Brain and heart protection: Looking for treatments for NAXD

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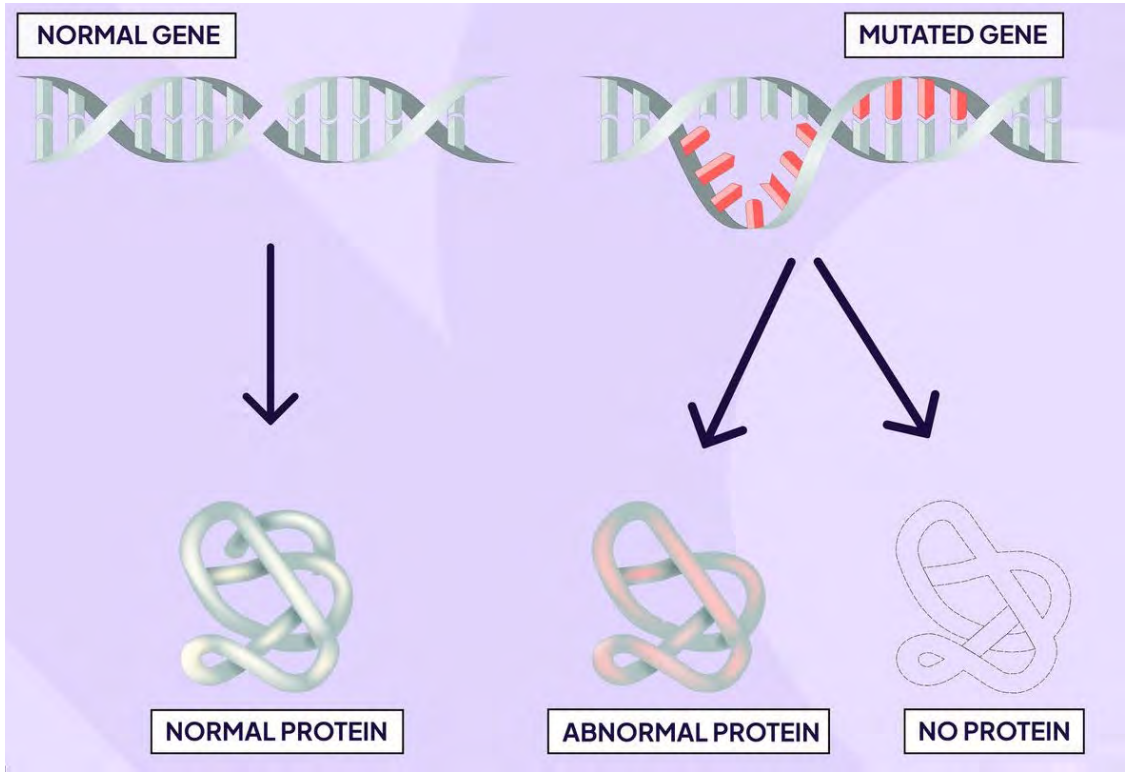
What is NAXD protein?

- NAXD is a normal protein in the mitochondria and other parts of the cell.
- Chemicals inside cells can become ‘broken’ under stress or high temperatures.
- These ‘broken’ chemicals have the wrong shape.
- These ‘broken’ chemicals are toxic.
- NAXD protein is critical for ‘repairing’ these toxic chemicals to their original shape.

What causes NAXD-mito?

- Genetic ‘mistakes’ in the DNA of the cell that makes NAXD protein.
- This causes problems with the NAXD protein.
- These genetic ‘mistakes’ are inherited.
- A child needs to inherit this from both parents (recessive).



What happens with NAXD-mito?

- Children with NAXD-mito are born healthy.
- Infection, fever, illness and injury triggers disease.
- Children have a rapid decline in their health.
- They have brain, heart, skin and other problems.
- Sadly, most children do not survive.

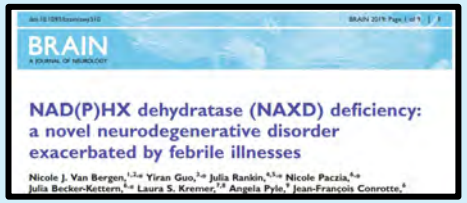
The journey of NAXD-mito discovery

First individual from Sydney

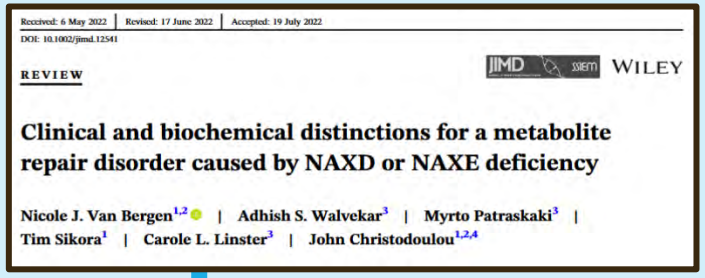
We identified additional cases around the world

Lab testing and genetics

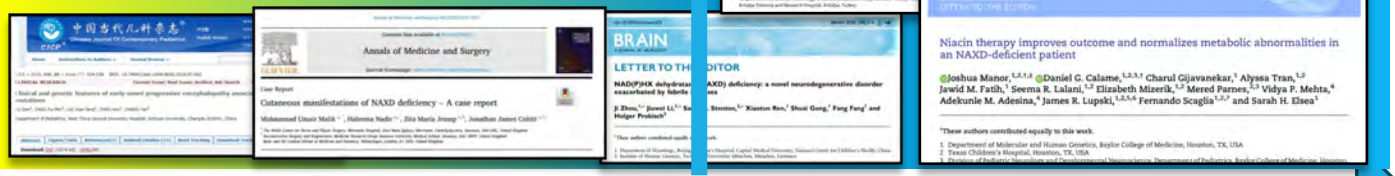
Published landmark paper



Found more individuals with different clinical presentations



Many more individuals identified



2017 2018 2019 2020 2021 2022 2023 2024

Mito Foundation Award

Mito Foundation funding

Recognized as a Mito condition

Mito Foundation funding

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Hope for mitochondrial disease

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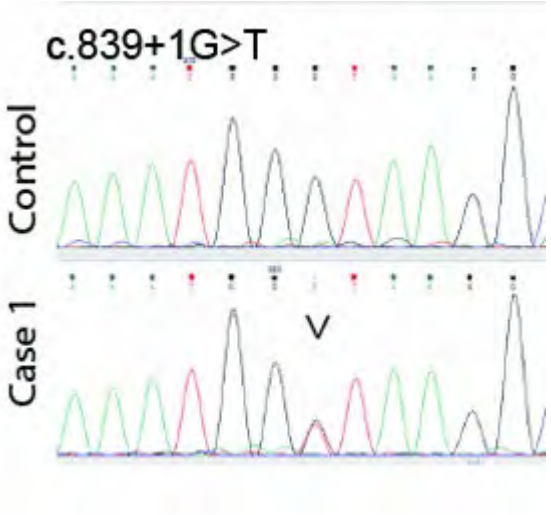
Hope for mitochondrial disease

Building the evidence for NAXD-mito

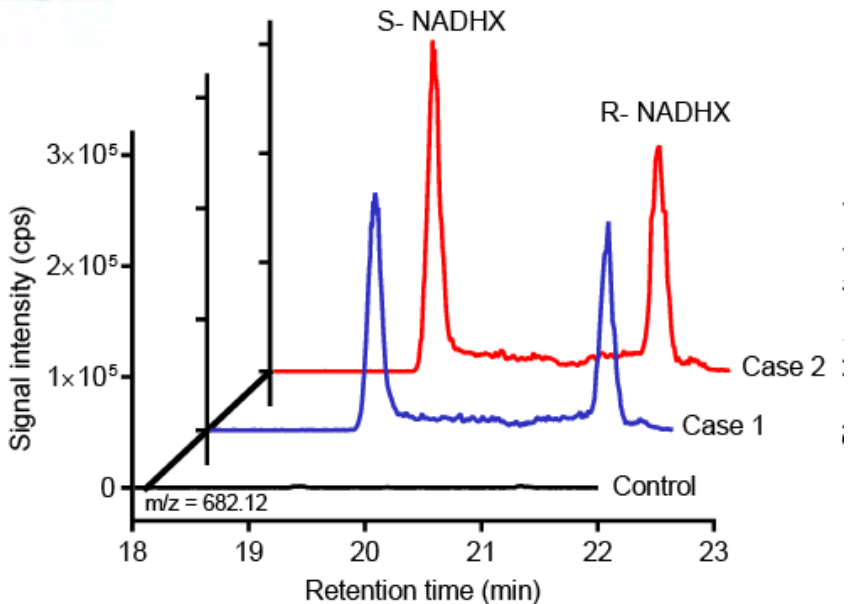
1. Multiple cases with similar symptoms

Clinical presentation	NAXD individuals					
	1	2	3	4	5	6
Gender	M	F	F	M	F	F
Fever or illness prior to deterioration	Y	N	Y	Y	Y	Y
Neurodegeneration	Y	Y	N	Y	?	Y
Skin lesions	Y	Y	N	Y	N	Y
Early death	Y	Y	Y	Y	Y	Y

2. Genetic testing

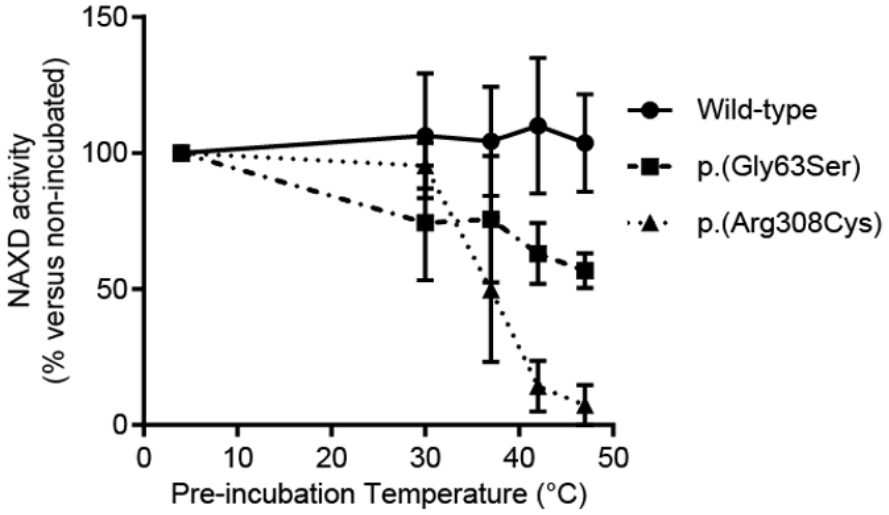


3. Lab studies using patient cells to look at the 'toxic' chemicals



Building the evidence for NAXD-mito

4. Lab studies to help us predict NAXD protein doesn't work properly



5. Working with lots of people working together across the world

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The Royal Children's Hospital Foundation

The Sydney children's Hospitals Network

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Royal Brompton & Harefield NHS Foundation Trust

Newcastle University

wellcome centre mitochondrial research

NHS Royal Devon and Exeter NHS Foundation Trust

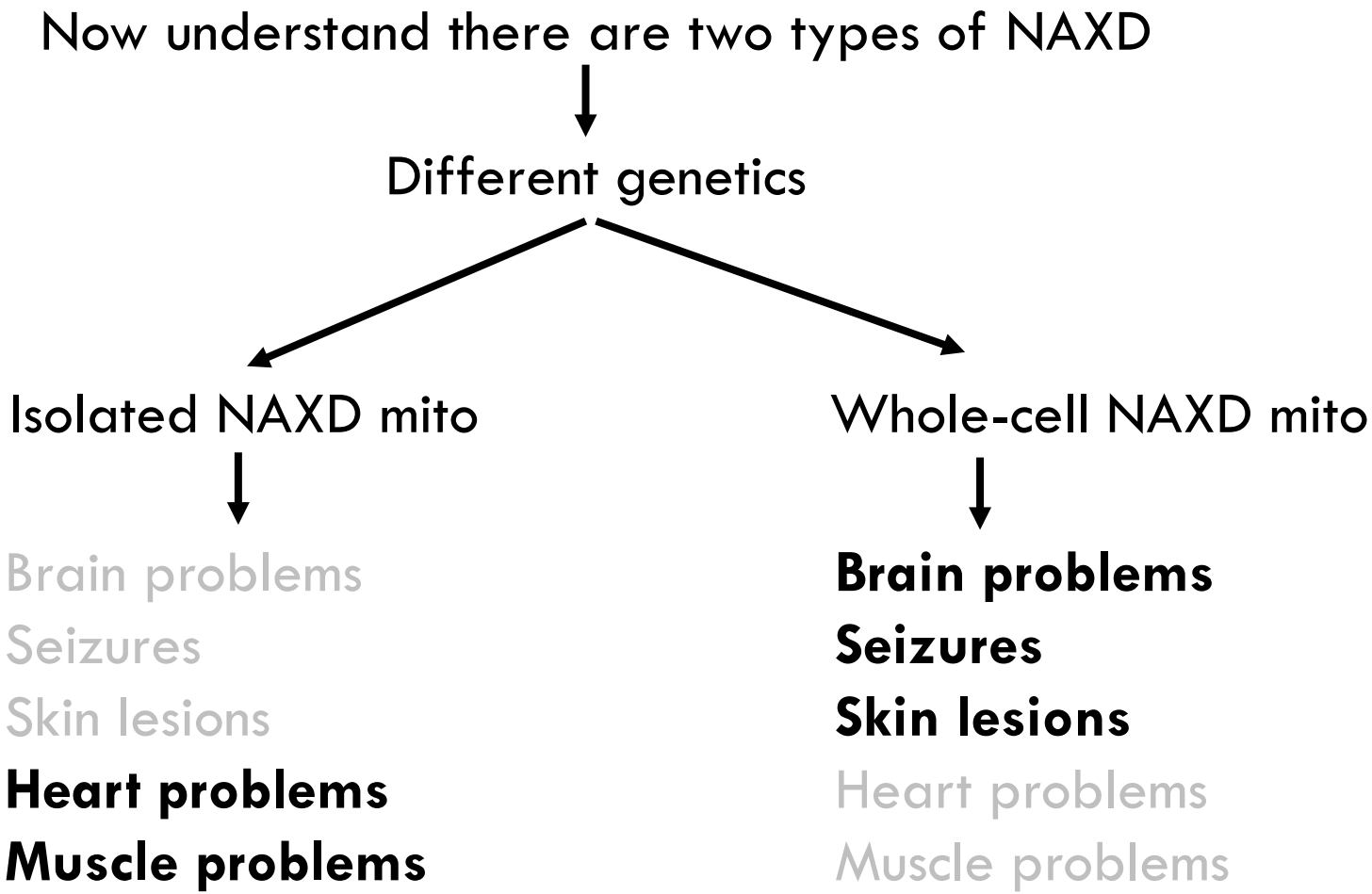
The Children's Hospital of Philadelphia RESEARCH INSTITUTE

CENTER FOR APPLIED GENOMICS

NHS Birmingham Women's and Children's NHS Foundation Trust

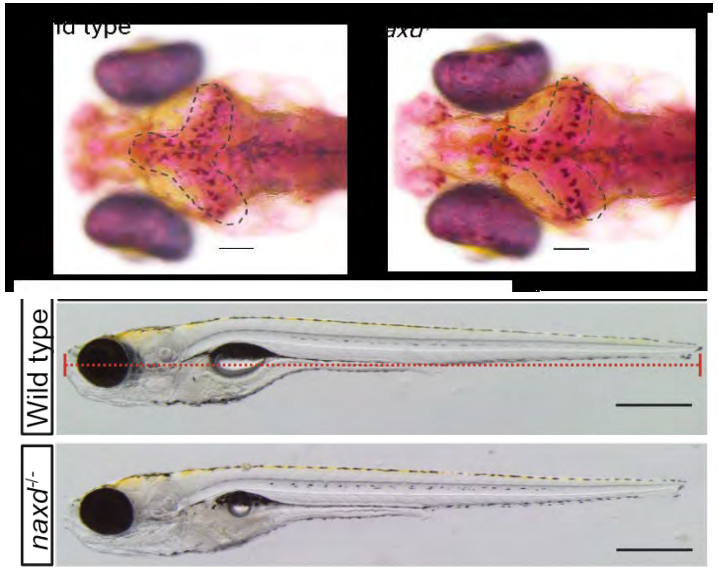
Common symptoms as we have more cases

Better understanding of clinical and molecular links

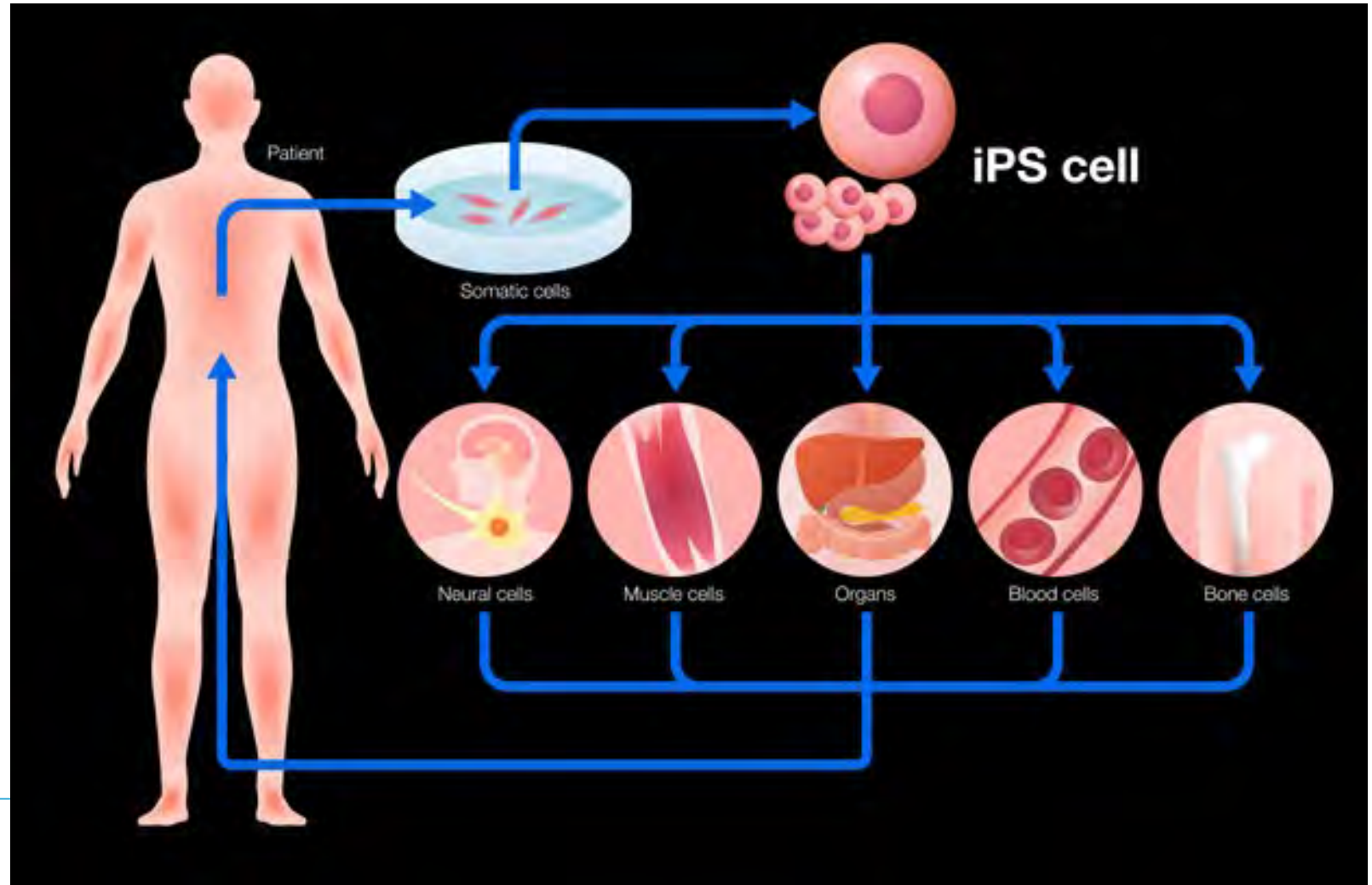


Better models to understand NAXD-mito

Animal models
(fish and mice)



Stem cell models



The need for a treatment for NAXD mito

- Most people with NAXD-mito don’t survive.

- Very short treatment ‘window’

- Limited options for treatment
  - careful management of fever
  - Avoiding infections and illness (isolation)
  - Very high dose niacin therapy (vitamin B3 or nicotinic acid)

Can we find better treatments by testing existing drugs?

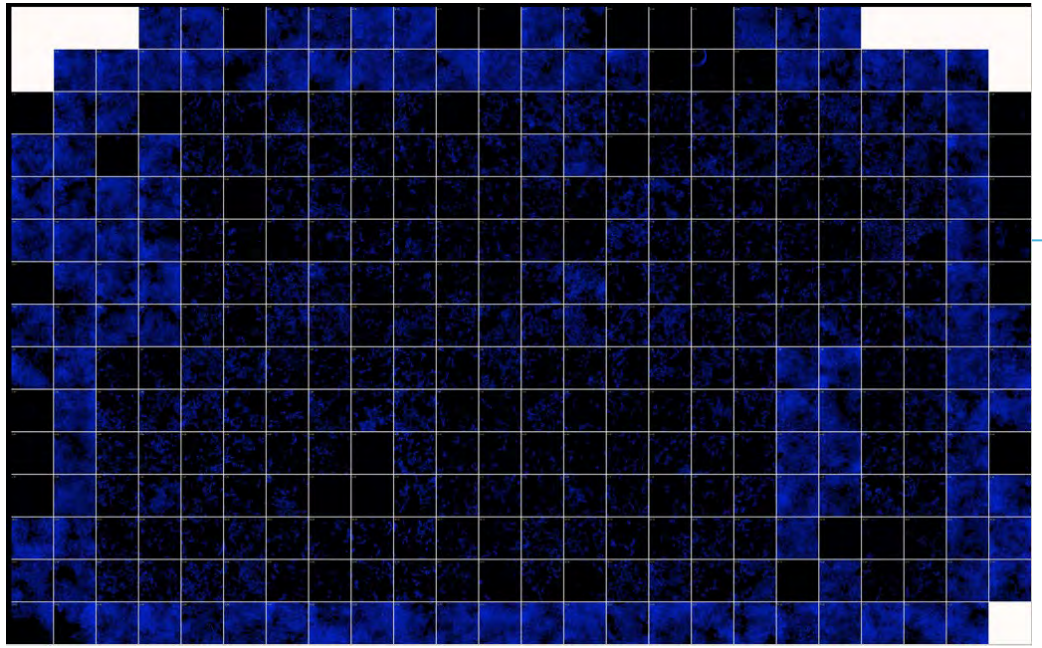
High throughput drug testing

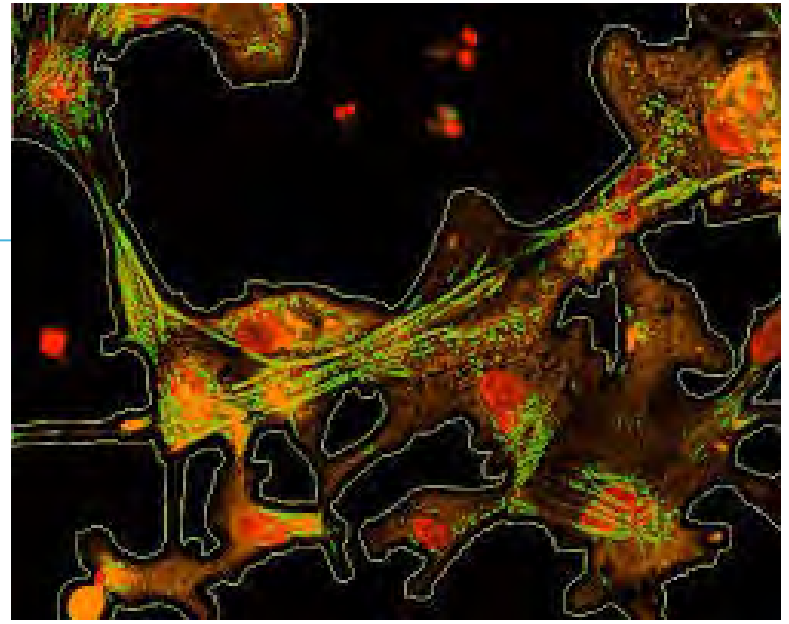
MCRI's Disease Modelling and Drug Discovery Facility

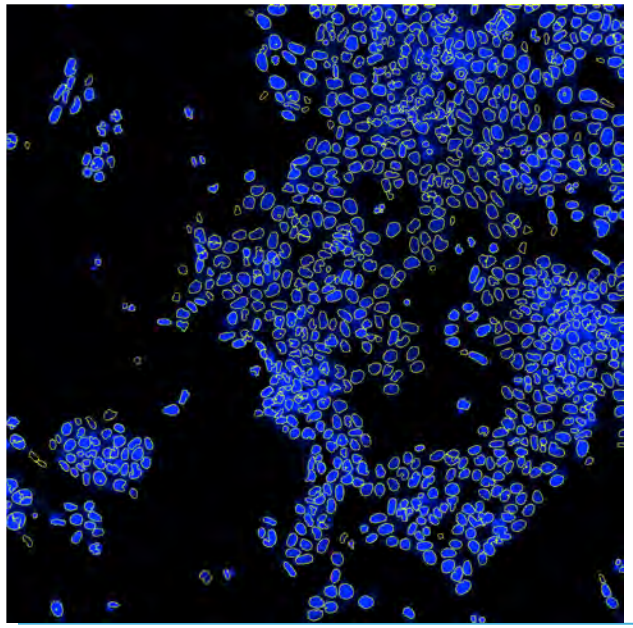
Alejandro Hidalgo-Gonzalez, Henry Beetham and Tim Sikora

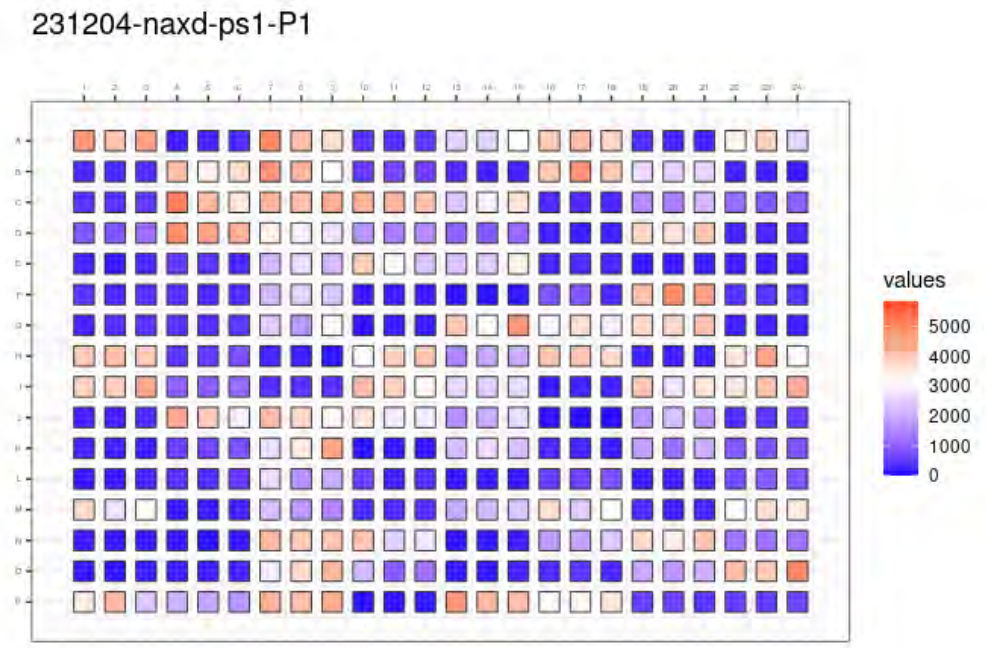
Group1_TL1_20x_2D

No	Objective Lens	Method	Emission	Light Source	Exposure	Z Range	Z Step	Bin	
1	20x Dry (20x)	ConfocalFluorescence	BP445/45	405nm 40 % 488nm 40 % 561nm 40 %	250 [ms]	6.0 [µm]	2.0 [µm]	1 x 1	MaxIP
2	20x Dry (20x)	ConfocalFluorescence	BP525/50	405nm 40 % 488nm 40 % 561nm 40 %	250 [ms]	6.0 [µm]	2.0 [µm]	1 x 1	MaxIP
3	20x Dry (20x)	ConfocalFluorescence	BP600/37	405nm 40 % 488nm 40 % 561nm 40 %	250 [ms]	6.0 [µm]	2.0 [µm]	1 x 1	MaxIP
4	20x Dry (20x)	BrightField	BP525/50	Lamp 30 %	250 [ms]	--- [µm]	--- [µm]	1 x 1	Slice



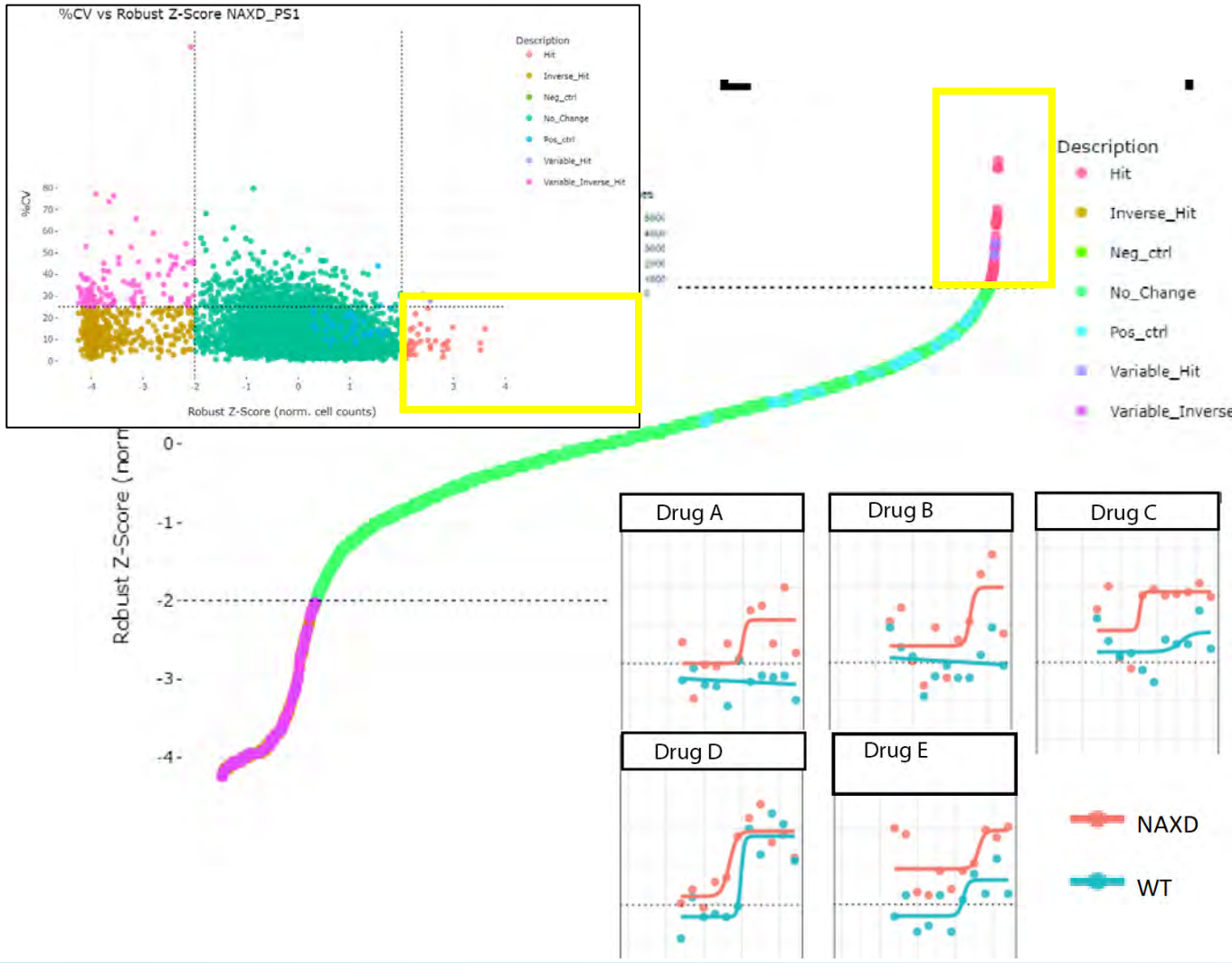






- **Alejandro Hidalgo-Gonzalez, Henry Beetham and Tim Sikora**

Novel drugs identified from >4000 drugs



Drug	Mechanism of action
7	Potentially prevents mitochondrial-related apoptosis
12	Drug targets a mitochondrial protein that regulates AMPK/mTOR pathway
13	Mitochondrial activation via PGC1α deacetylation
18	Antioxidant protecting against mitochondrial oxidative stress
36	Increased β-oxidative metabolism in mitochondria
39	Antioxidant activity and restoration of mitochondrial dysfunction
41	Regulation of mitochondrial dynamics
45	p38 MAPK inhibitor to protect mitochondria

- **Alejandro Hidalgo-Gonzalez, Henry Beetham and Tim Sikora**

Next steps

- Further drug testing in NAXD-mito cells
- Reversal of disease in animal models
- Testing in stem cell models (e.g. brain and heart cells)
- Continue helping diagnose new NAXD-mito individuals

Acknowledgements and Funding

mito FOUNDATION
Hope for mitochondrial disease

Phenomics Australia
Enabling precision medicine

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