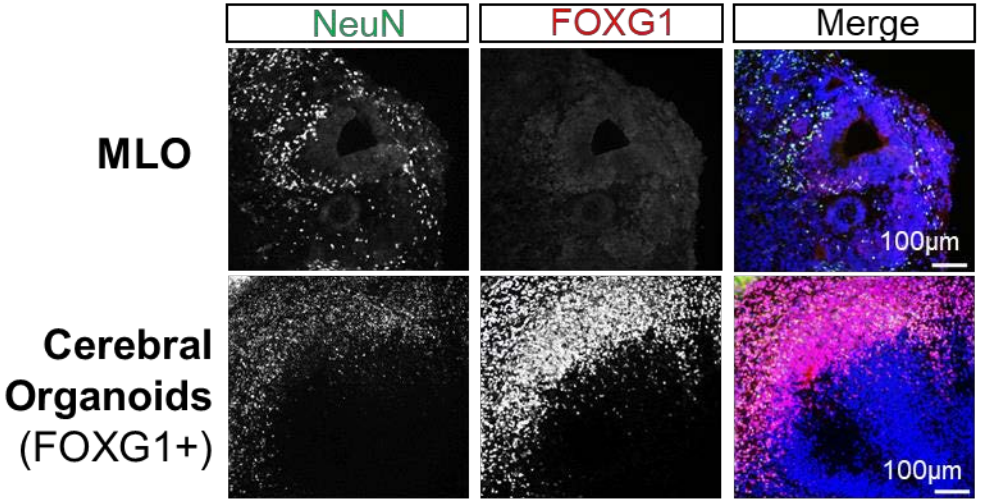
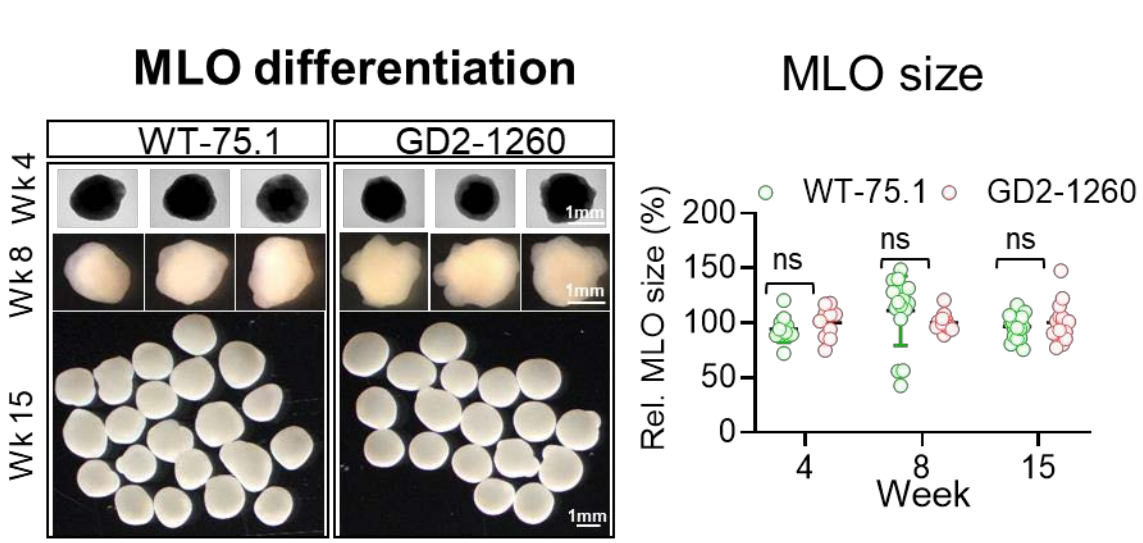
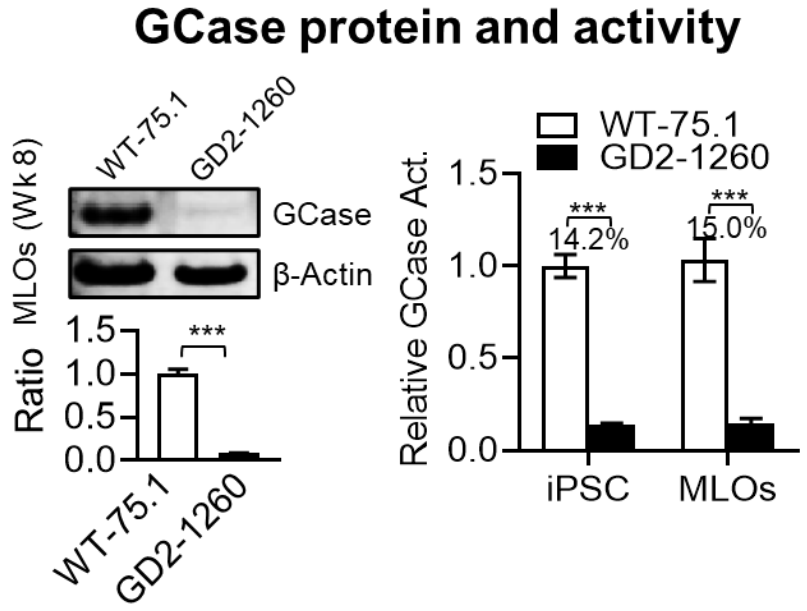
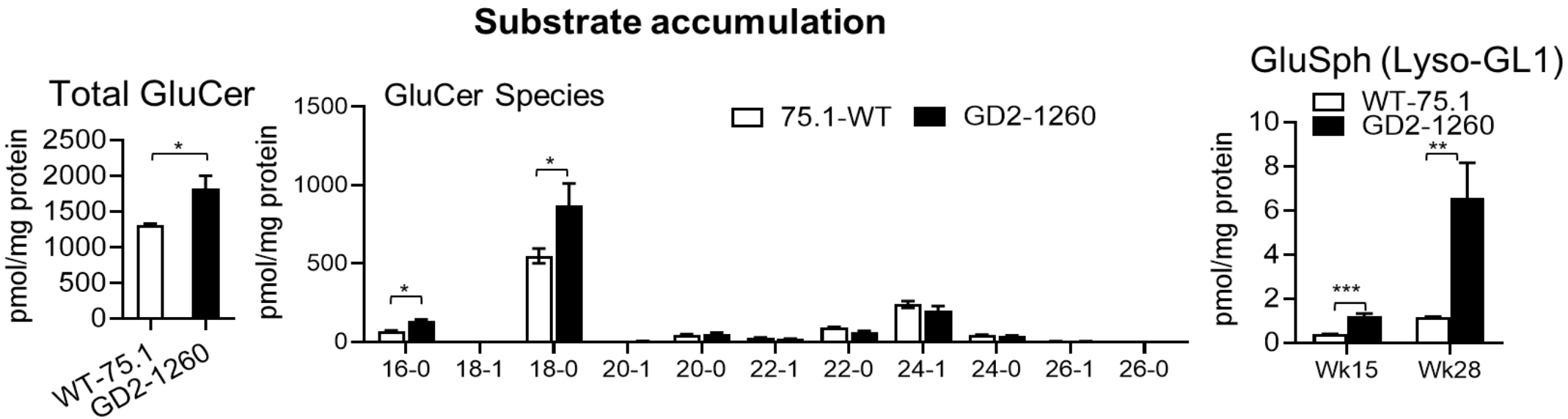




GCase deficiency in nGD MLOs







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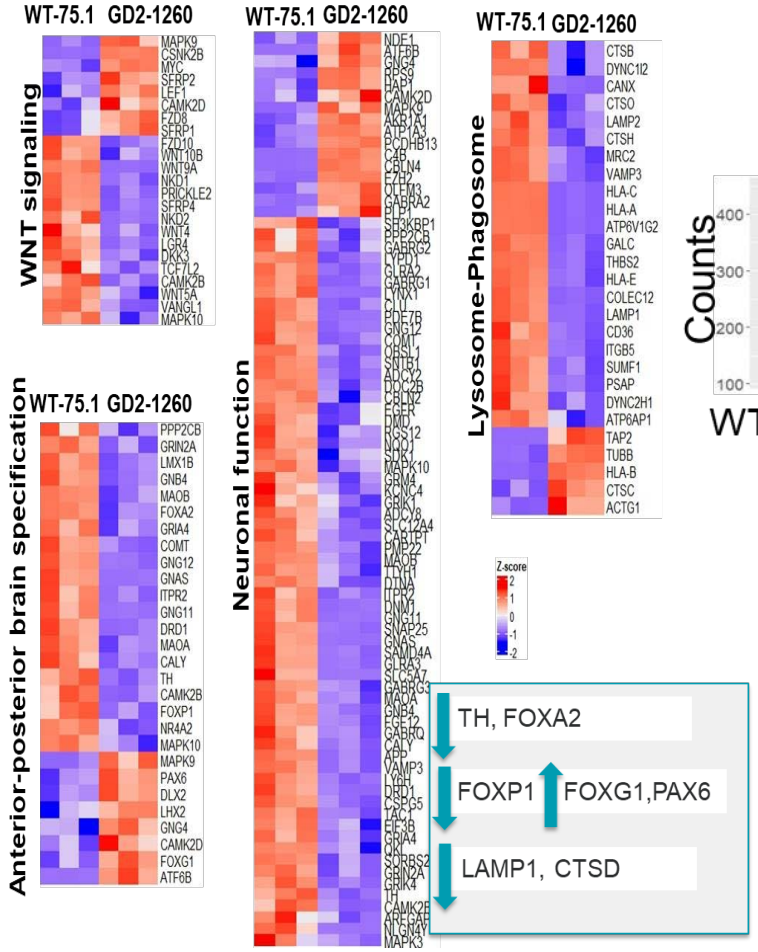
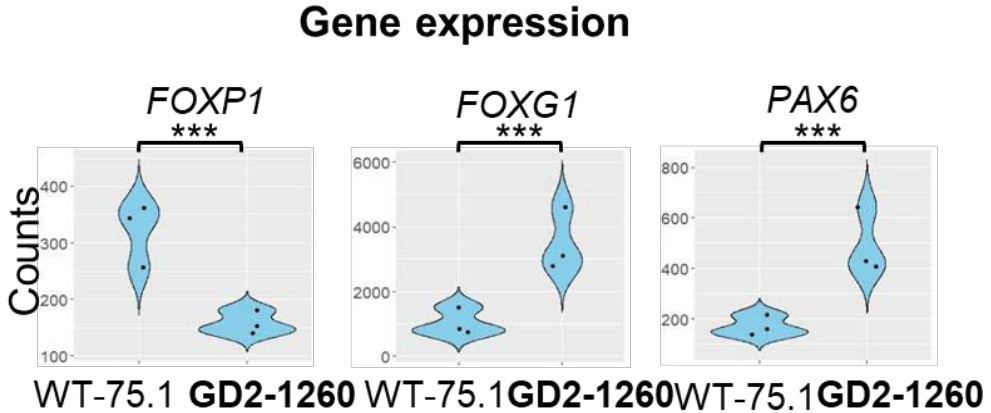
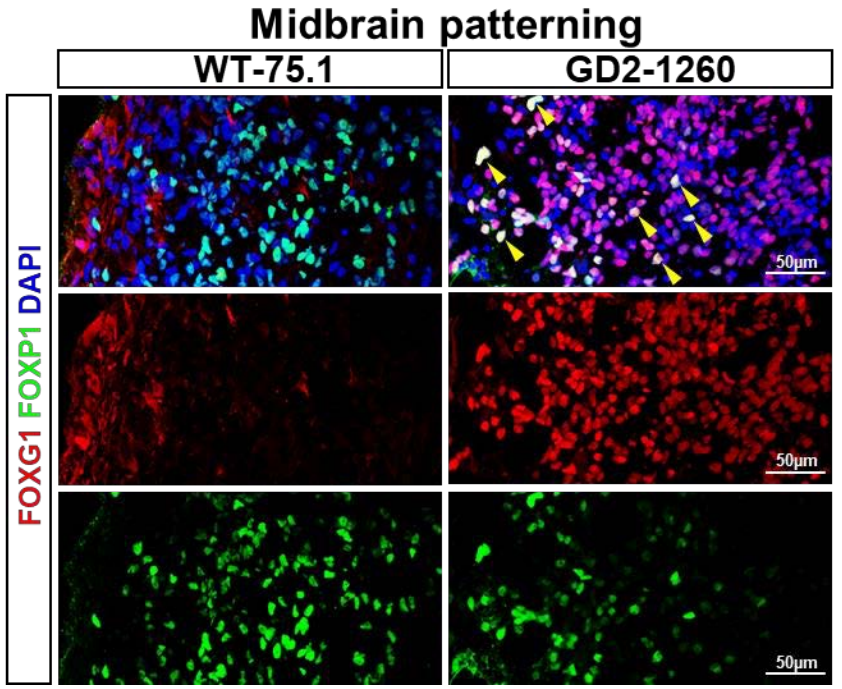
Skewed specification of midbrain patterning in nGD MLOs

Aberrant expression of fate determining regulators: FOXG1, FOXP1, PAX6

Transcriptomic profile







FOXP1: midbrain patterning
FOXG1: forebrain patterning
PAX6: forebrain patterning

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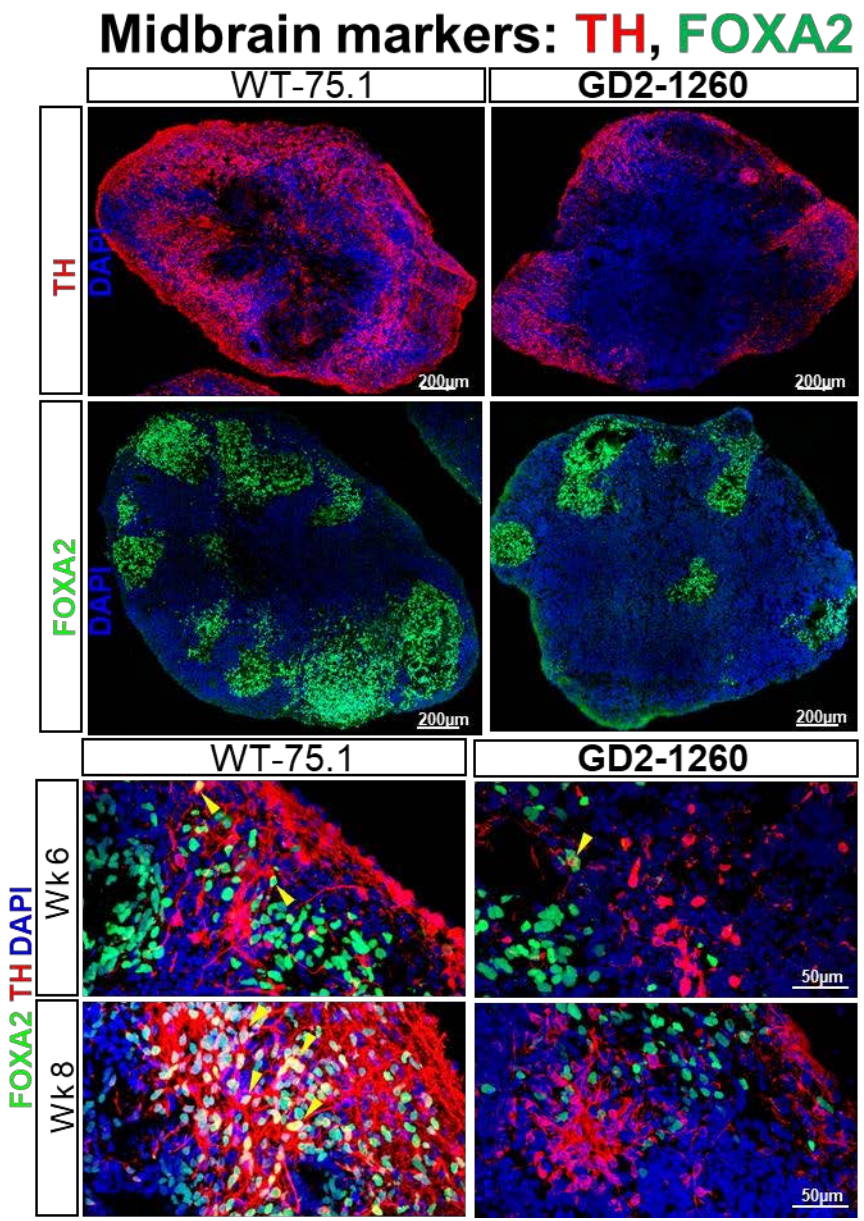
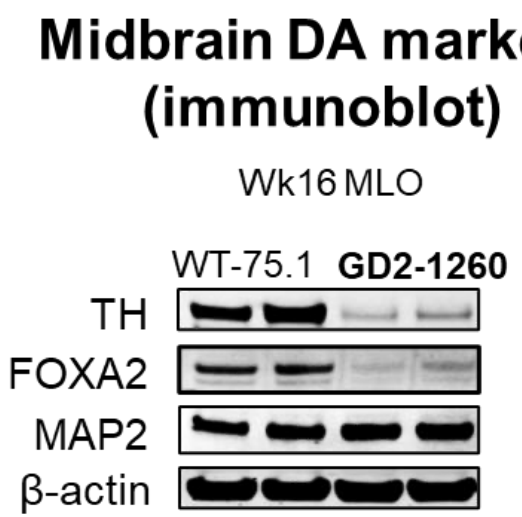
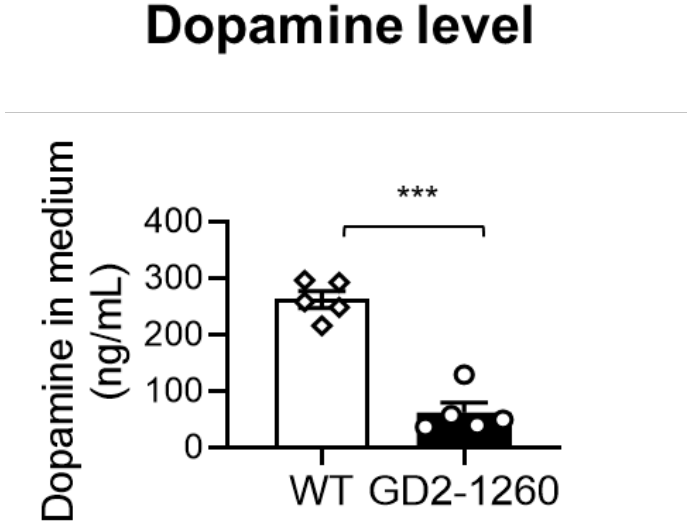
Aberrant dopaminergic neuron differentiation in nGD MLOs







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nGD patient iPSCs-derived MLOs

- Exhibited key GD phenotypes
  - Diminished GCase enzymatic function
  - Accumulation of glycosphingolipid substrates
- Altered transcriptomic changes on neural development and lysosomal function.
- Impaired dopaminergic neuron differentiation

nGD MLO offers patient-specific, 3D neural models for studying disease mechanisms and drug discovery of nGD.

New therapies in development for nGD

Gene therapy

RNA-based

Gene transfer by virus

Genome editing

CNS-enzyme therapy

Receptor-mediated

Nanovesicle delivery

Small molecules

Substrate Reduction

Pharmacological chaperone

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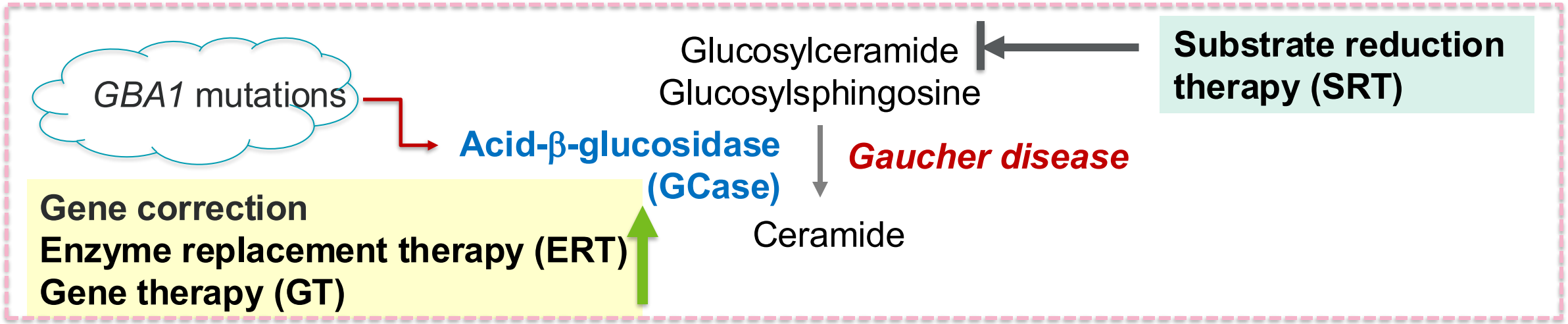
Evaluating therapies using nGD patient iPSCs-derived MLOs

Therapeutic strategies

- Genome editing for gene correction using CRISPR-Cas9
- Substrate reduction therapy - GZ452 (analogue of Venglustat)
- CNS enzyme therapy - SapC-DOPS-GCase
- Gene Therapy - AAV9-GBA1



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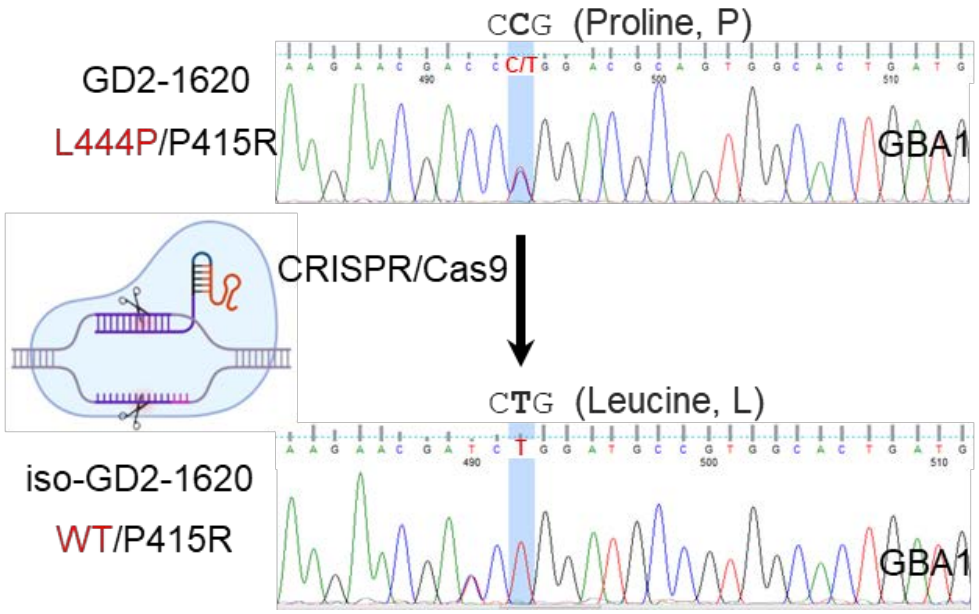
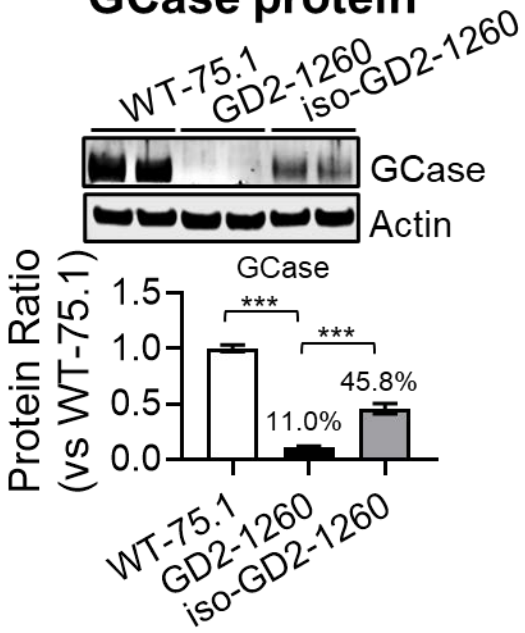
Mutation correction rescued GD phenotypes in nGD MLOs

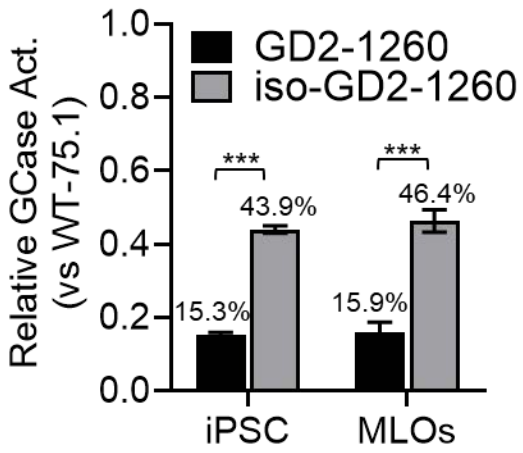
Gene therapy
Genome editing



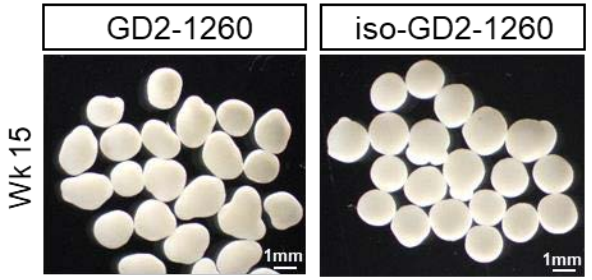
GCase protein

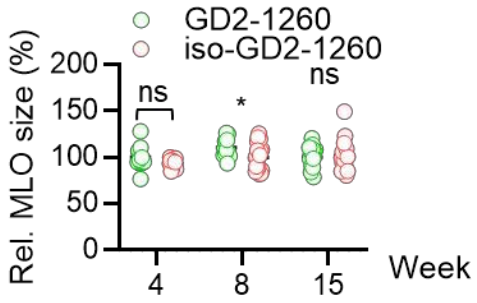


GCase activity

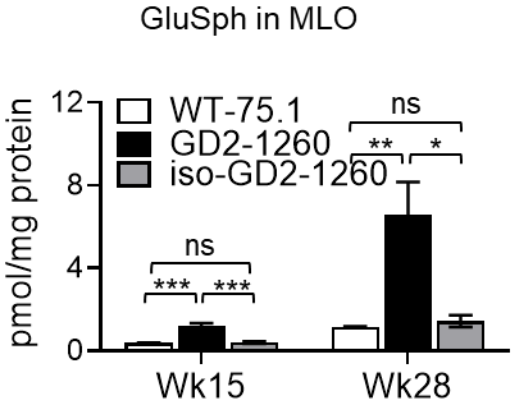


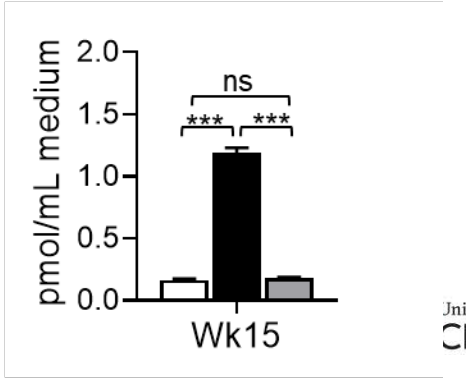
MLO size





Substrate





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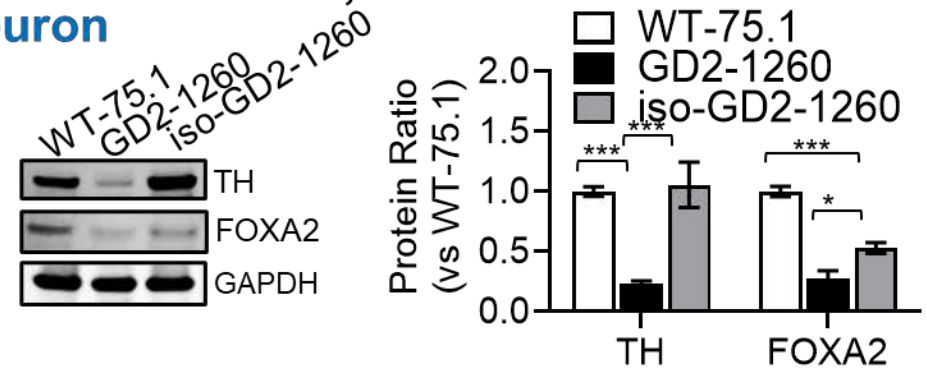
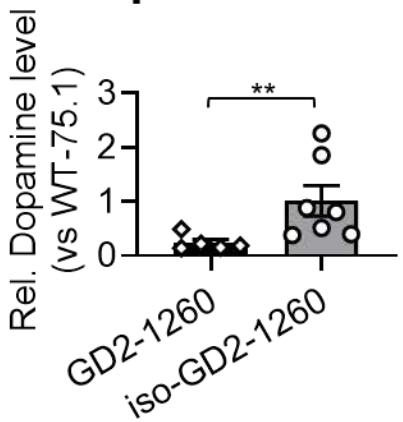
Dopaminergic neuron

TH, FOXA2

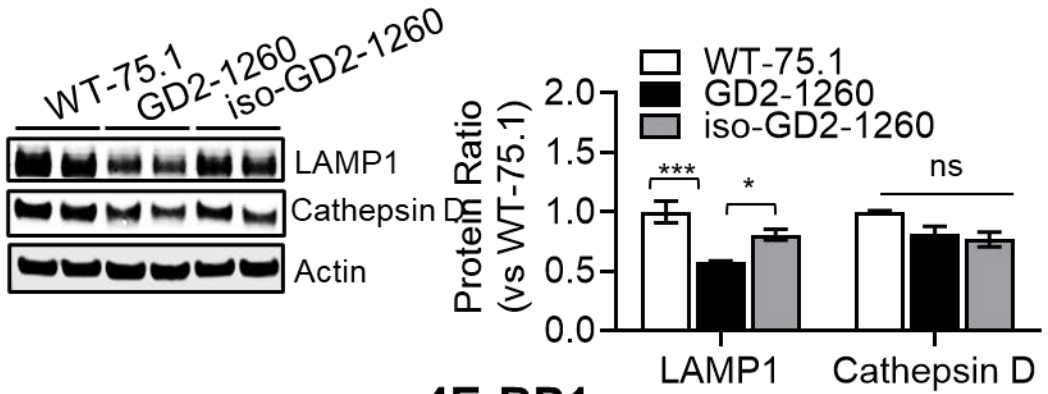


Dopamine level



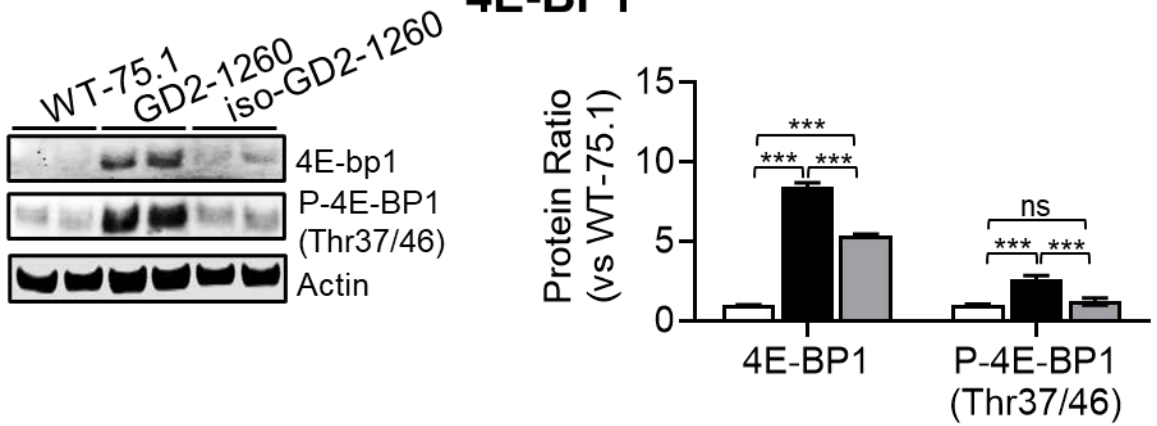
Lysosome

Lamp1, Cathepsin D



mTOR

4E-BP1



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CRISPR/Cas9-mediated correction of GBA1 mutation in nGD MLOs

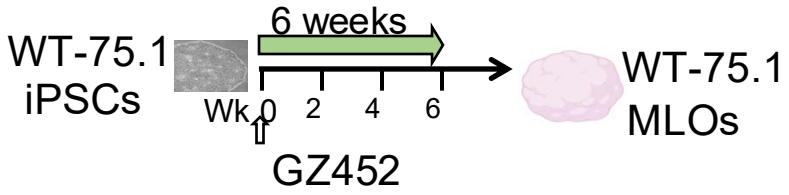
- Rescued key nGD phenotypes and downstream effects
  - Improved GCase activity
  - Reduced substrate accumulation
  - Restored dopaminergic neuron differentiation
  - Partially corrected abnormal lysosomal and mTOR pathways

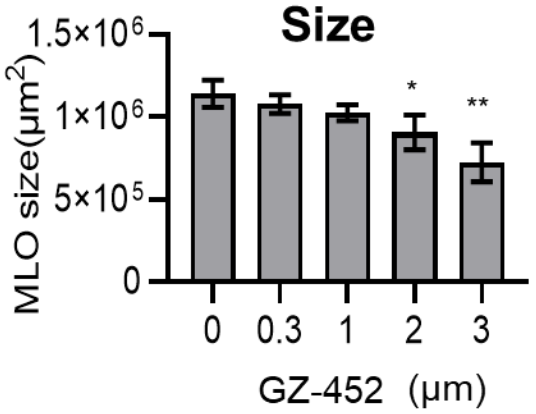
- Validated nGD MLOs as a preclinical disease model
- Supports the genomic editing/gene correction as a therapeutic strategy for nGD

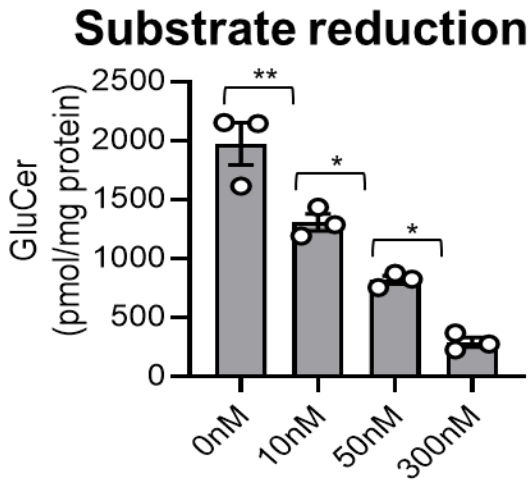
SRT (GZ452) treatment effects on nGD MLOs

Small molecules
Substrate Reduction

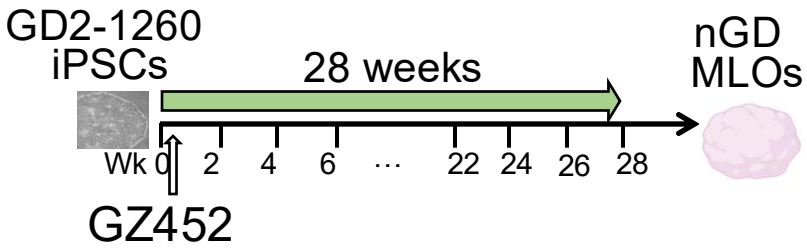
Testing SRT dose and toxicity

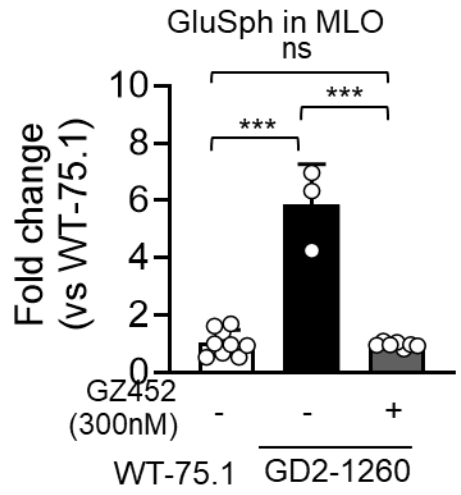


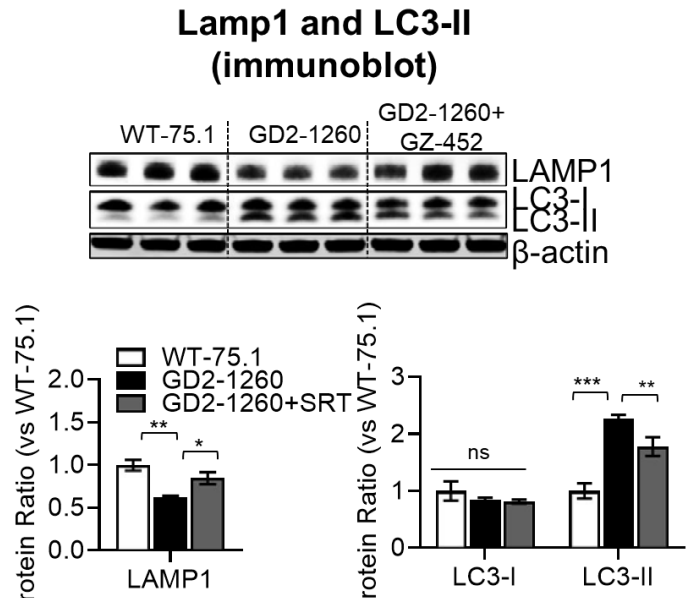




Long-term SRT



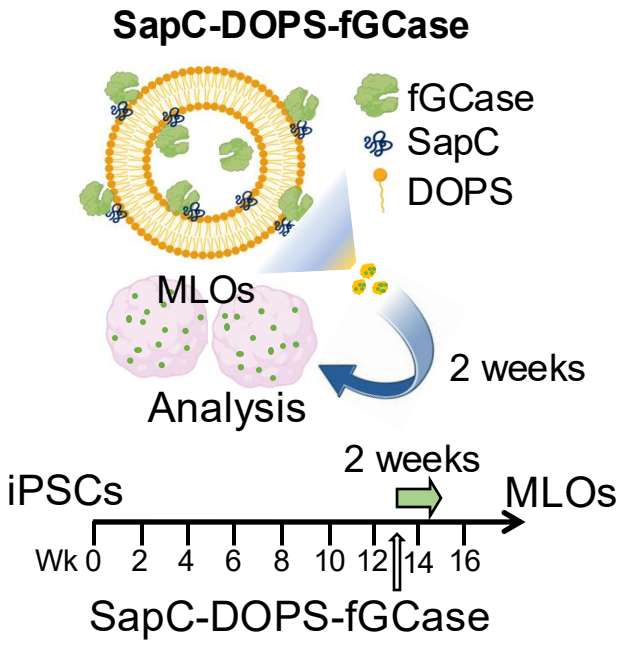




SRT treatment corrected substate accumulation and improved lysosomal-autophagy abnormality in nGD MLOs.

GCase delivery to MLOs via SapC-DOPS nanoparticles rescued GD phenotypes

CNS-enzyme therapy
Nanovesicle delivery



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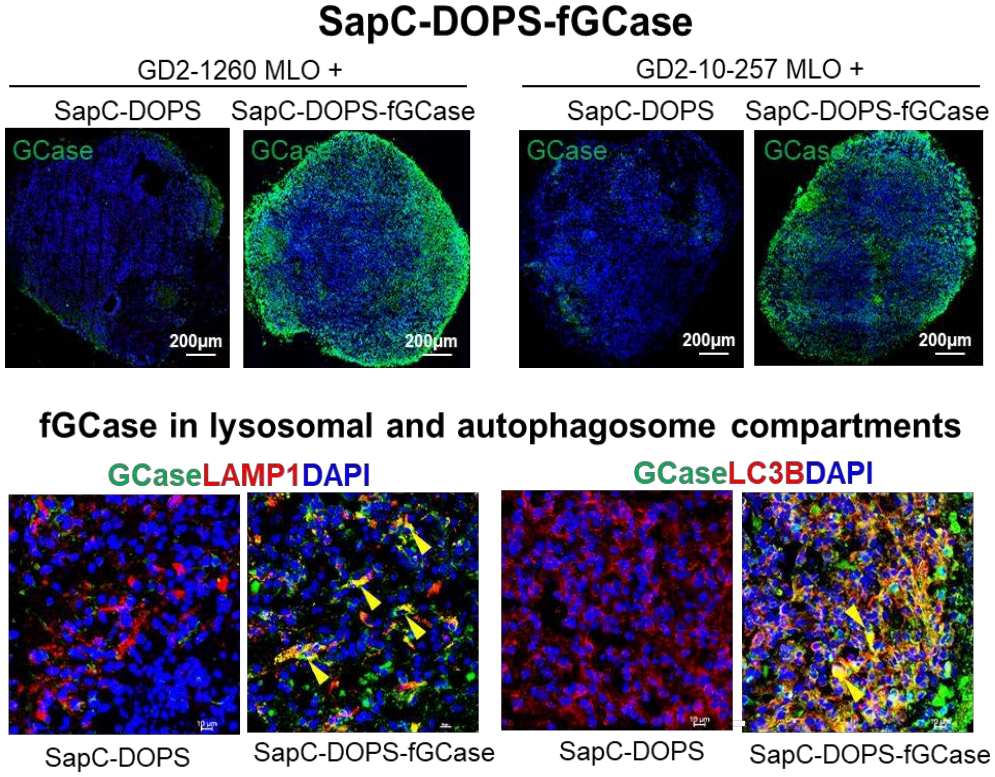
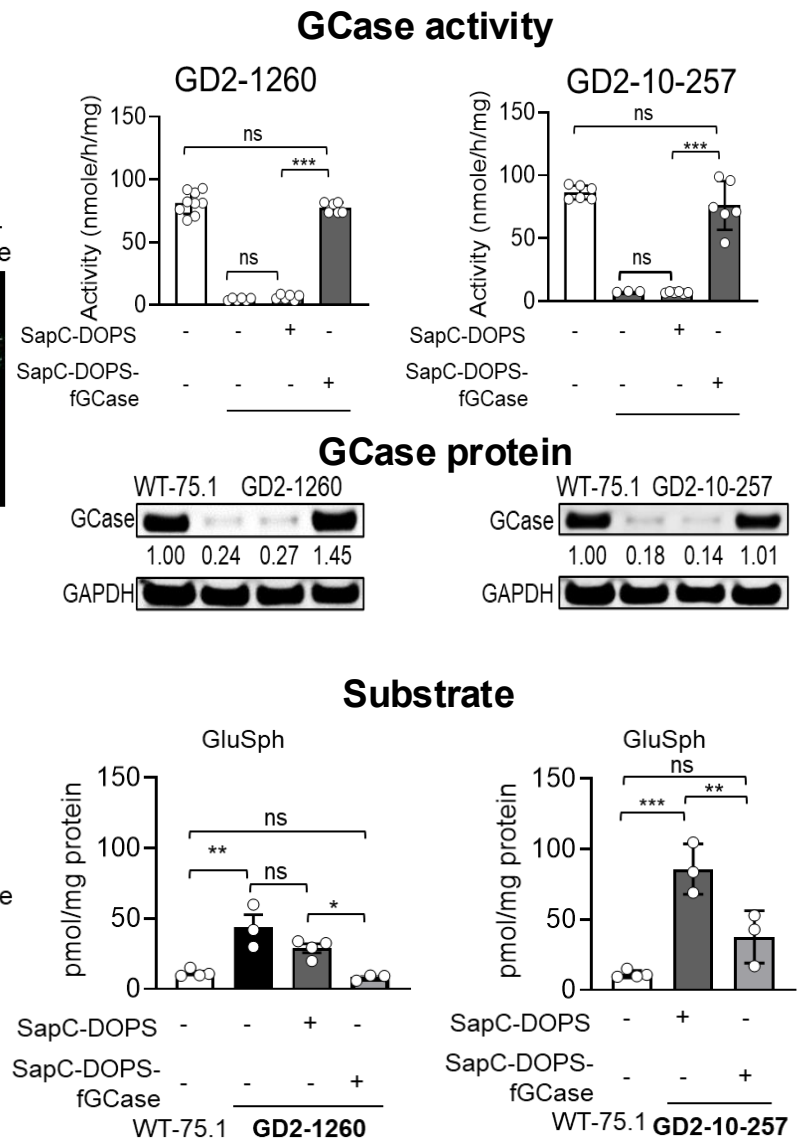
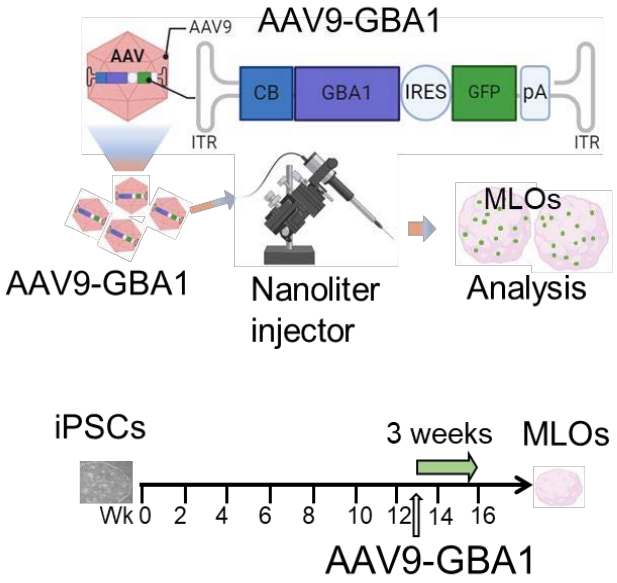


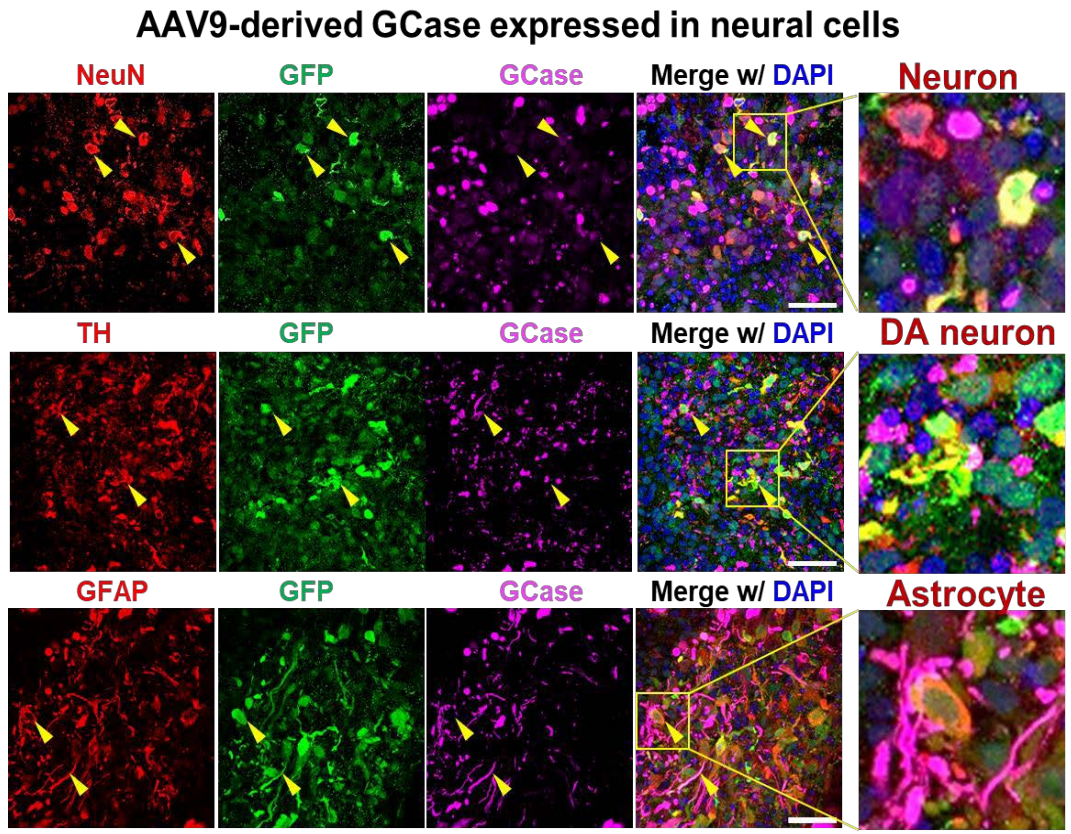
fGCase: a recombinant GCase variant with longer active half life than wild type GCase (Spur/Sygnature Discovery Limited).
Comper, F. et al., Mol Ther (2025); 33: 3789

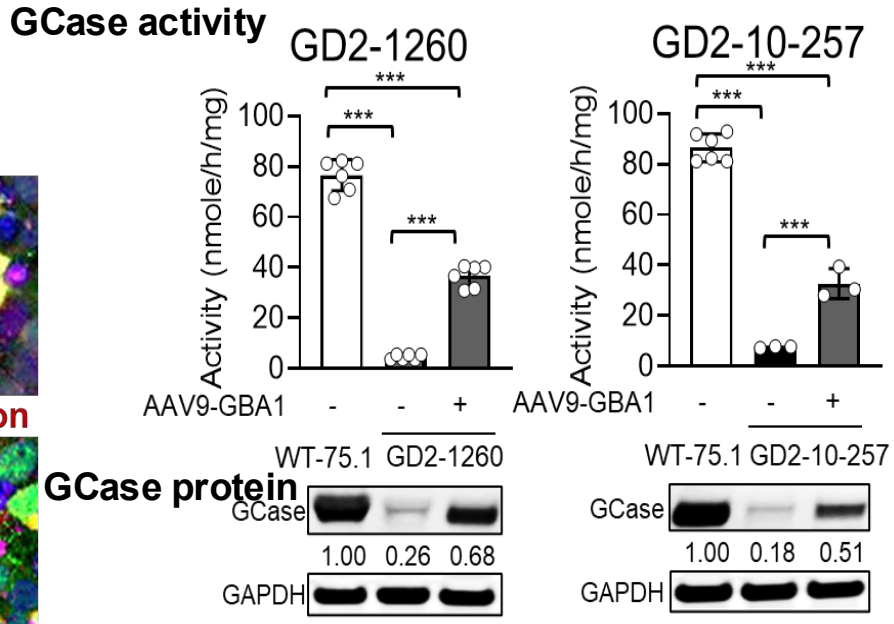


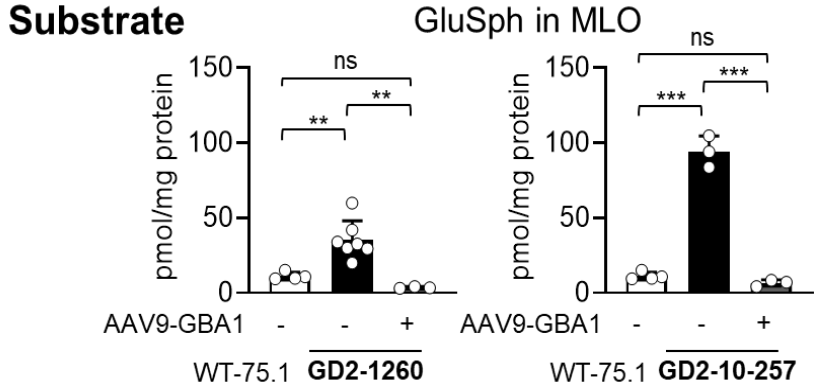
AAV9-GBA1 gene therapy mitigated GD phenotypes in nGD MLOs

Gene therapy
Gene transfer by AAV





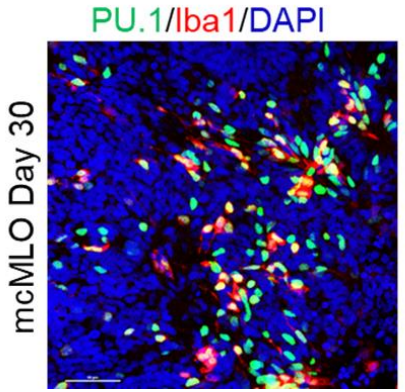




Summary and future direction

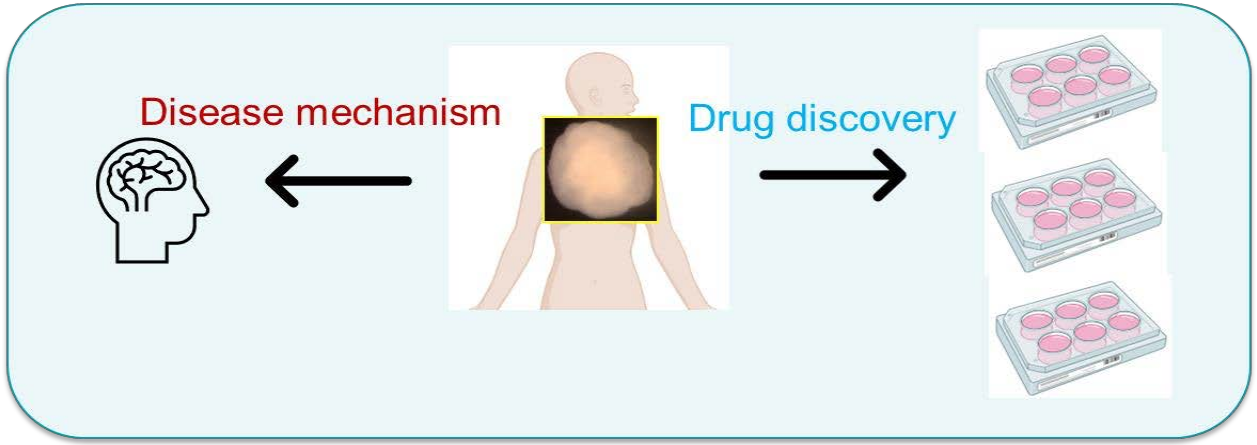
- **Feasibility of growing nGD MLOs from patient iPSCs**
  - Comparable early neural rosette formation and organoid growth as controls.
- **nGD MLOs recapitulated key GD phenotypes**
  - GCase deficiency, Substrate accumulation
  - Abnormal lysosomal, autophagy, and mTOR activities
- **nGD MLOs showed aberrant differentiation of DA neurons**
  - These abnormalities were rescued in iso MLOs
- **nGD MLOs serve a platform for drug testing**
  - Restore GCase and improve downstream cellular functions
- **To improve cell diversity in current MLOs**
  - Integrated microglia cells in MLOs (in progress).
  - Coupling angiogenesis in MLOs would add vasculatures.

Therapy	GCase	Substrate
ERT	↑	↓
GT	↑	↓
SRT	–	↓
Gene correction	↑	↓



Perspectives

- nGD MLOs enable individualized preclinical models, supporting precision therapies.
- Brain organoids has the potential to improve preclinical testing and reduce reliance on animal models.



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