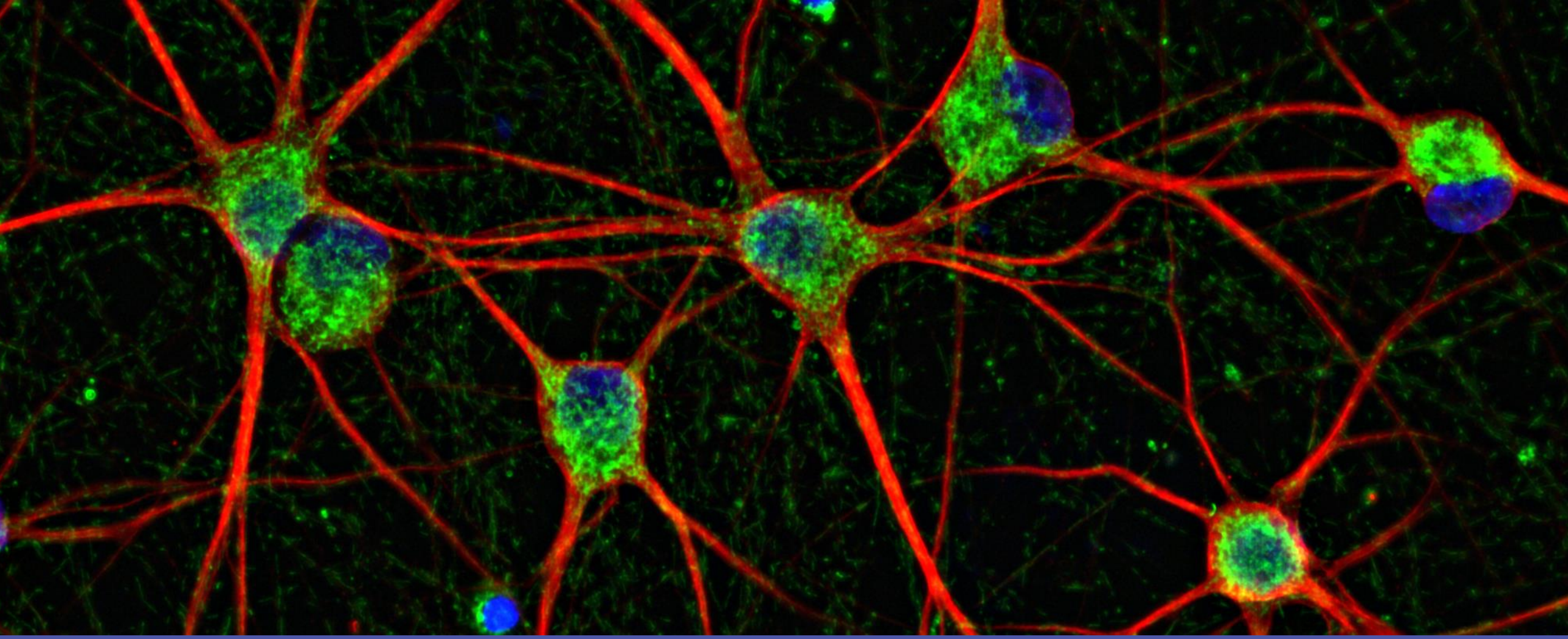
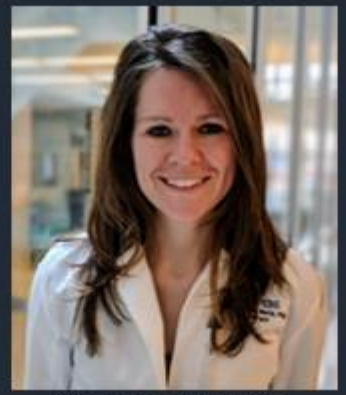


Christina Nemeth Mertz, PhD

Kennedy Krieger Institute
Johns Hopkins Medical Institutions
Baltimore, MD

Moser Center for Leukodystrophies
at Kennedy Krieger Institute

Ali Fatemi, MD, MBA
Principal Investigator



Christina Nemeth Mertz, PhD
Assistant Professor

Inés Garofolo
Research Technician

Manouchehr Amanat, MD
Postdoctortal Fellow

Adam Ratajczak
Research Technician

Mingyao Ying, PhD
Associate Professor

Bela Turk, MD
Postdoctoral Fellow

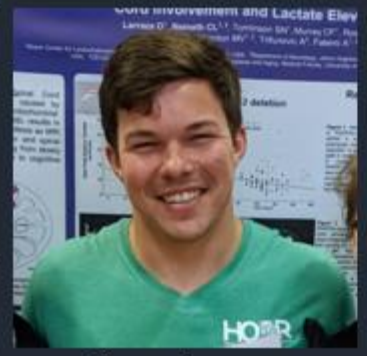
Past Members

Shiqi Guang, MD
Postdoctortal Fellow
2019-2021

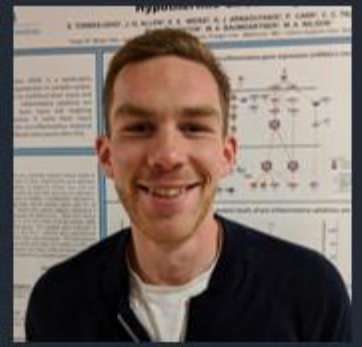
Seung Woo Baek
Research Technician
2020-2022

Sophia Tomlinson
Research Technician
2017-2021

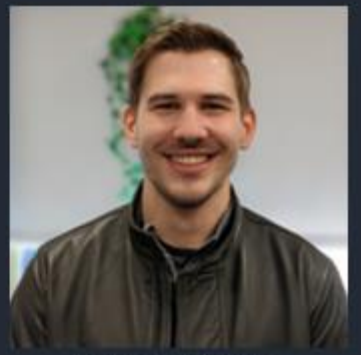
Brett O'Brien
Research Technician
2018-2020



Oscar Larraza
Undergraduate Researcher
2016-2019



Philippe Hubo
Postdoctortal Fellow
2017-2018



Connor Murray
Research Technician
2016-2017

Roadmap in LBSL – an ultra-rare disorder

Kennedy Krieger Institute

Project Planning

Establish model systems in the lab

Testing Therapeutics in model systems (anti-oxidants, small molecules, ASO, gene therapy)

Natural History Study in USA

Outcome Measure Studies in USA, Netherlands, Finland

FDA

9/14 First meeting with McGinn Family

PHARMA

Tox studies

FDA

First In Human Trials

2015 2016 2017 2018 2019 2020 2021 2022 2023 2024 2025 2026 2027

Overview

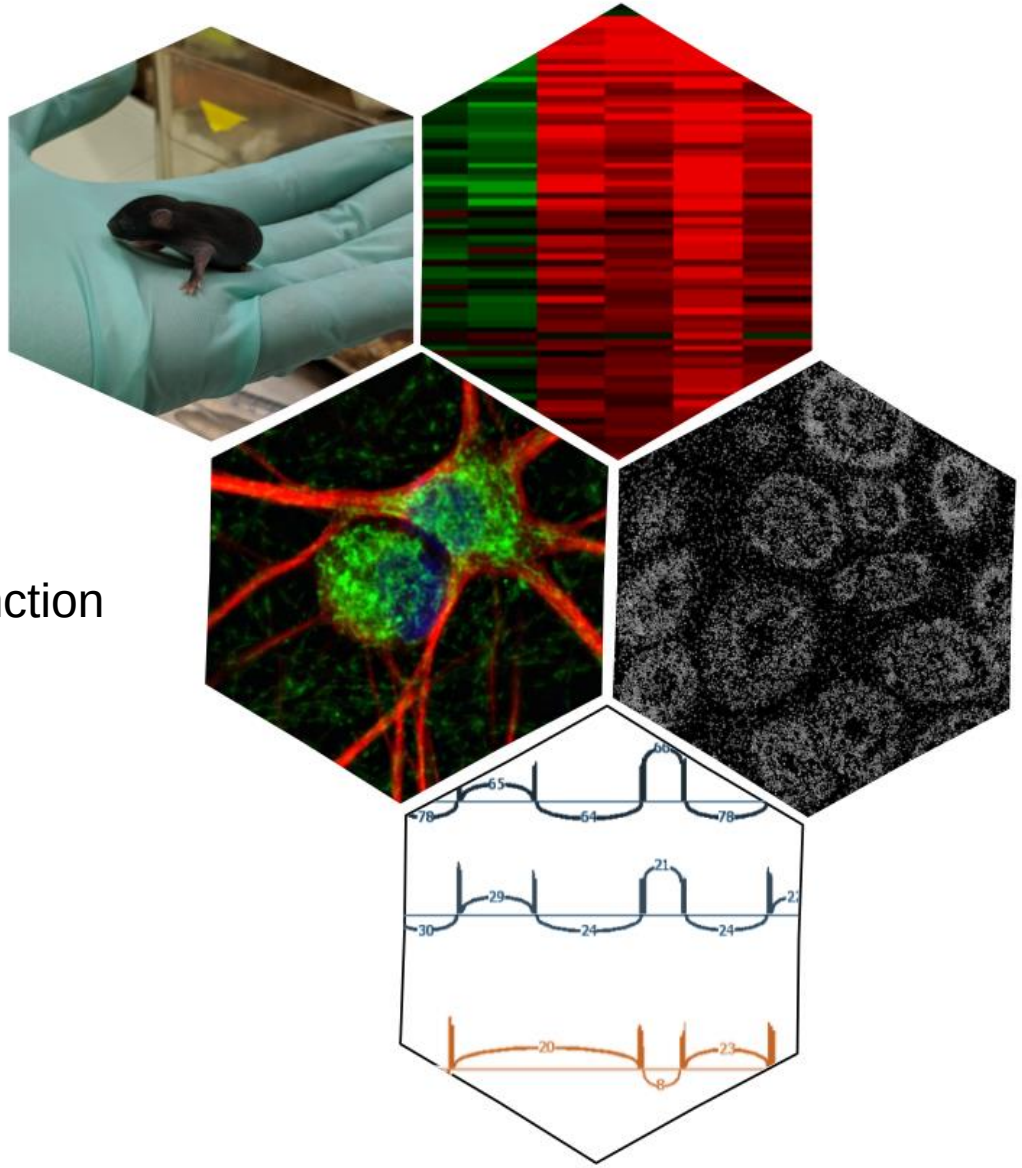
- Modeling disease
- Summarize mouse data
- Overview of future mouse projects (Inés)

- Review of patient cell data
  - Characterization of neuronal growth and function

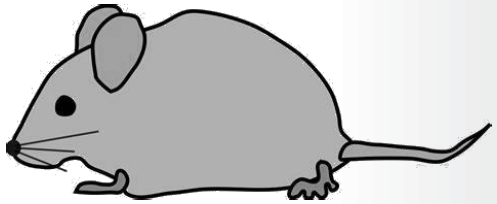
- “Mini brain” study and findings

- Therapeutic strategies:
  - AAV9 (Adam)
  - Antisense oligonucleotides (Manou)

- Conclusions



How to model disease



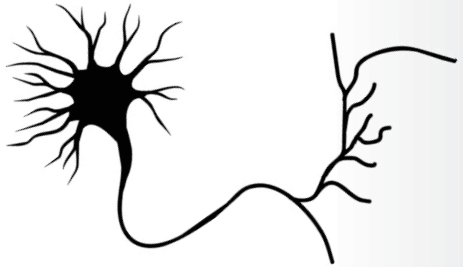
MOUSE

PROS

- Well established methods for analysis
- System-wide effects of a mutation
- Optimal for therapeutic testing
- Many variations can be made

CONS

- Can’t replicate all types of mutations
- Mice don’t always develop a disease phenotype
- Experiments can be very long
- Expensive



CELL

- Can be variant or patient-specific
- Can assess cell type-specific effects
- Respond to therapies
- Relatively quick

- Often takes time to optimize ideal conditions
- Cell behavior may change in 2D
- Expensive

Modeling LBSL in Mice

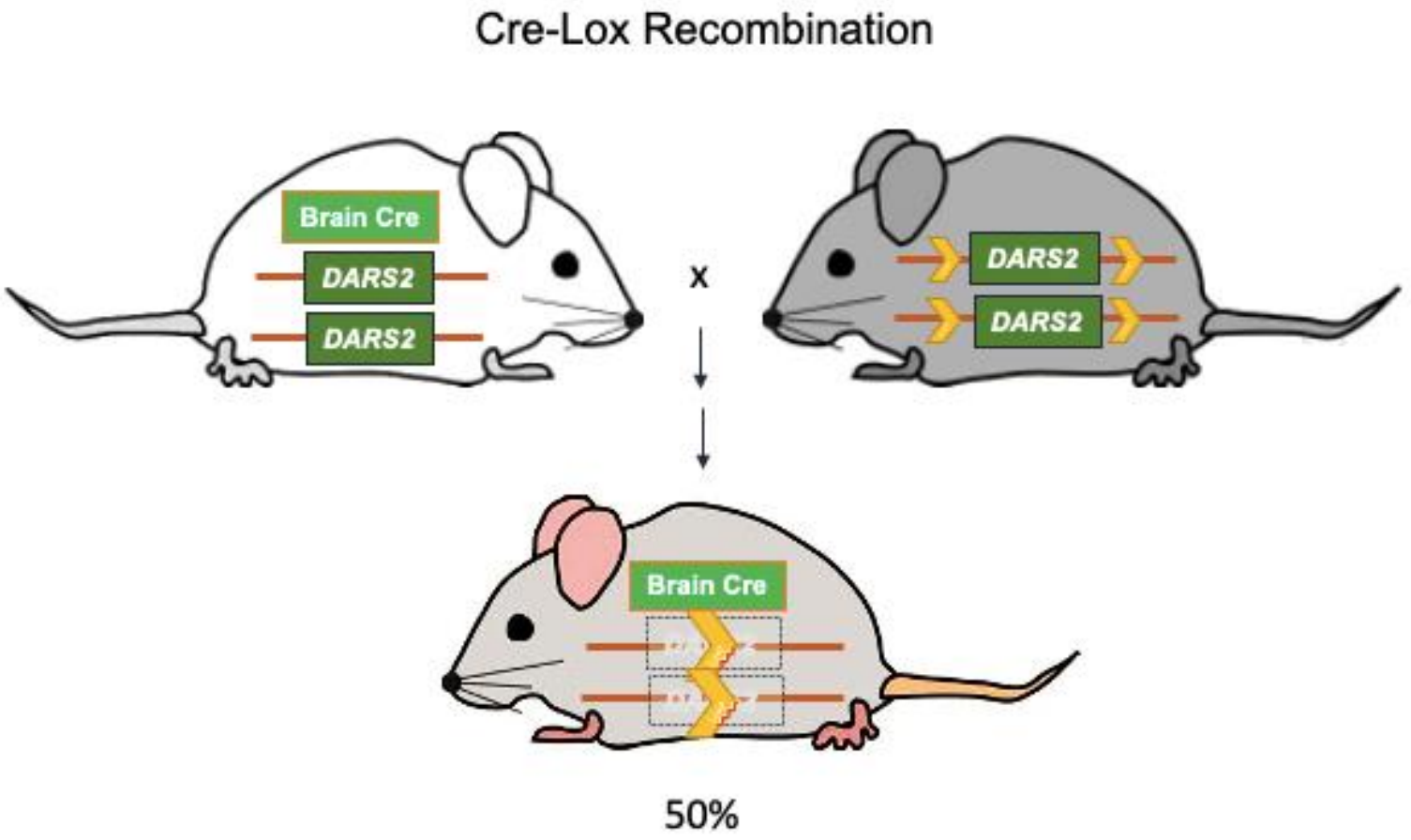
Inés Garofolo

Why use Transgenic Mice?

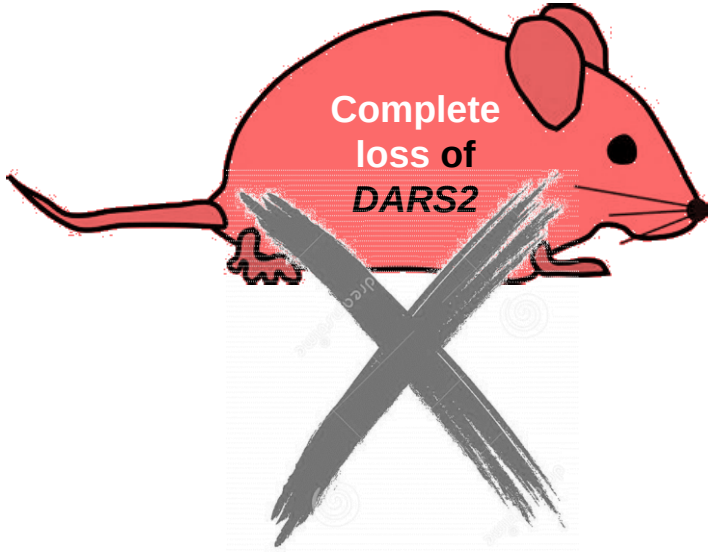
- Share ~70% of the same protein-coding gene sequences
- Can specifically target genes of interest in a controlled environment.
- Allows us to test new therapy treatments at a faster pace

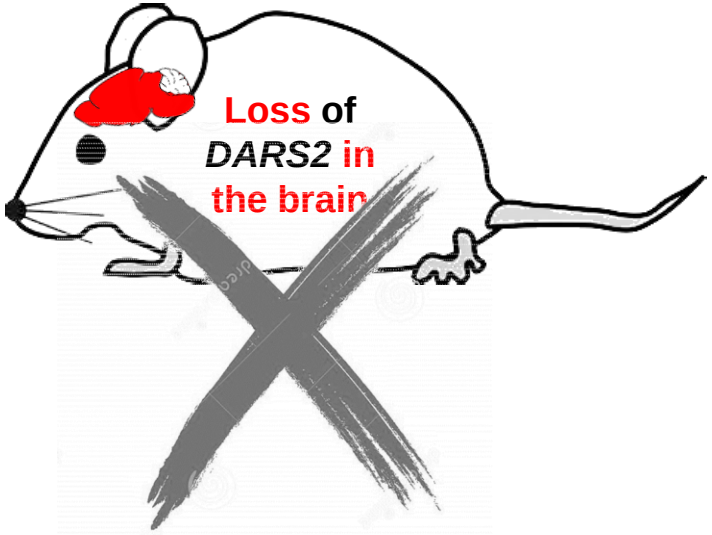
DARS2 mouse model

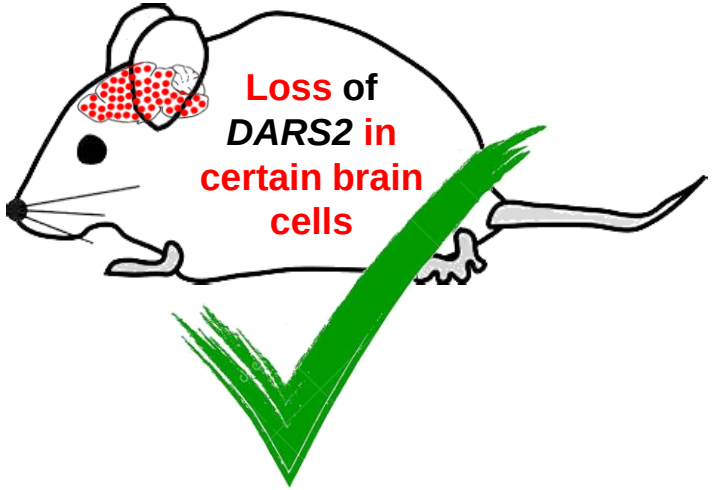
DARS2: Codes for mitochondrial aspartyl-tRNA synthetase



Modifying *Dars2* in mice



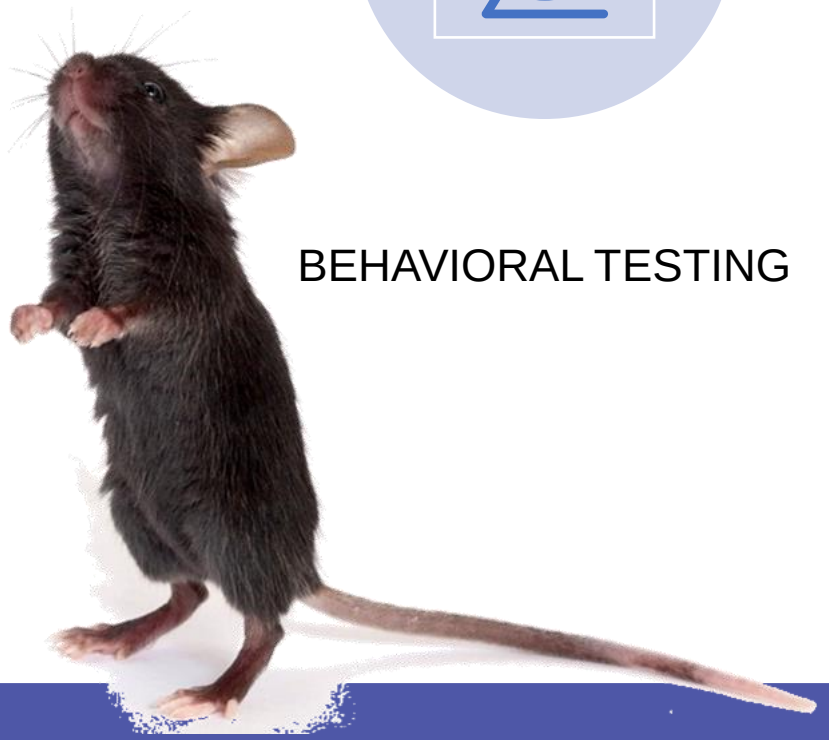




Full knockout of DARS2 is embryonic lethal

CamKIIα: subtype of “excitatory” neuron found in the hippocampus and cortex

Methods of Measurement



BEHAVIORAL TESTING

TISSUE SECTIONING AND STAINING

VISUALIZATION OF TARGET CELLS AND PATHWAYS

Dars2 deletion in CamKIIα leads to progressive increased activity

Experimental Neurology 326 (2020) 113164

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journal homepage: www.elsevier.com/locate/yexnr

Research Paper

Neuronal ablation of mt-AspRS in mice induces immune pathway activation prior to severe and progressive cortical and behavioral disruption

Christina L. Nemeth[a], Sophia N. Tomlinson[a], Melissa Rosen[a], Brett M. O'Brien[a], Oscar Larraza[a], Mahim Jain[b], Connor F. Murray[a], Joel S. Marx[a], Michael Delannoy[c], Amena S. Fine[a,d], Dan Wu[e], Aleksandra Trifunovic[f], Ali Fatemi[a,g,*]

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[g] Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD, USA

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Leukoencephalopathy
Mitochondria
DARS2
tRNA synthetase

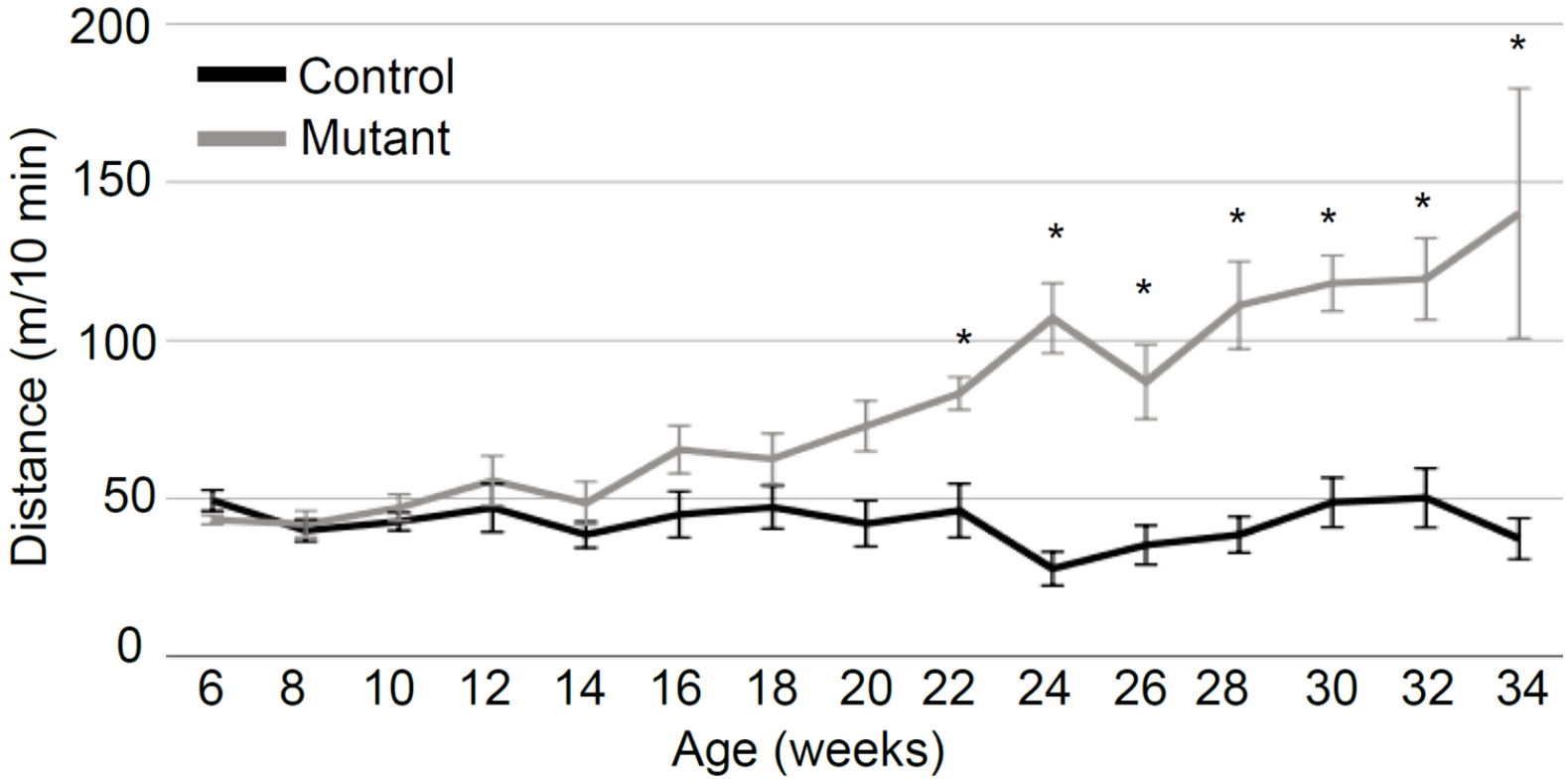
ABSTRACT

Leukoencephalopathy with brainstem and spinal cord involvement and lactate elevation (LBSL) is a rare, slowly progressive white matter disease caused by mutations in the mitochondrial aspartyl-tRNA synthetase (mt-AspRS, or DARS2). While patients show characteristic MRI T2 signal abnormalities throughout the cerebral white matter, brainstem, and spinal cord, the phenotypic spectrum is broad and a multitude of gene variants have been associated with the disease. Here, *Dars2* disruption in CamKIIα-expressing cortical and hippocampal neurons results in slowly progressive increases in behavioral activity at five months, and culminating by nine months as severe brain atrophy, behavioral dysfunction, reduced corpus callosum thickness, and microglial morphology indicative of neuroinflammation. Interestingly, RNAseq based gene expression studies performed prior to the presentation of this severe phenotype reveal the upregulation of several pathways involved in immune activation, cytokine production and signaling, and defense response regulation. RNA transcript analysis demonstrates that activation of immune and cell stress pathways are initiated in advance of a behavioral phenotype and cerebral deficits. An understanding of these pathways and their contribution to significant neuronal loss in CamKII-*Dars2* deficient mice may aid in deciphering mechanisms of LBSL pathology.

1. Introduction

Leukoencephalopathy with brainstem and spinal cord involvement and lactate elevation (LBSL) is a rare, autosomal recessive disorder characterized by slowly progressive spasticity, ataxia, proprioceptive deficits, and in some cases, cognitive decline. Most patients harbor compound heterozygous mutations in the *DARS2* gene (Tzoulis et al., 2012) which encodes mitochondrial aspartyl-tRNA synthetase (mt-AspRS), a ubiquitously expressed enzyme which charges tRNA molecules with cognate amino acids essential for mitochondrial protein translation. Diagnosis of LBSL includes identification of pyramidal, spectroscopy (Scheper et al., 2007; van Berge et al., 2013). Age of onset and degree of disability vary widely with genotypic variation complicating a genotype-phenotype correlation (van Berge et al., 2014). With this said, more severe early infantile onset cases with seizures, microcephaly and global delay have also been reported (Sauter et al., 2015; Steenweg et al., 2012). Since the first descriptions of LBSL, human diseases have now been associated with each of the 19 mitochondrial tRNA synthetases, all presenting with diverse clinical symptoms (Sissler et al., 2017; Theisen et al., 2017).

Recapitulating *DARS2* deficiency and pathology in mouse or cell systems has proven difficult. Previous efforts to develop model animals



Nemeth et al., 2019

Dars2 deletion in CamKIIα leads to progressive increased activity

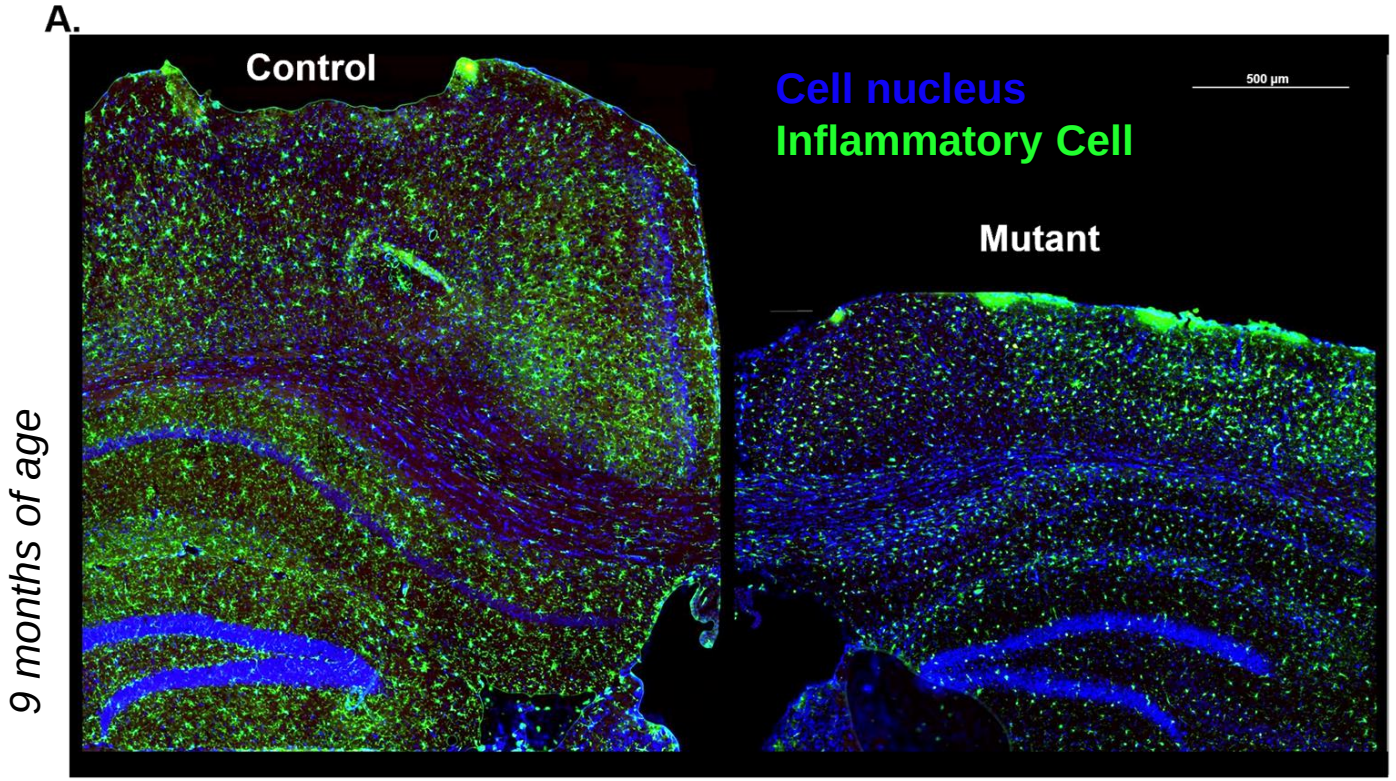
Methods of Measurement

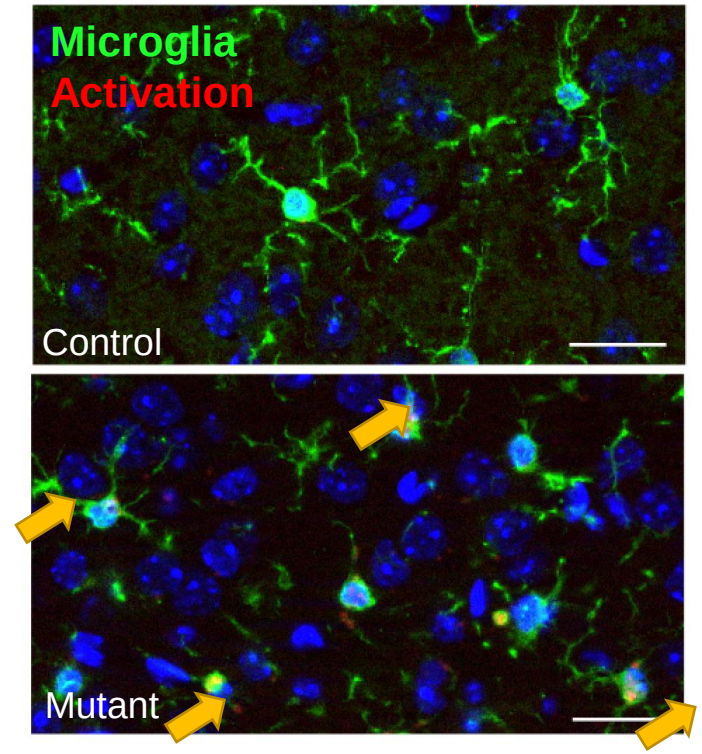
BEHAVIORAL TESTING

TISSUE SECTIONING AND STAINING

VISUALIZATION OF TARGET CELLS AND PATHWAYS

Dars2 deletion in CamKIIα leads to neuronal loss and inflammation





Nemeth et al., 2019

Methods of Measurement

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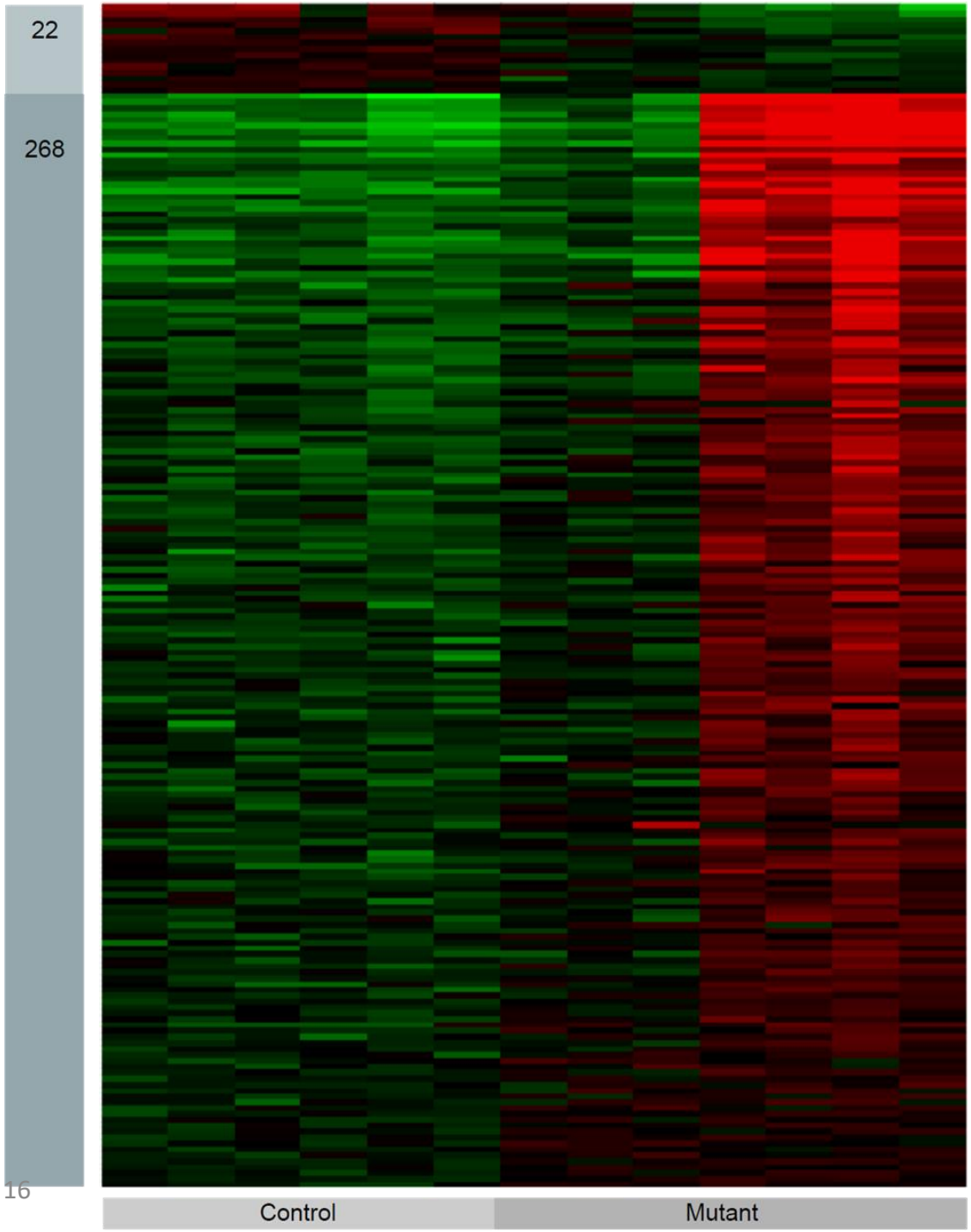
TISSUE SECTIONING AND STAINING

VISUALIZATION OF TARGET CELLS AND PATHWAYS



GO Biological Process	Adj *p*
Trans-synaptic signaling	1.7e-05
Chemical synaptic transmission	1.7e-05
Anterograde trans-synaptic signaling	1.7e-05
Synaptic signaling	1.7e-05
Synapse organization	3.2e-05
Immune response	3.9e-16
Response to biotic stimulus	1.0e-13
Innate immune response	1.8e-12
Immune effector process	1.1e-09
Reg of immune response	2.0e-08
Positive regulation of immune system process	1.5e-07
Cytokine production	1.9e-07
Inflammatory response	2.7e-07
Positive regulation of immune response	5.7e-07
Reg of cytokine production	5.7e-07
Response to cytokine	5.1e-07
Reg of defense response	2.8e-06
Adaptive immune response	6.4e-06
Leukocyte mediated immunity	8.8e-06
Defense resp to bacterium	4.1e-05
Response to virus	2.3e-05
Adaptive immune response based on somatic recombination of immune receptors built from immunoglobulin superfamily domains	3.6e-05
Lymphocyte mediated immunity	3.8e-05
Activation of immune response	2.8e-05
Cellular response to cytokine stimulus	1.9e-05

RNA Sequencing

Each row represents a gene's activity

Gene activity increased

Unchanged

Gene activity decreased

LBSL mice show strong increase in inflammatory genes

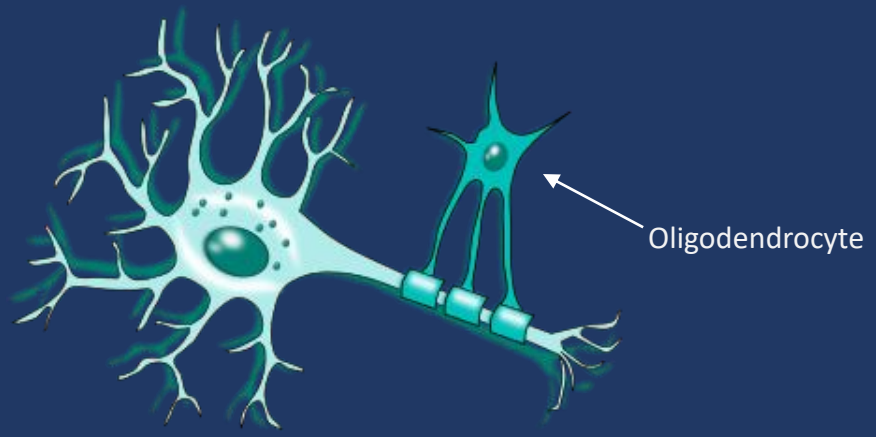
Nemeth et al., 2019

Downside of CamkIIα model: not precisely comparable to patients

New Models of Interest

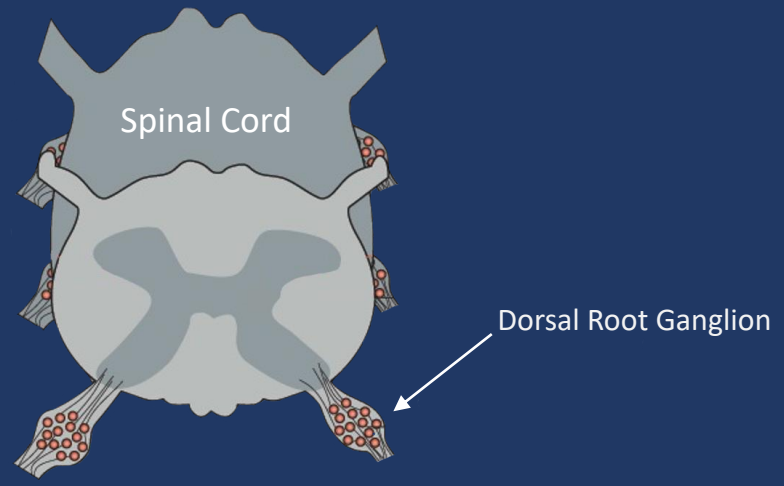
Oligodendrocyte Cre KO

- Deletion of *Dars2* in early white matter cells
- Currently building colony

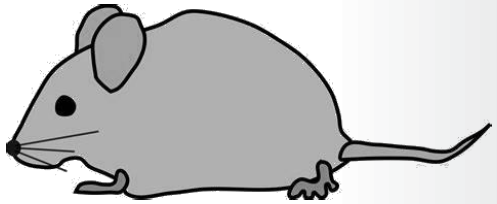


Advillin Cre KO

- Deletion of *Dars2* in the dorsal root ganglia
- Arrived last week



How to model disease



MOUSE

PROS

- Well established methods for analysis
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CONS

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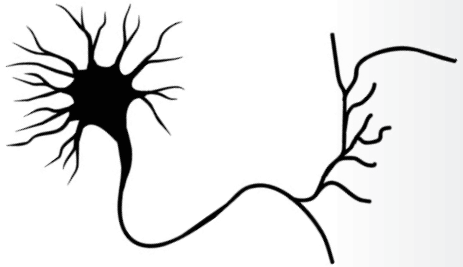

CELL

- Can be variant or patient-specific
- Can assess cell type-specific effects
- Respond to therapies
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- Often takes time to optimize ideal conditions
- Cell behavior may change in 2D
- Expensive

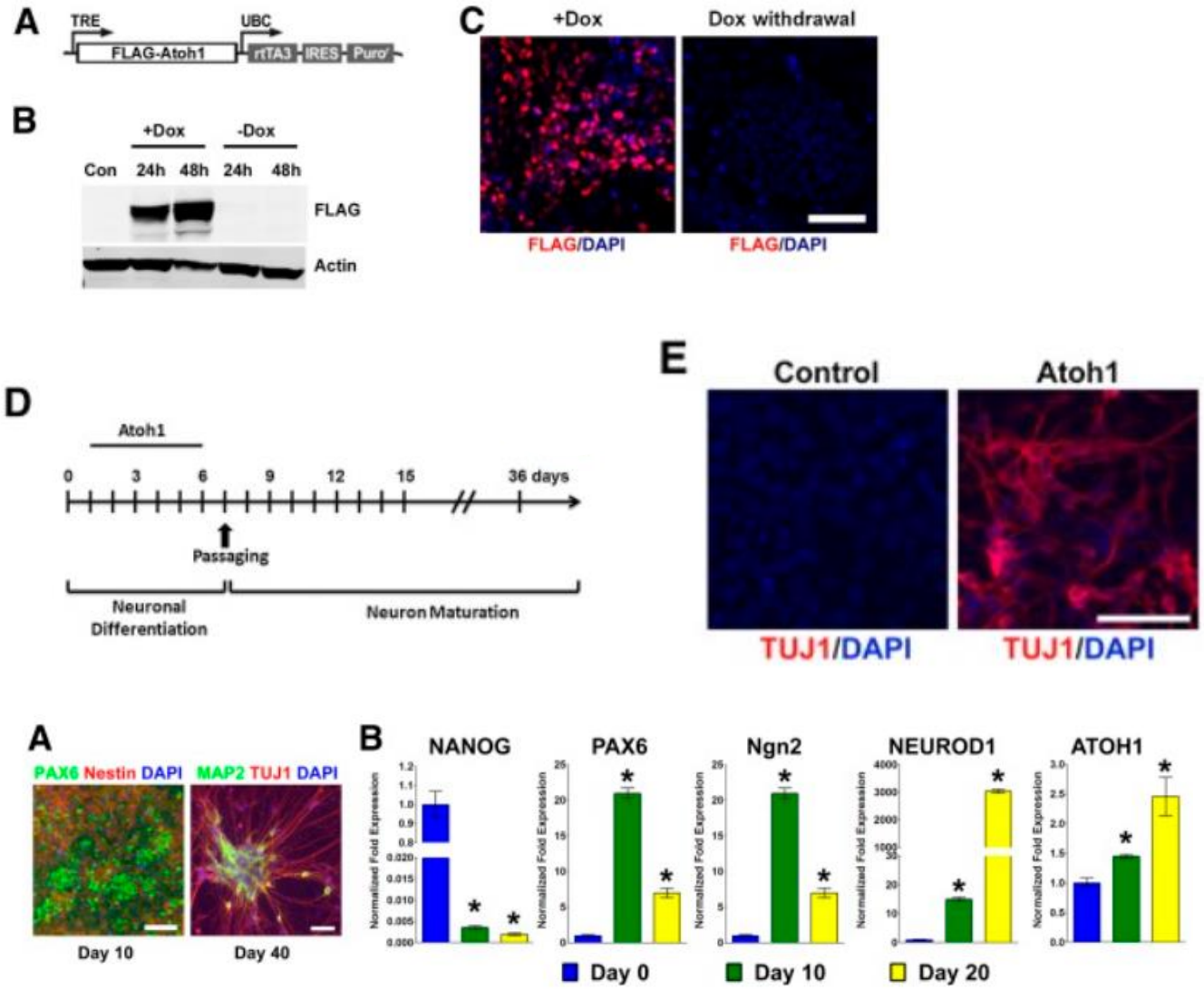
How do we make iPSCs?

Mingyao Ying, PhD

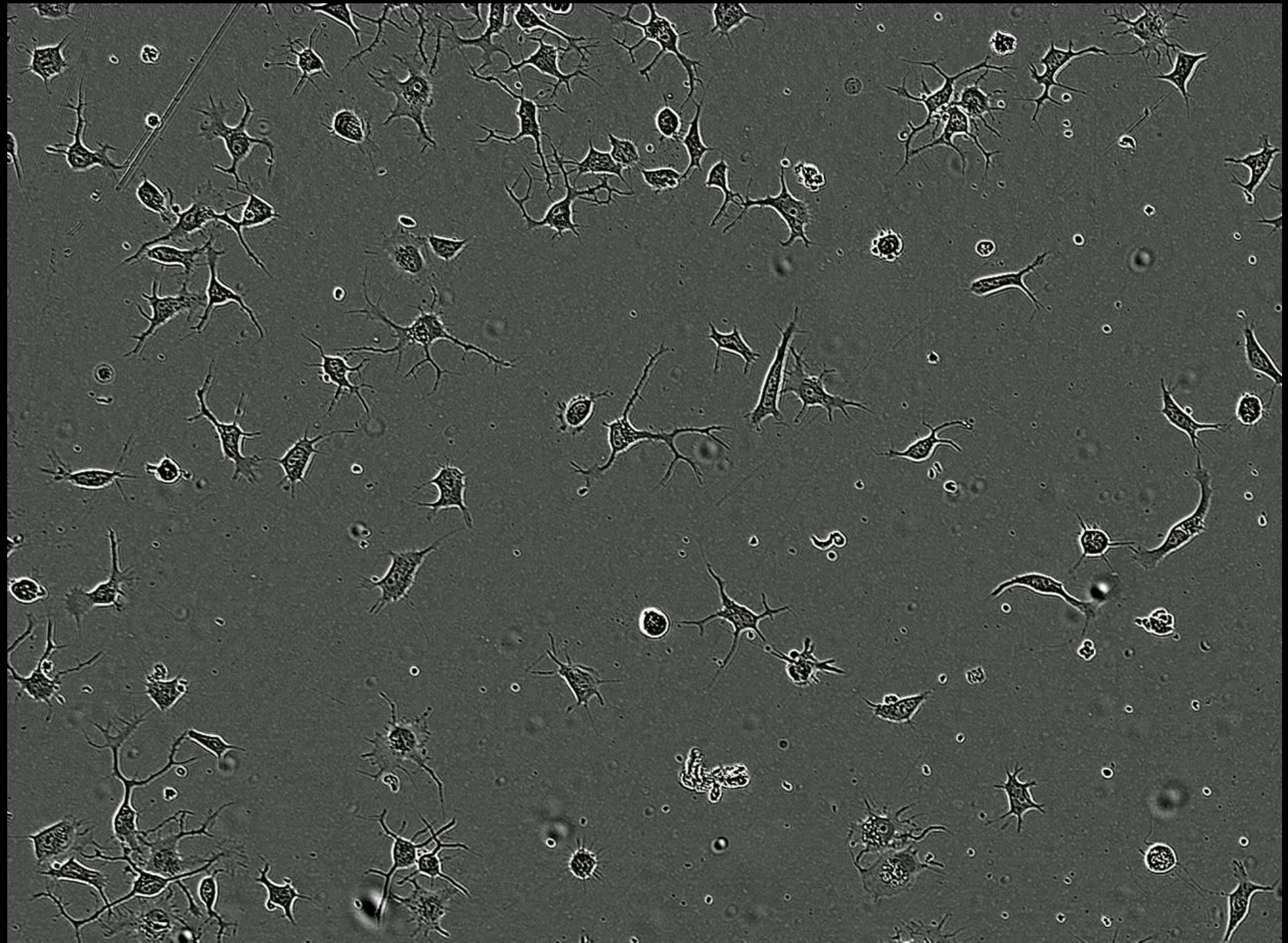
Figure modified from R&D Systems, Inc

iPSC to Motor Neurons

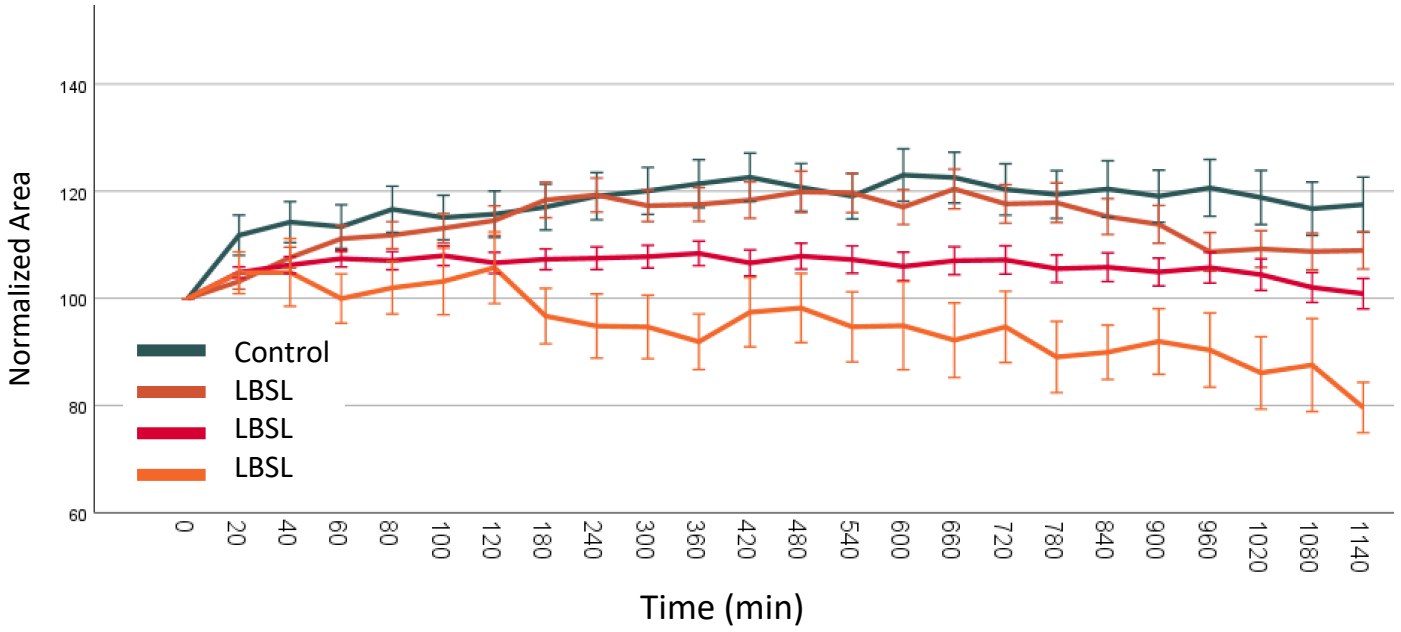
- 7 patient lines created from PBMCs collected at Kennedy Krieger Institute
- Reprogrammed at Cedars Sinai Induced Pluripotent Stem Cell Core (Los Angeles, CA)
- Lentiviral transduction with Ngn2
- Age and sex matched controls



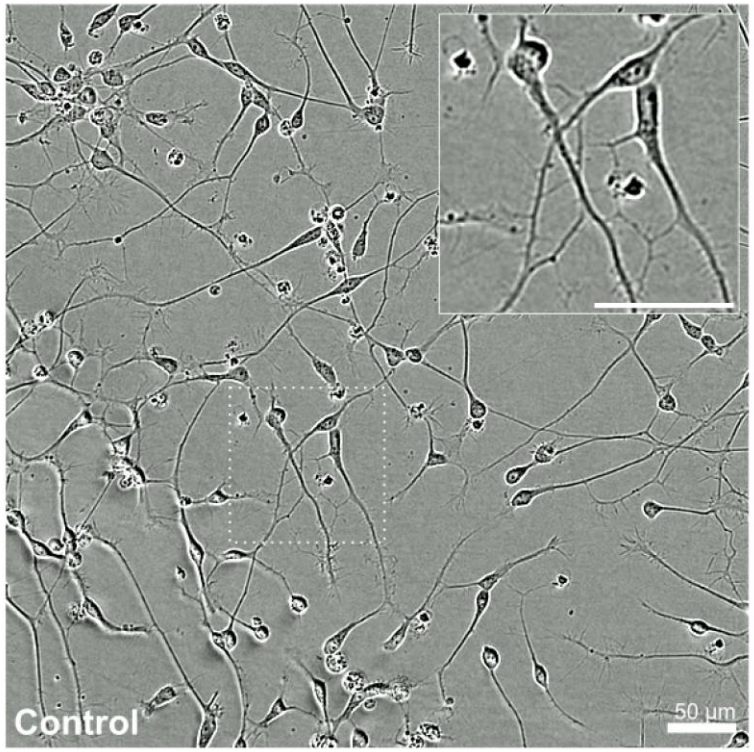
Sagal et al., 2014; *Stem Cell Transl Med*

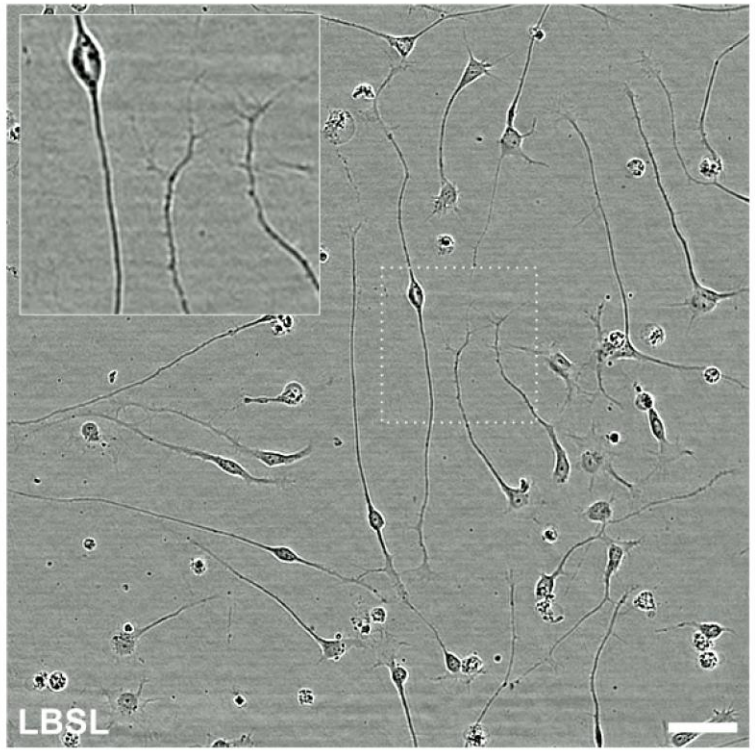


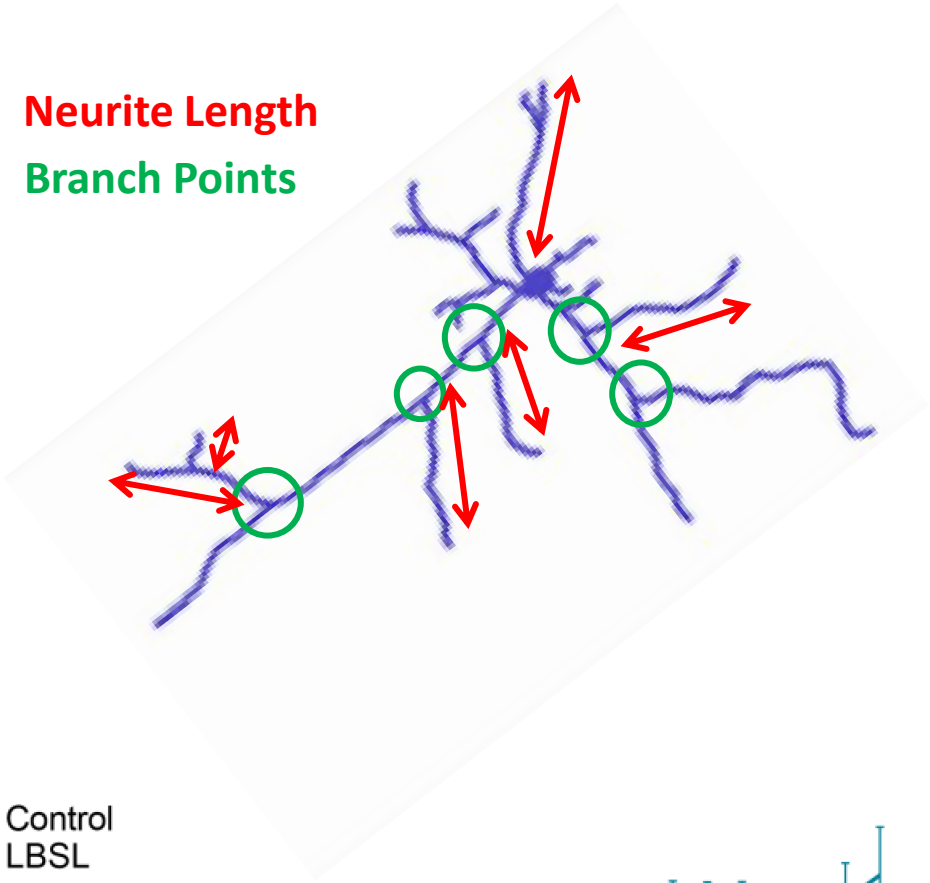
Analyze growth of patient-derived neurons

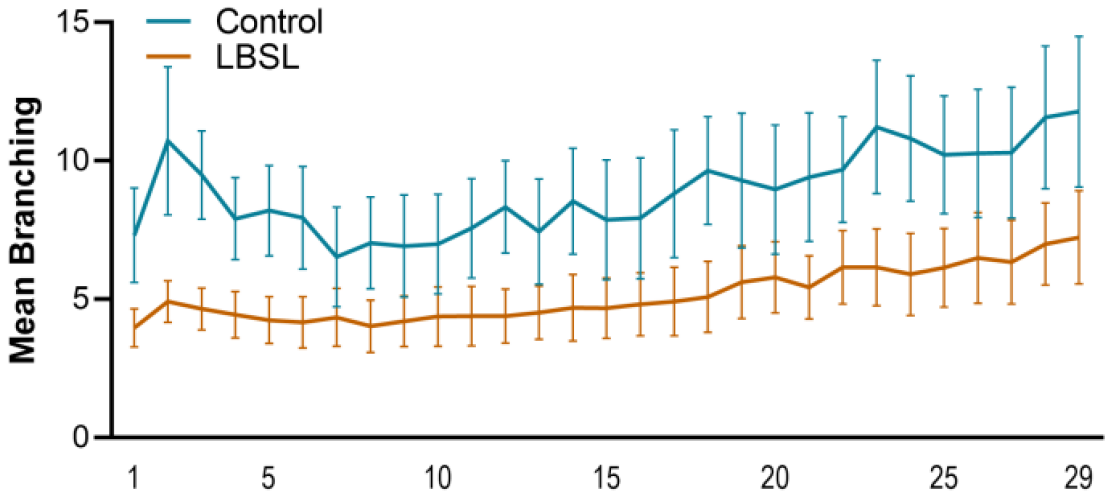


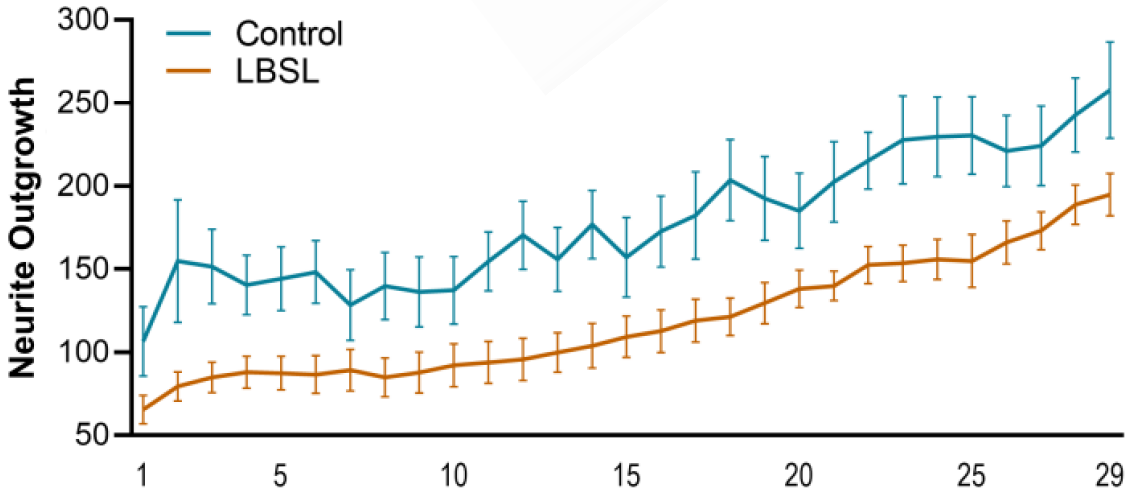
Using a microscope and imager that stays with the cells in an incubator


Control
50 µm

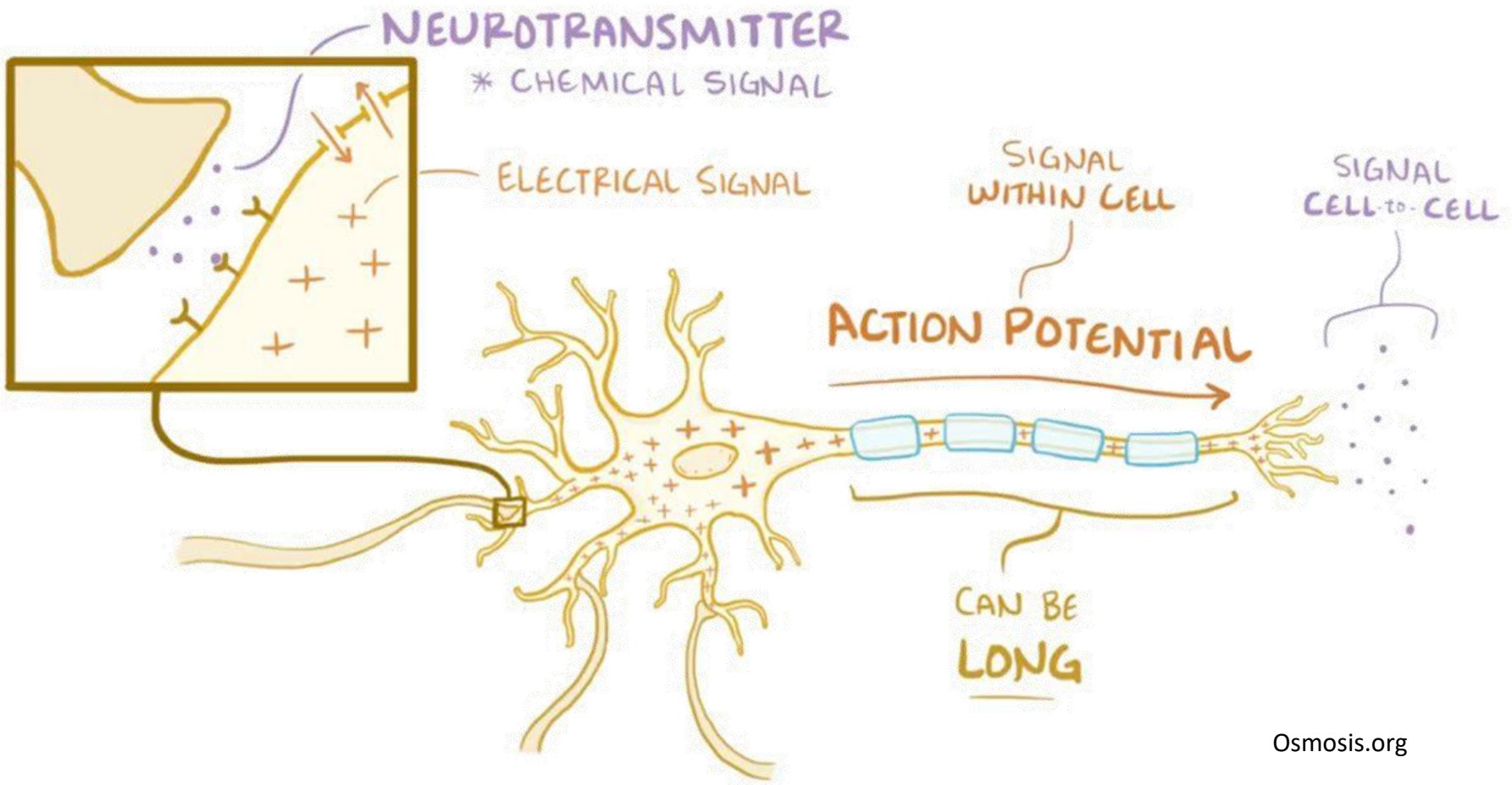

LBSL


Neurite Length
Branch Points


Mean Branching
Control
LBSL
15
10
5
0
1
5
10
15
20
25
29
Hours after placement in maturation media

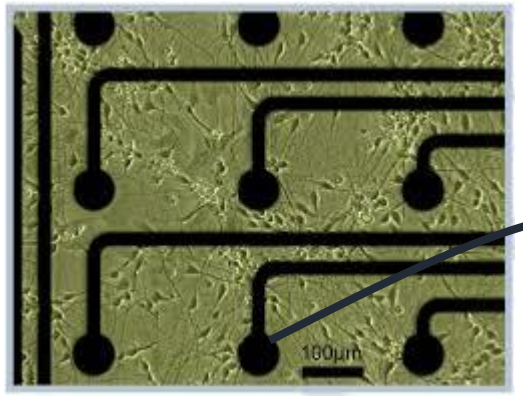

Neurite Outgrowth
Control
LBSL
300
250
200
150
100
50
1
5
10
15
20
25
29
Hours after placement in maturation media

Neurons are “electrically excitable”

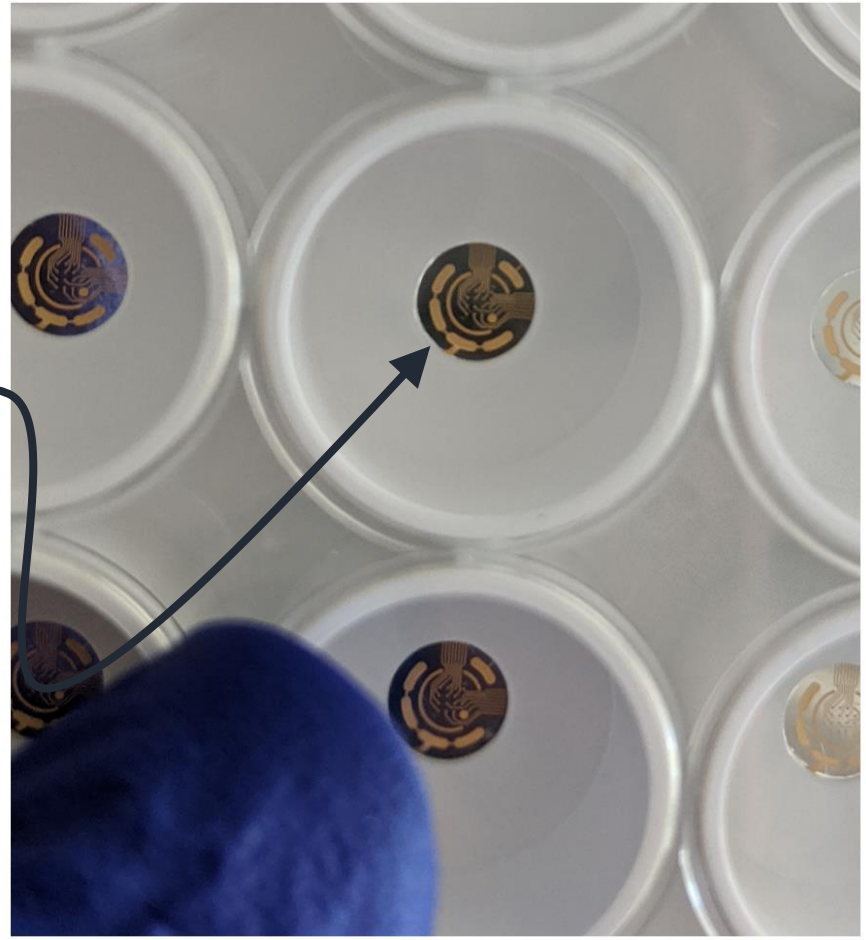


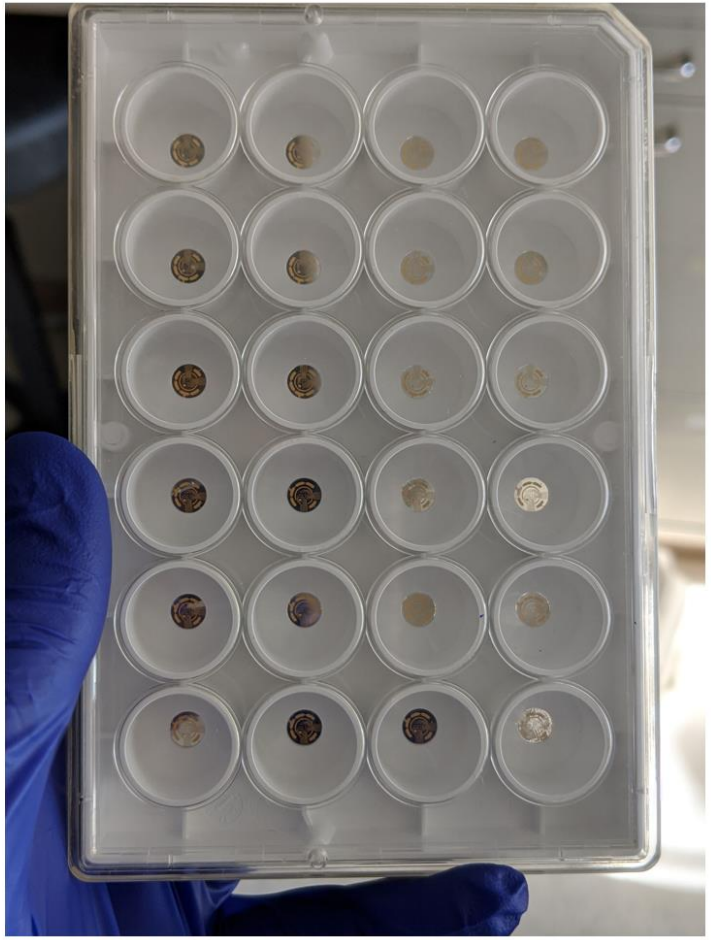
Osmosis.org

Measuring the electrical activity of neurons



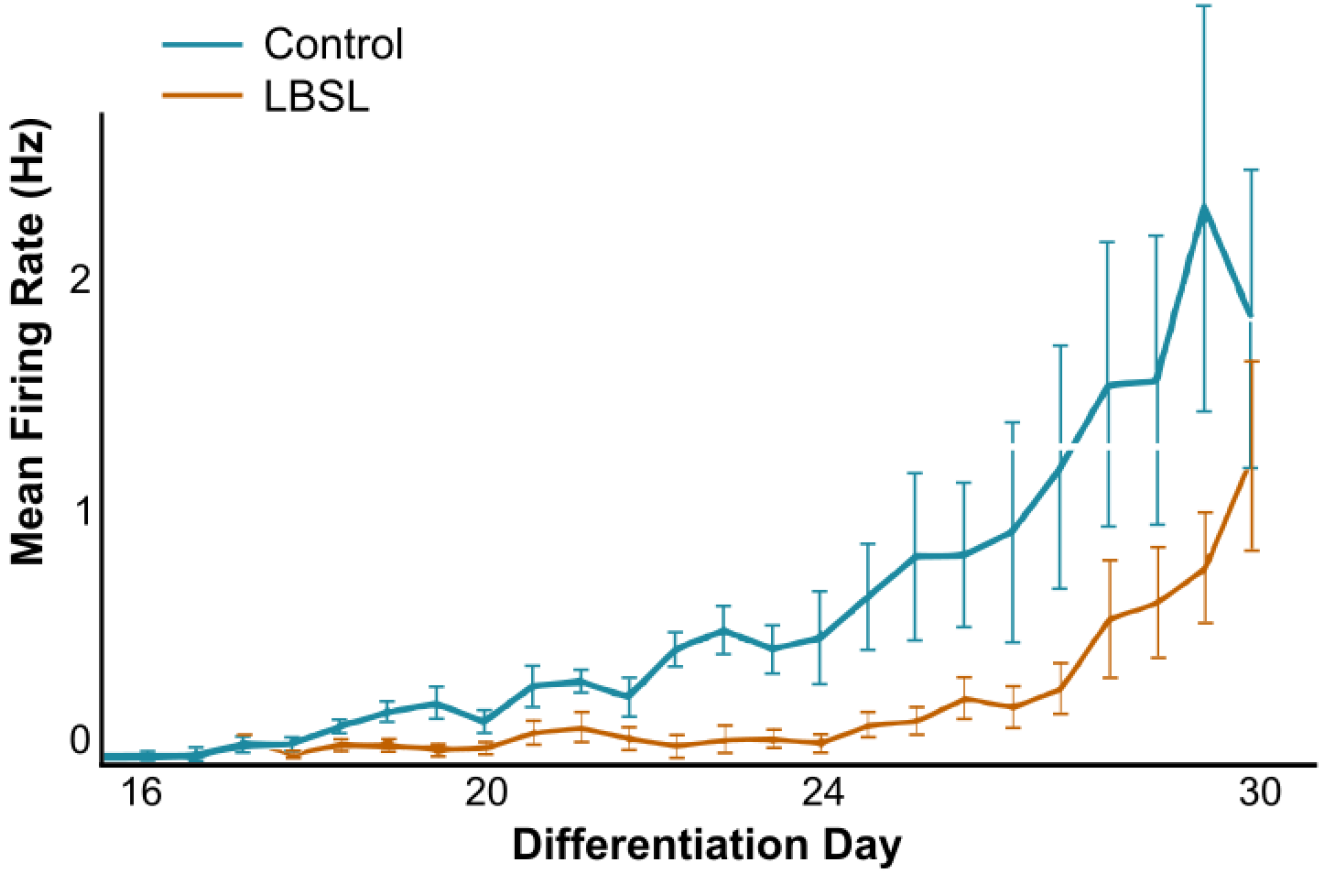
Cells are grown in a dish over top of very small electrodes.



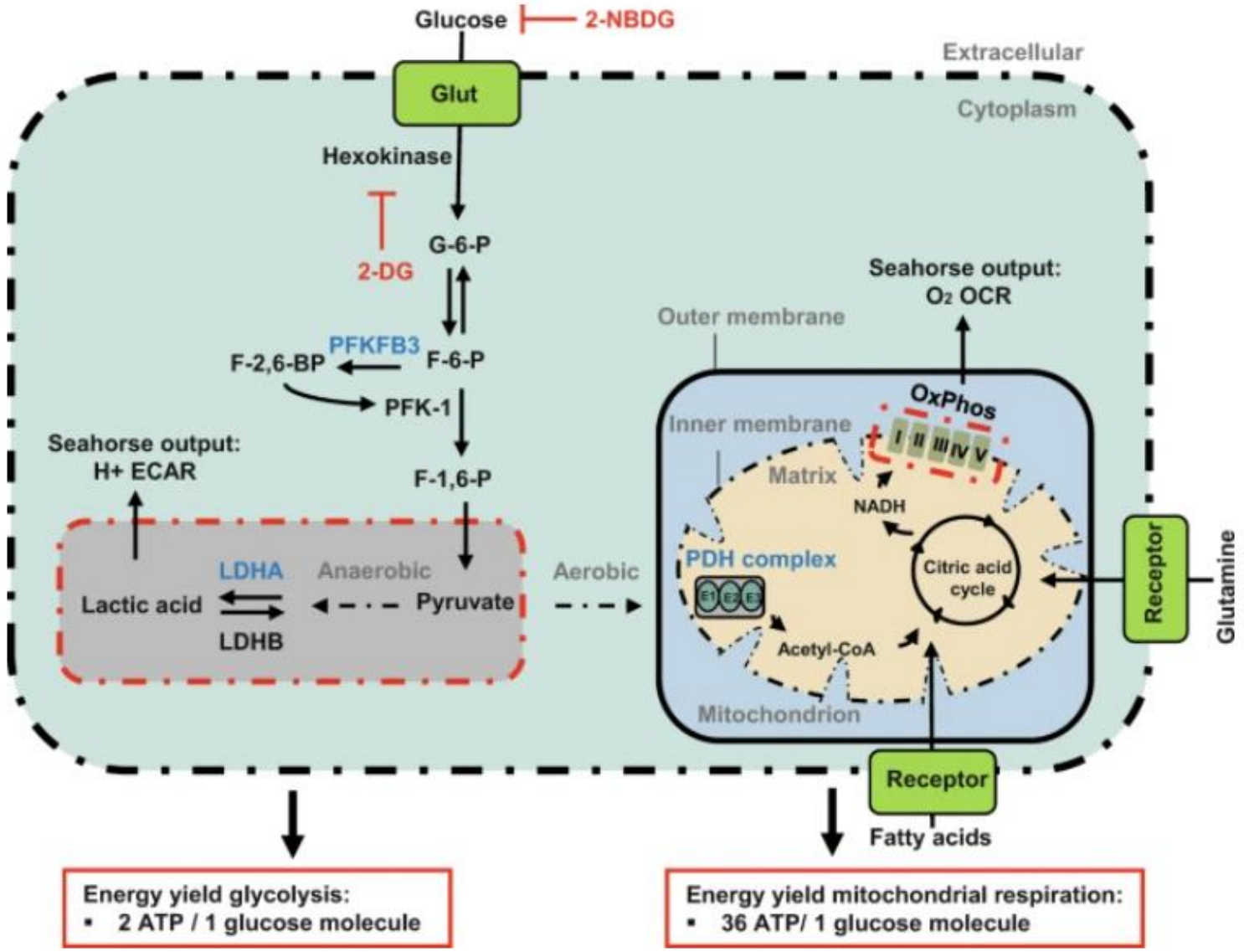


LBSL motor neurons show decreased spontaneous firing

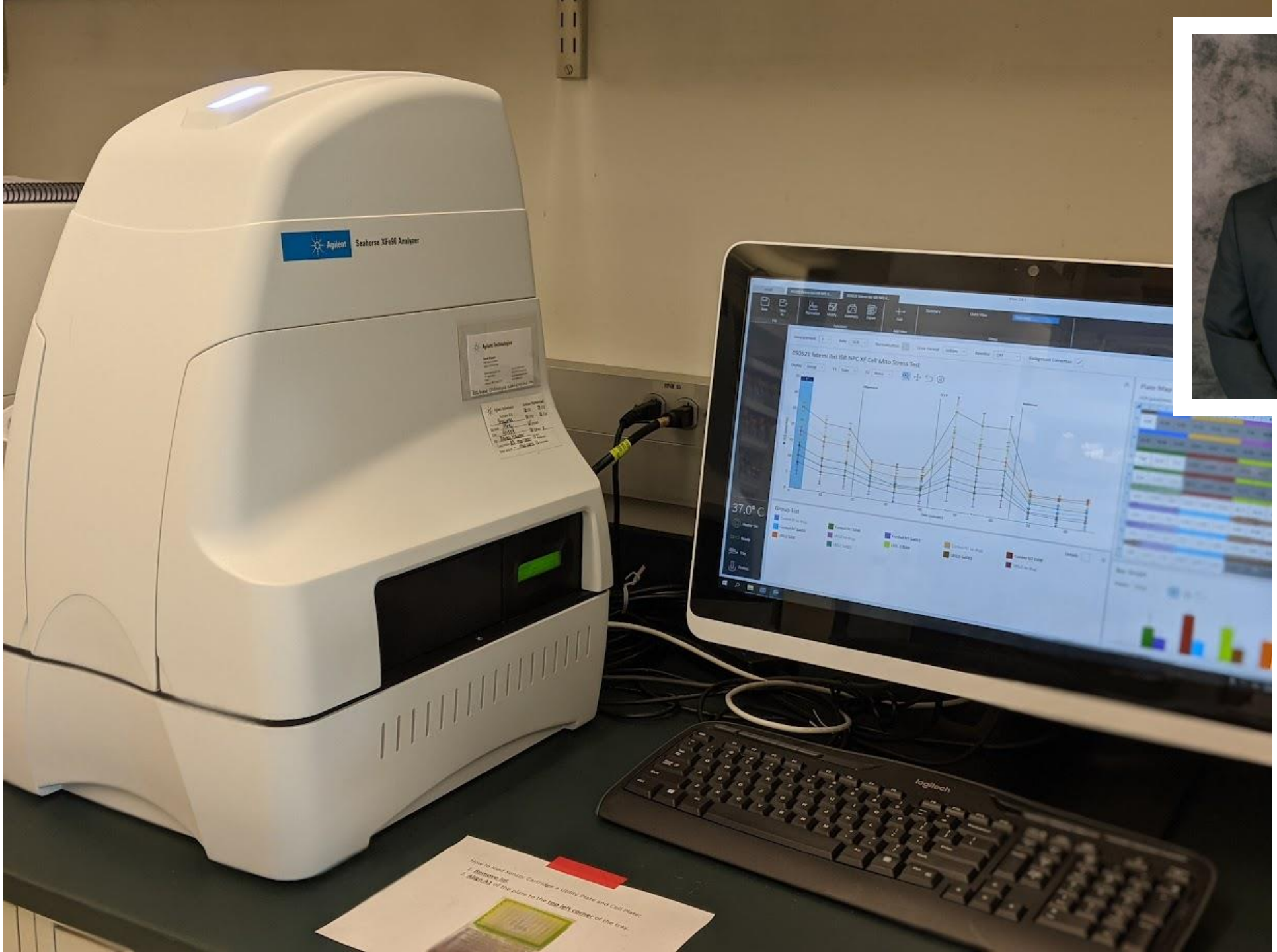
Axion Biosystems
Microelectrode Array system



LBSL motor neurons show diminished mitochondrial activity

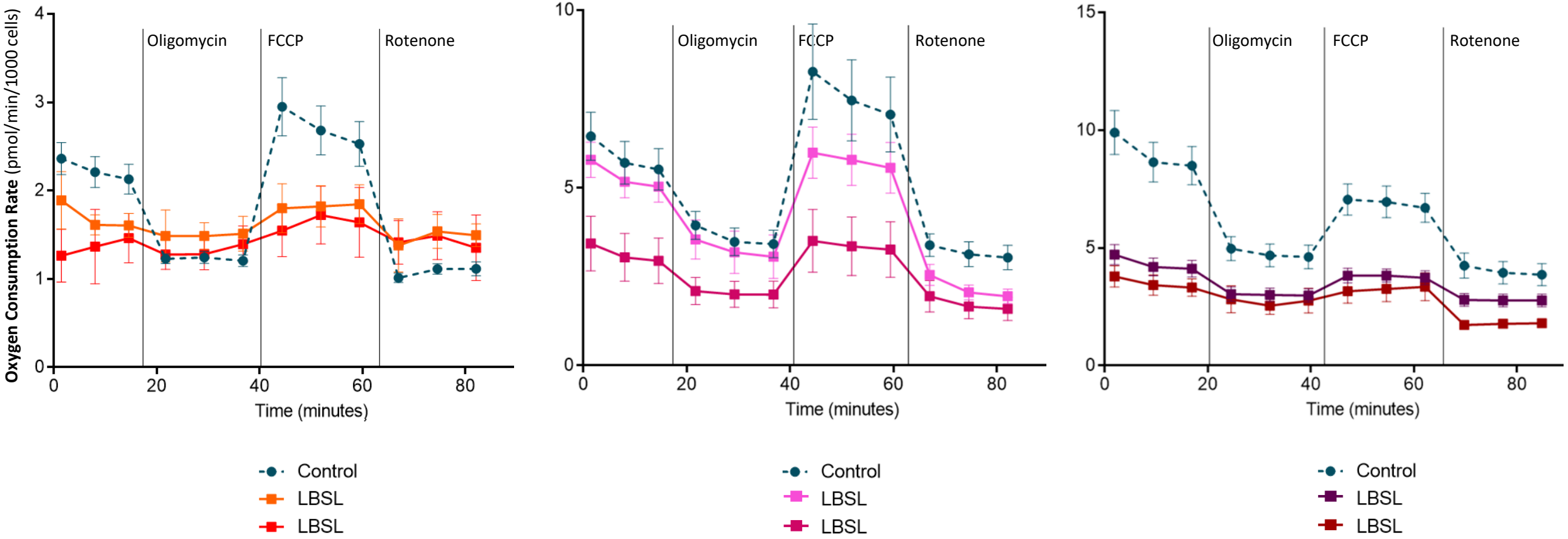


Yetkin-Arik et al., 2019; *Nature*

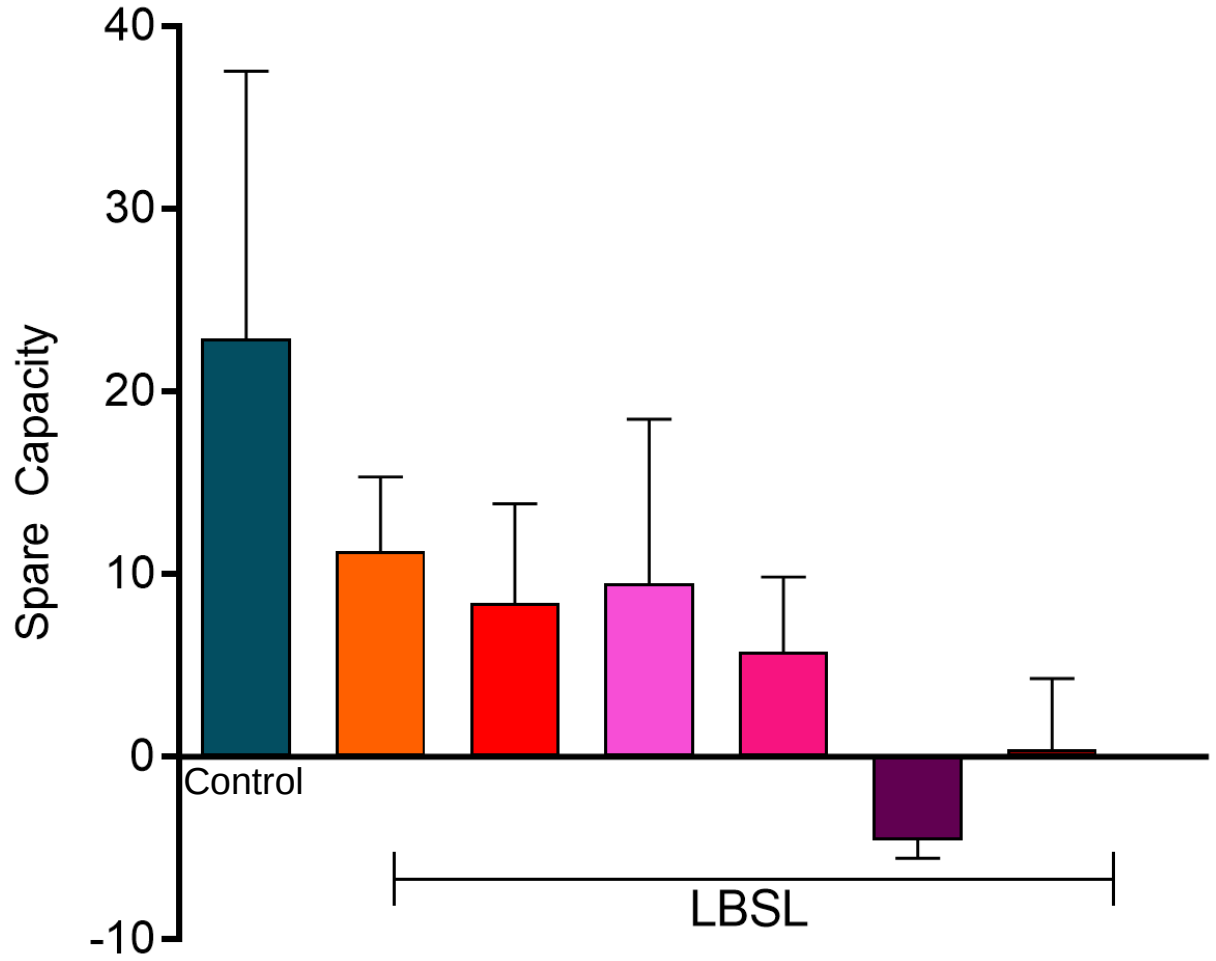


Dr. Joseph Scafidi

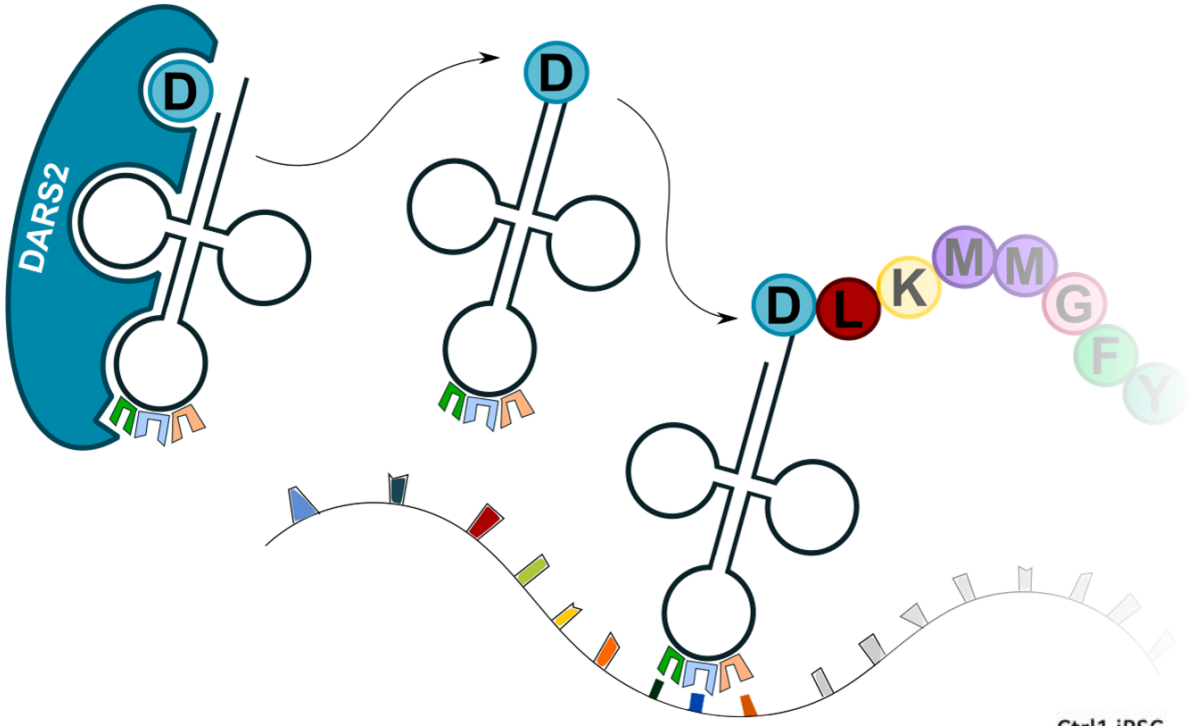
LBSL motor neurons show diminished mitochondrial activity

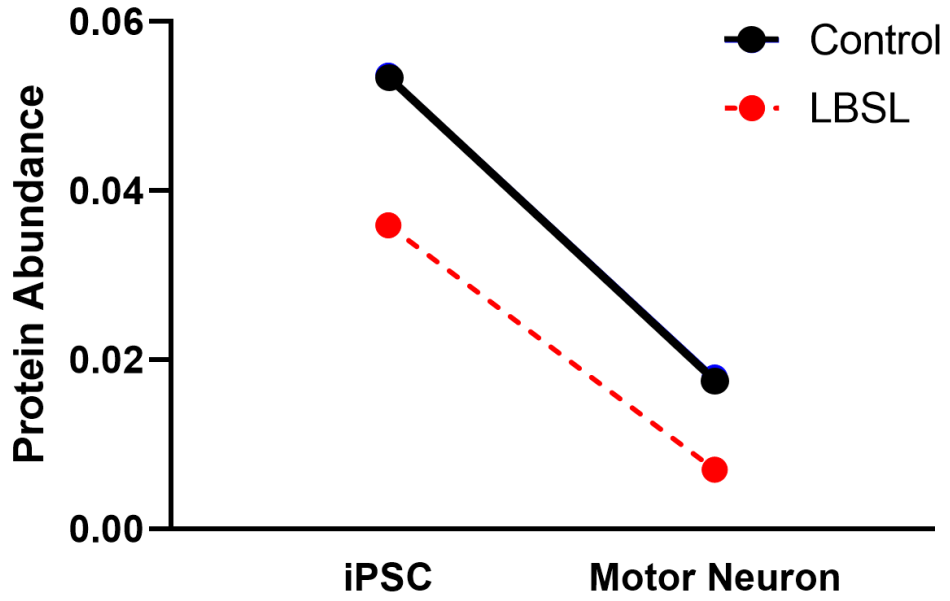


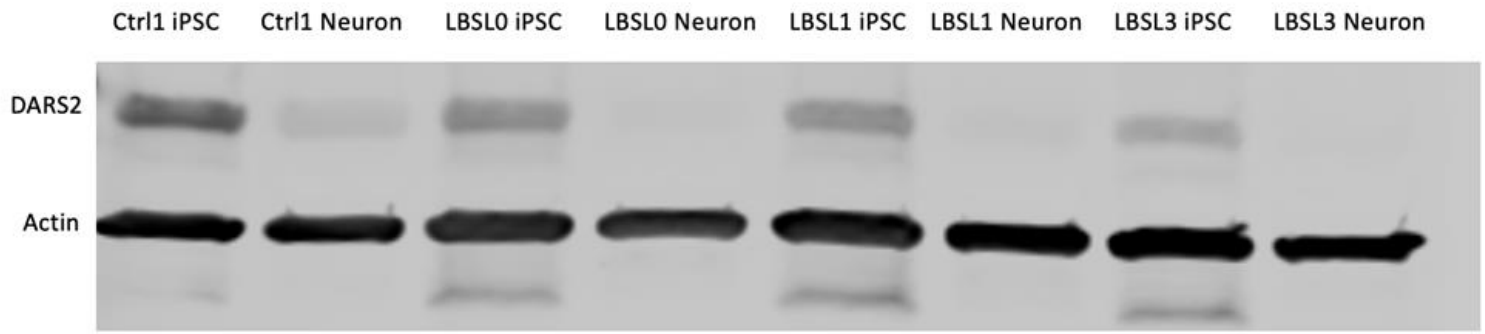
LBSL motor neurons show diminished mitochondrial activity



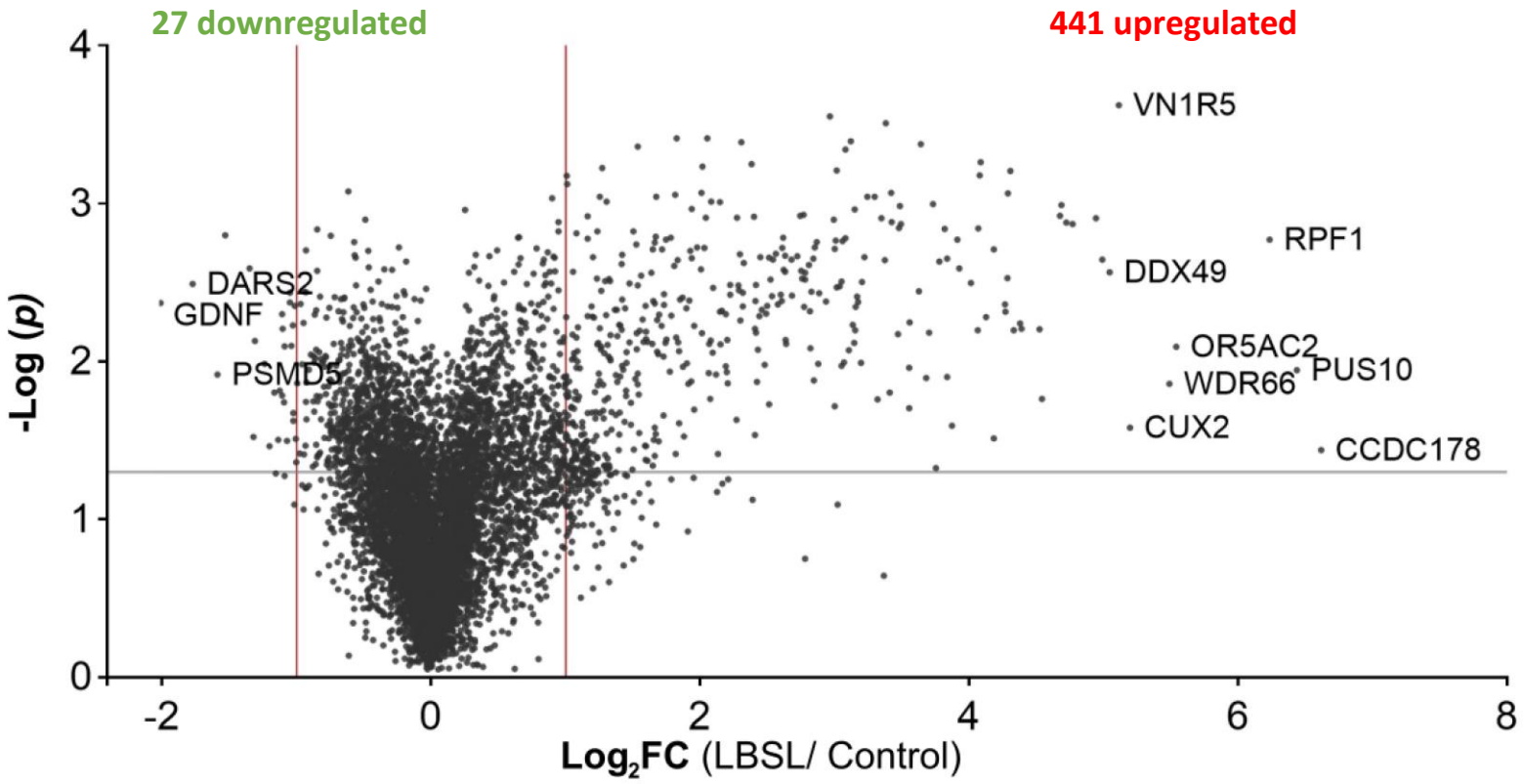
LBSL patient cells show reduced DARS2 protein

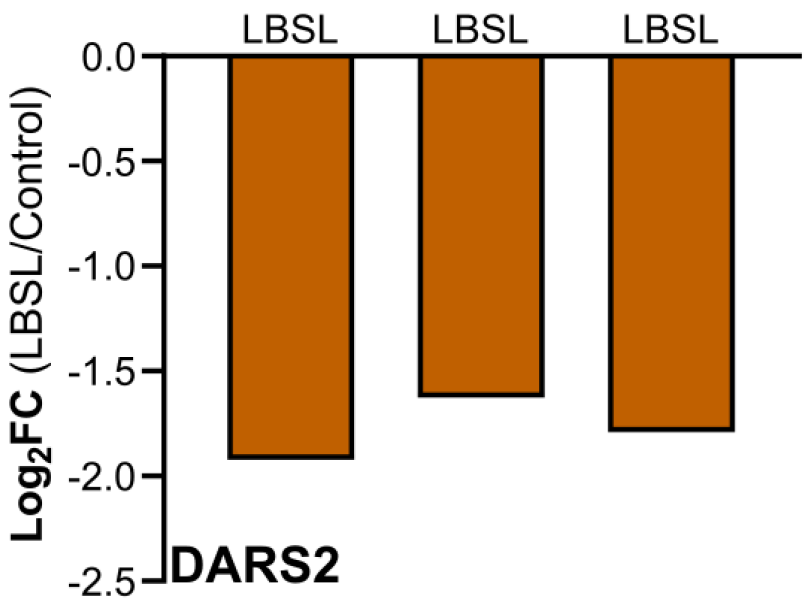




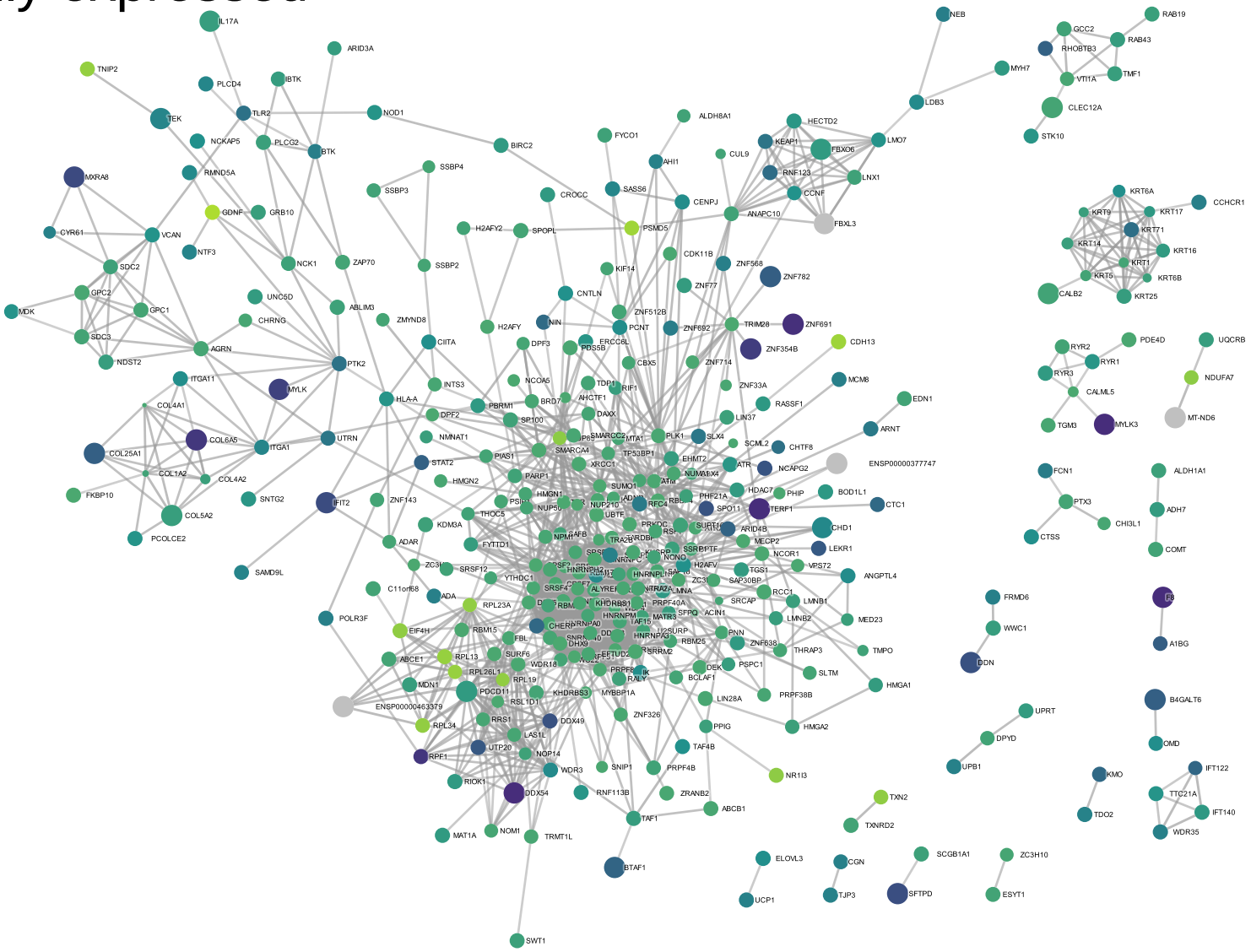


Proteomics of “mitochondrial-enriched” fraction

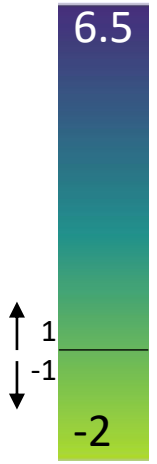




Differentially expressed

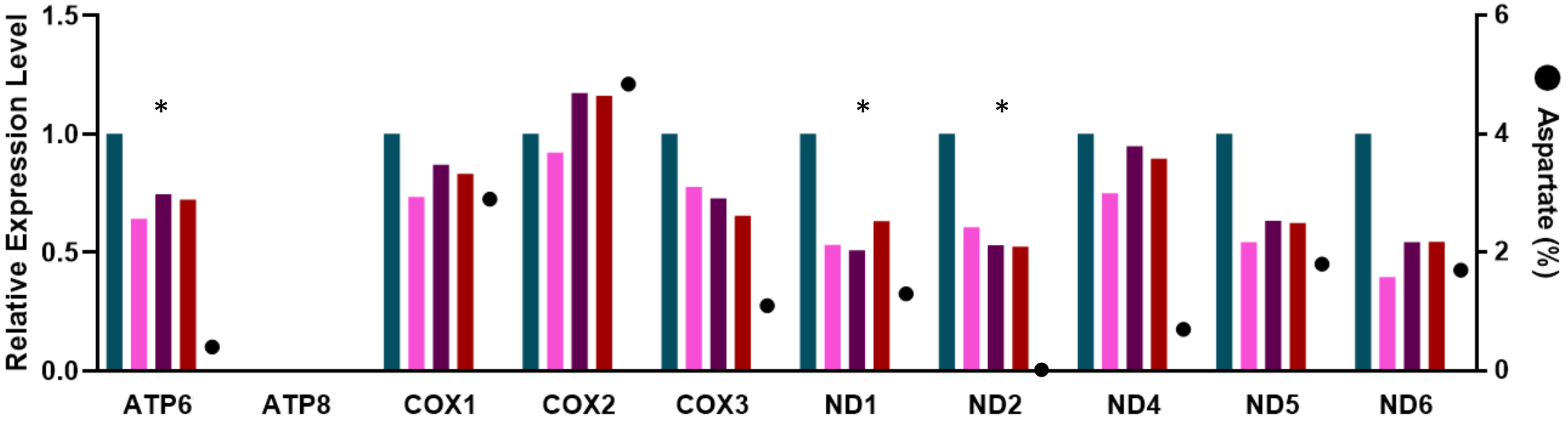


Fold Change

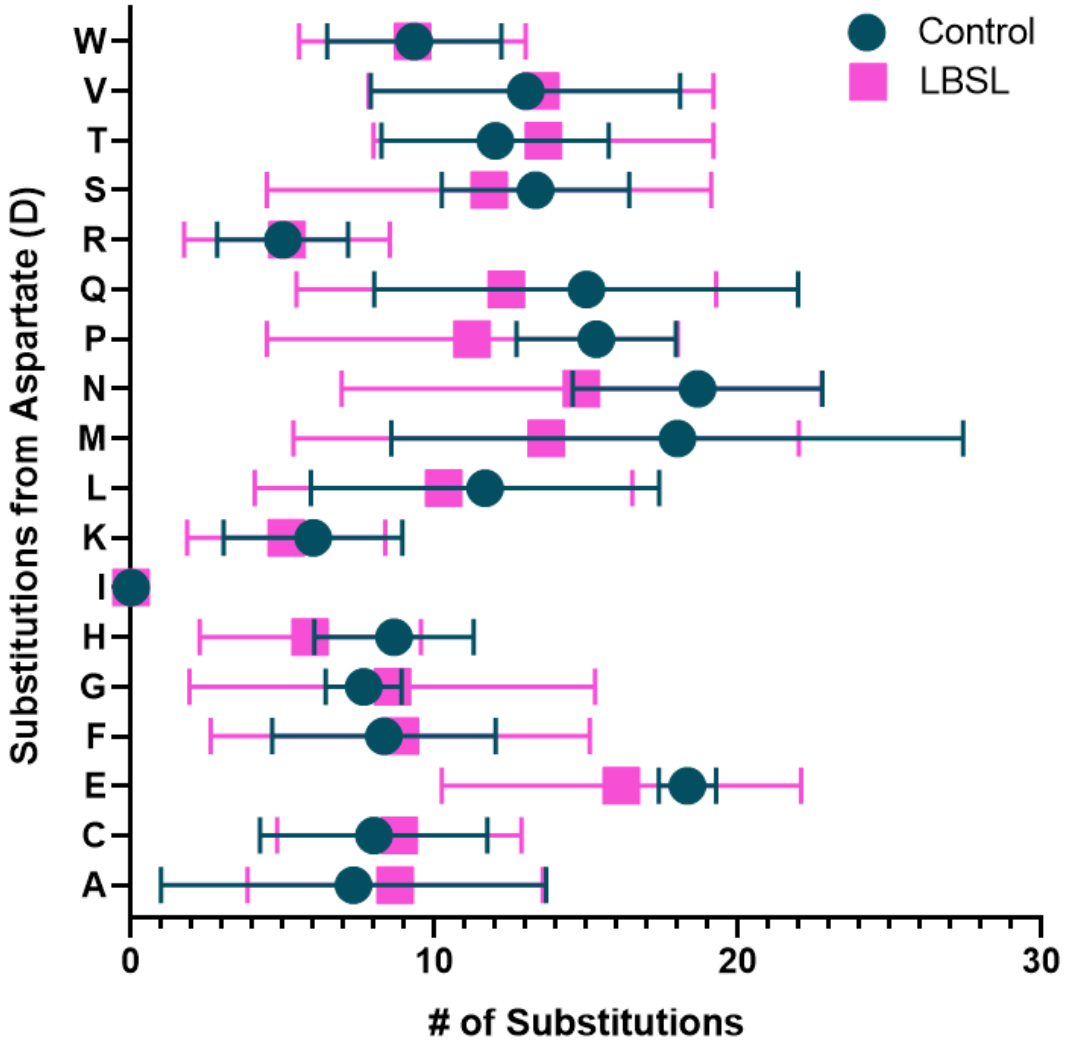


Larger dot = lower *p*

Expression of mitochondrially-encoded proteins

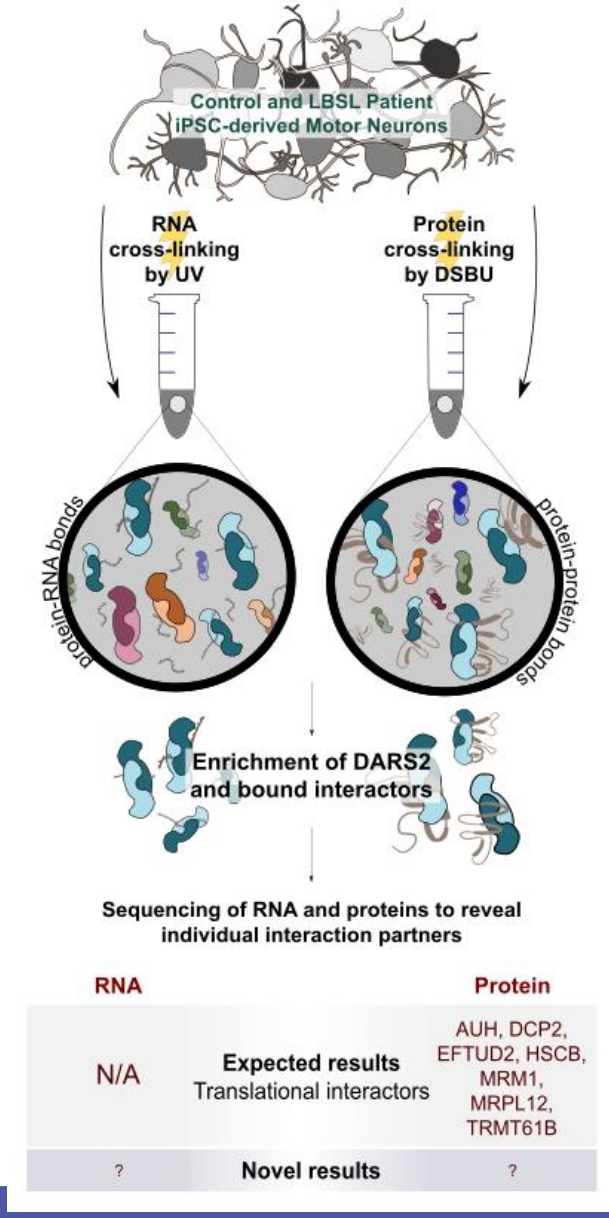


Does aspartic acid get incorporated into mito-proteins?

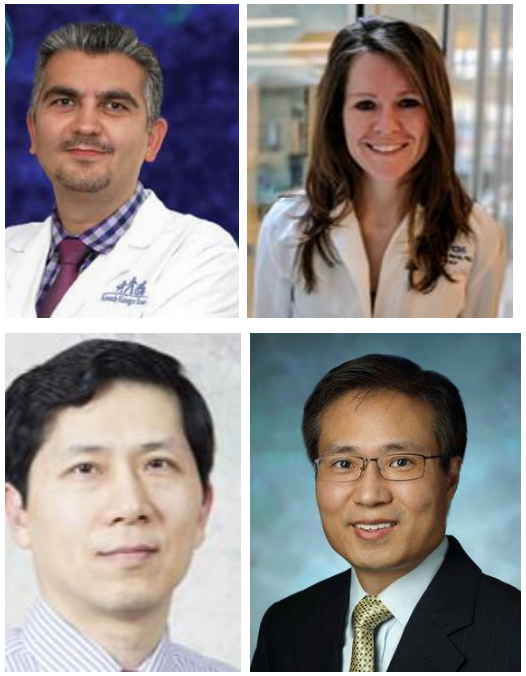


Discoveries

- **DARS2, as we know it, functions normally**
  - What, then, causes LBSL?

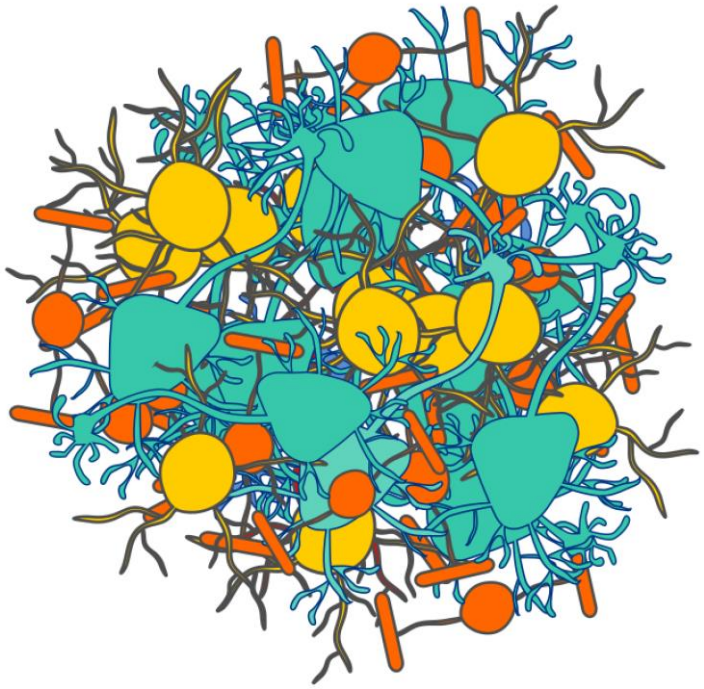


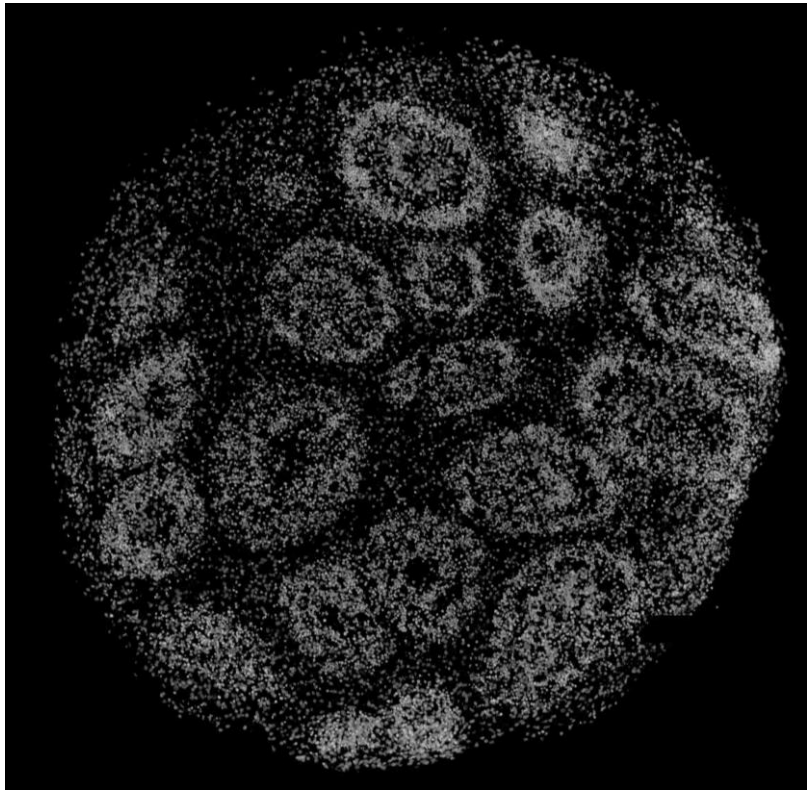
RNA		Protein
N/A	**Expected results** Translational interactors	AUH, DCP2, EFTUD2, HSCB, MRM1, MRPL12, TRMT61B
?	**Novel results**	?



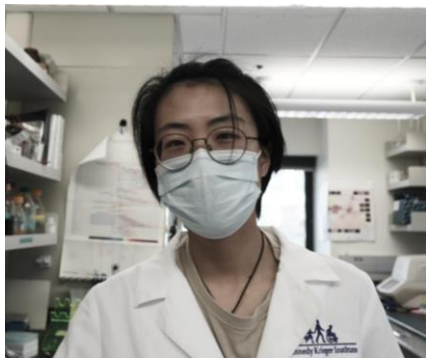
NIH funded grant to study LBSL

Organoids or “mini brains”

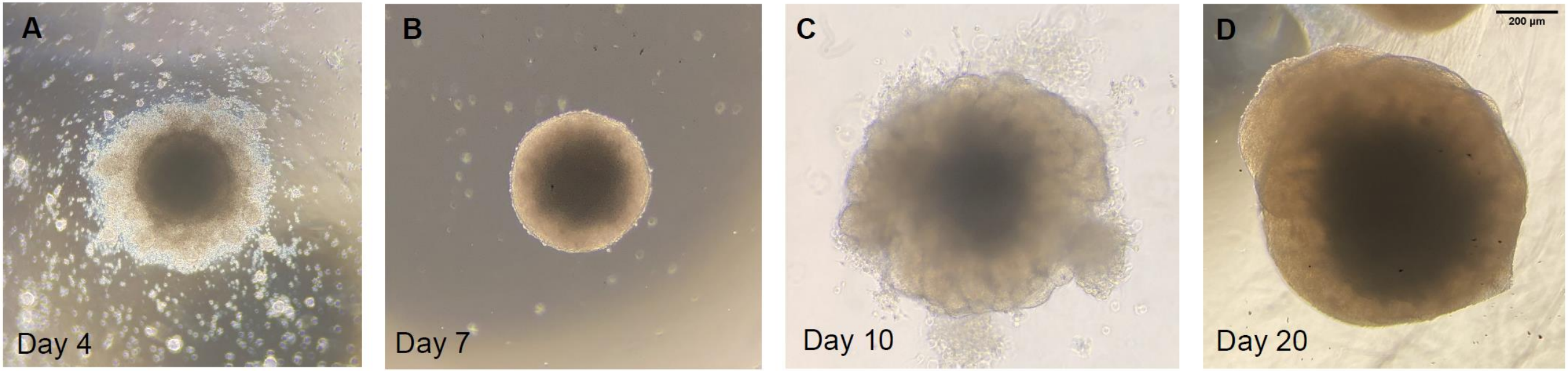




3D cell culture and the use of LBSL cerebral organoids

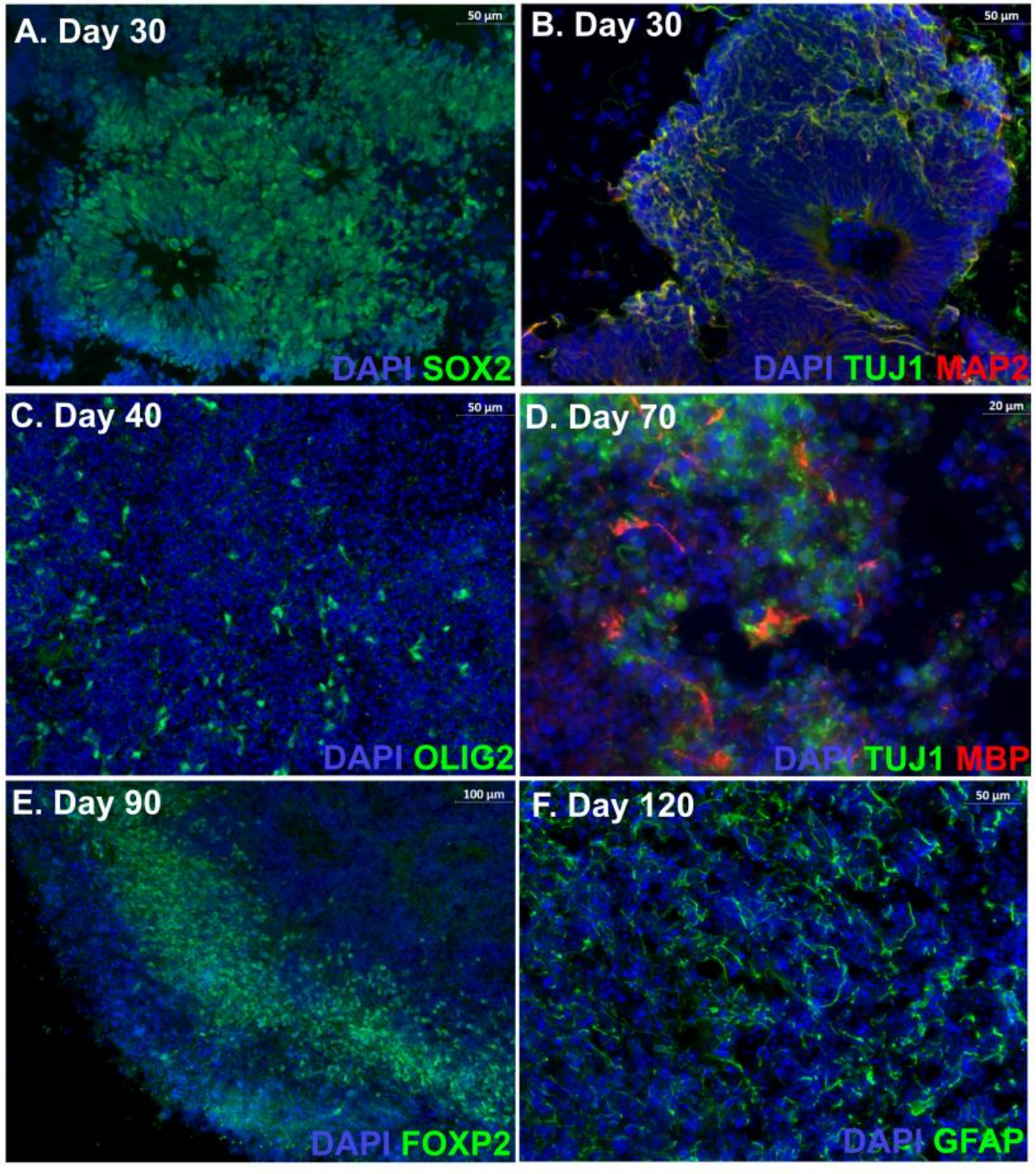


Shiqi Guang

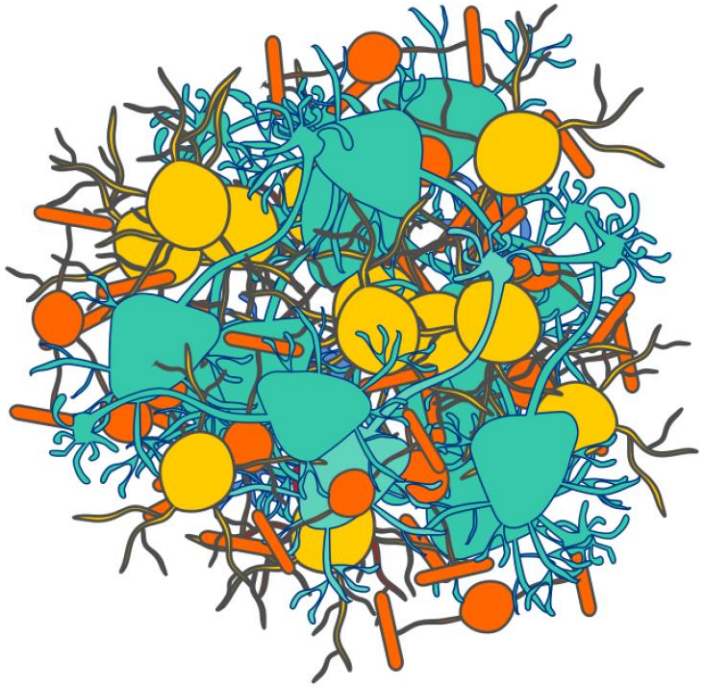


Created organoids using an unguided protocol adapted from Madhaven et al., 2018; *Nature Methods*

Organoids or “mini brains”



Single Cell RNA-Sequencing



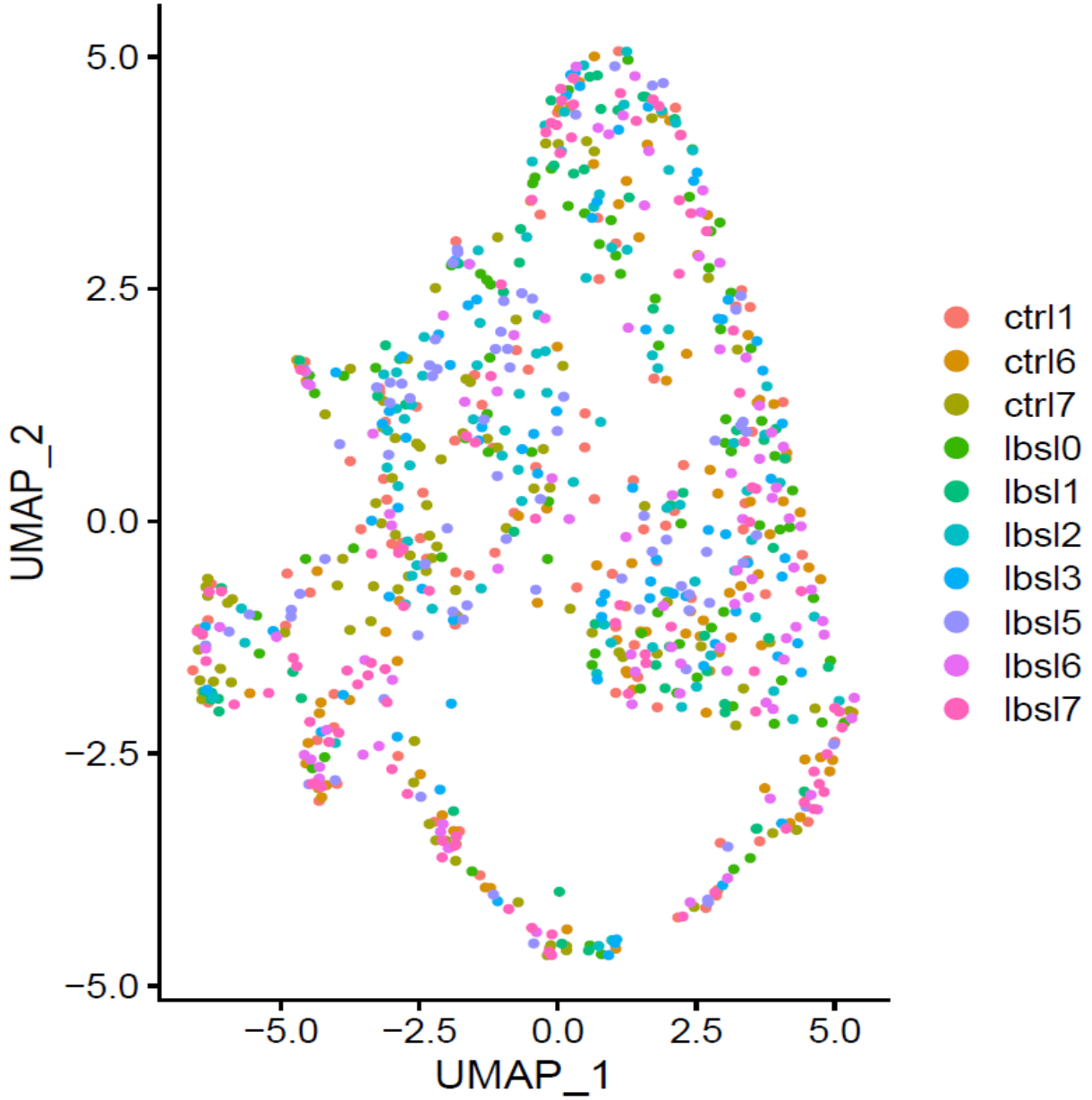
LBSL Organoid

Single-cell RNAseq of LBSL organoids

Smart-seq2

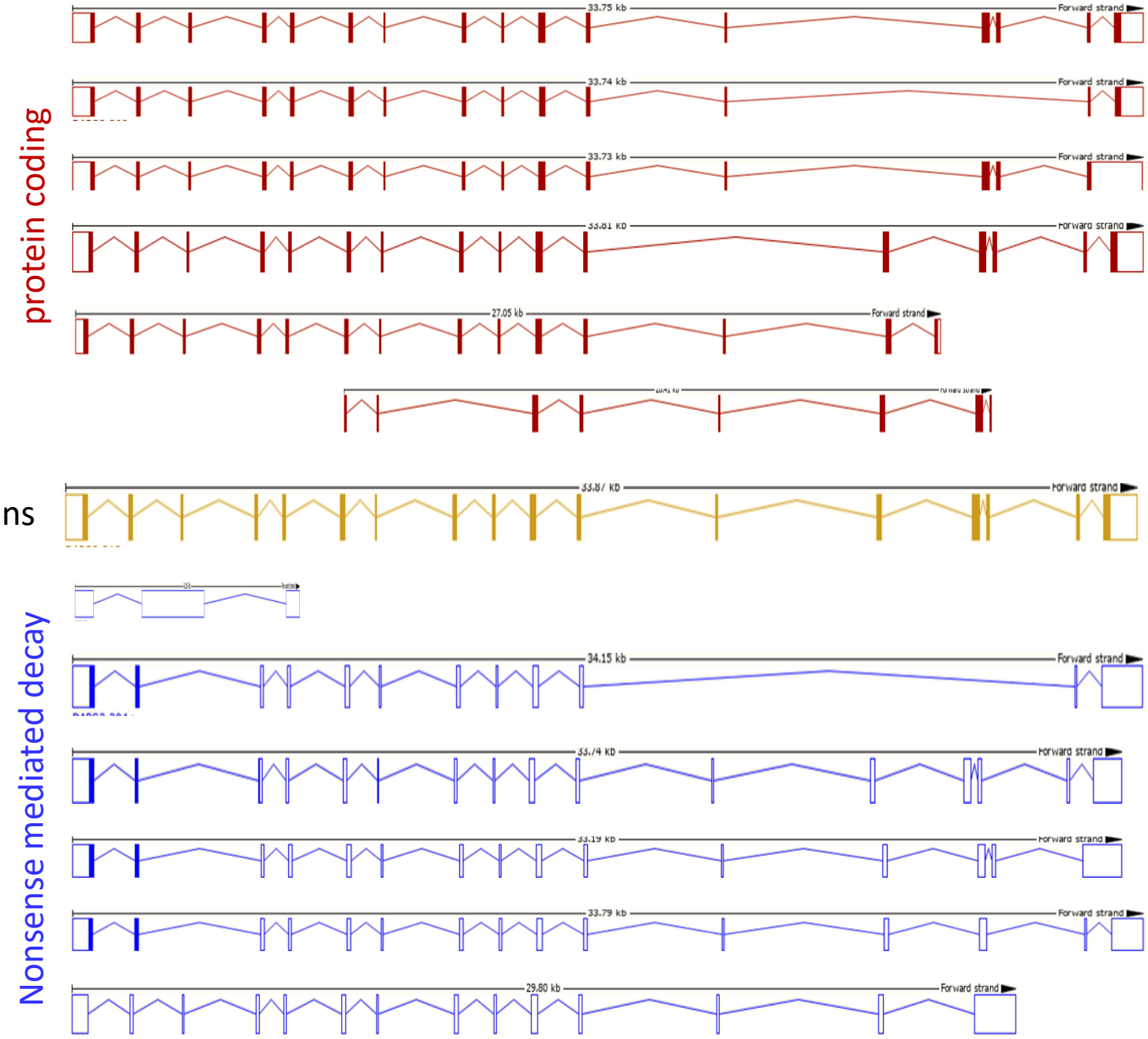
- Full length and even reads across transcripts
- Ideal for detection of alternative splice forms

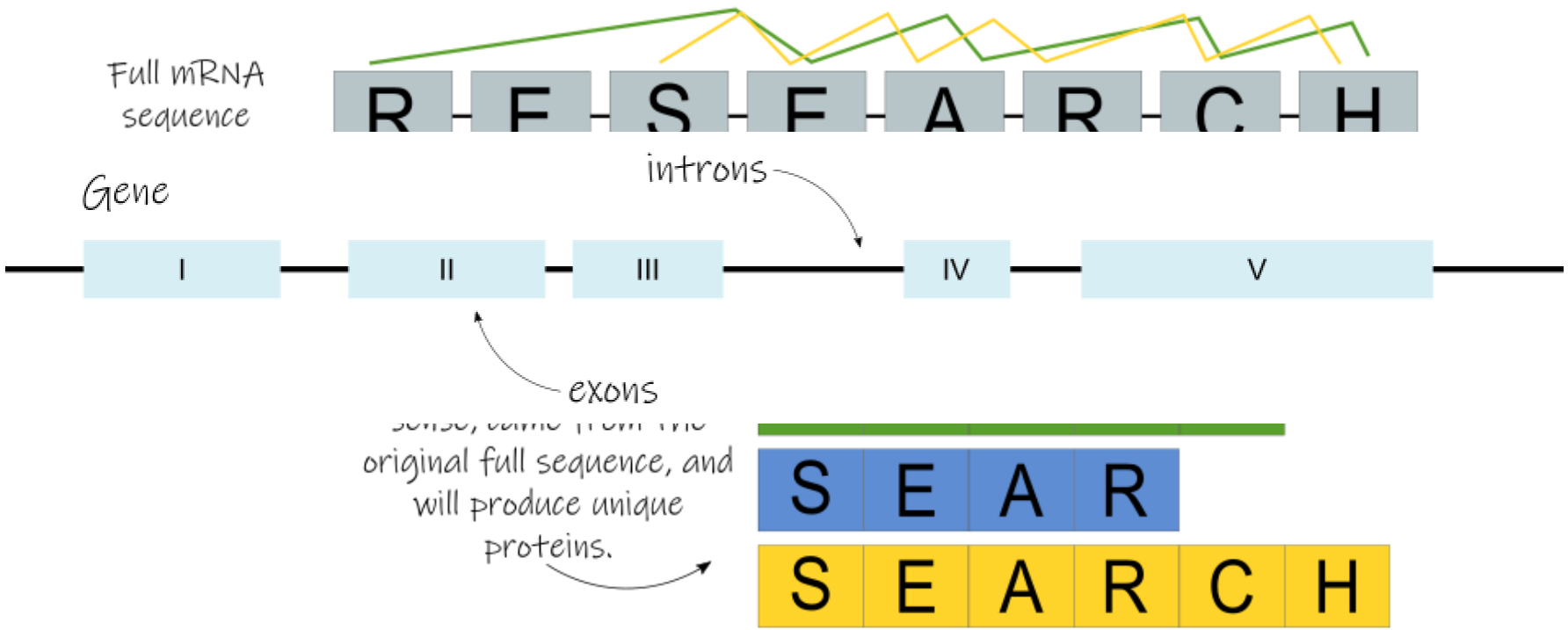
- 10 samples, 96 cells per sample
- 809 cells used in analyses



13 transcripts associated with *Dars2*

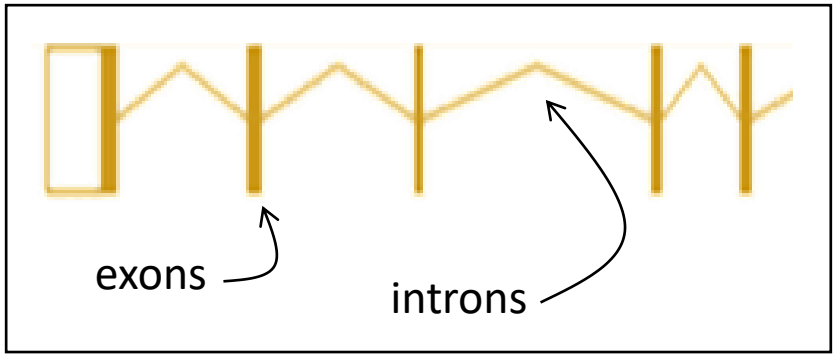
Roughly *half* produce protein




Full mRNA sequence
R E S E A R C H
introns
Gene
I
II
III
IV
V
exons
original full sequence, and will produce unique proteins.
S E A R
S E A R C H

13 transcripts associated with *Dars2*

Roughly *half* produce protein

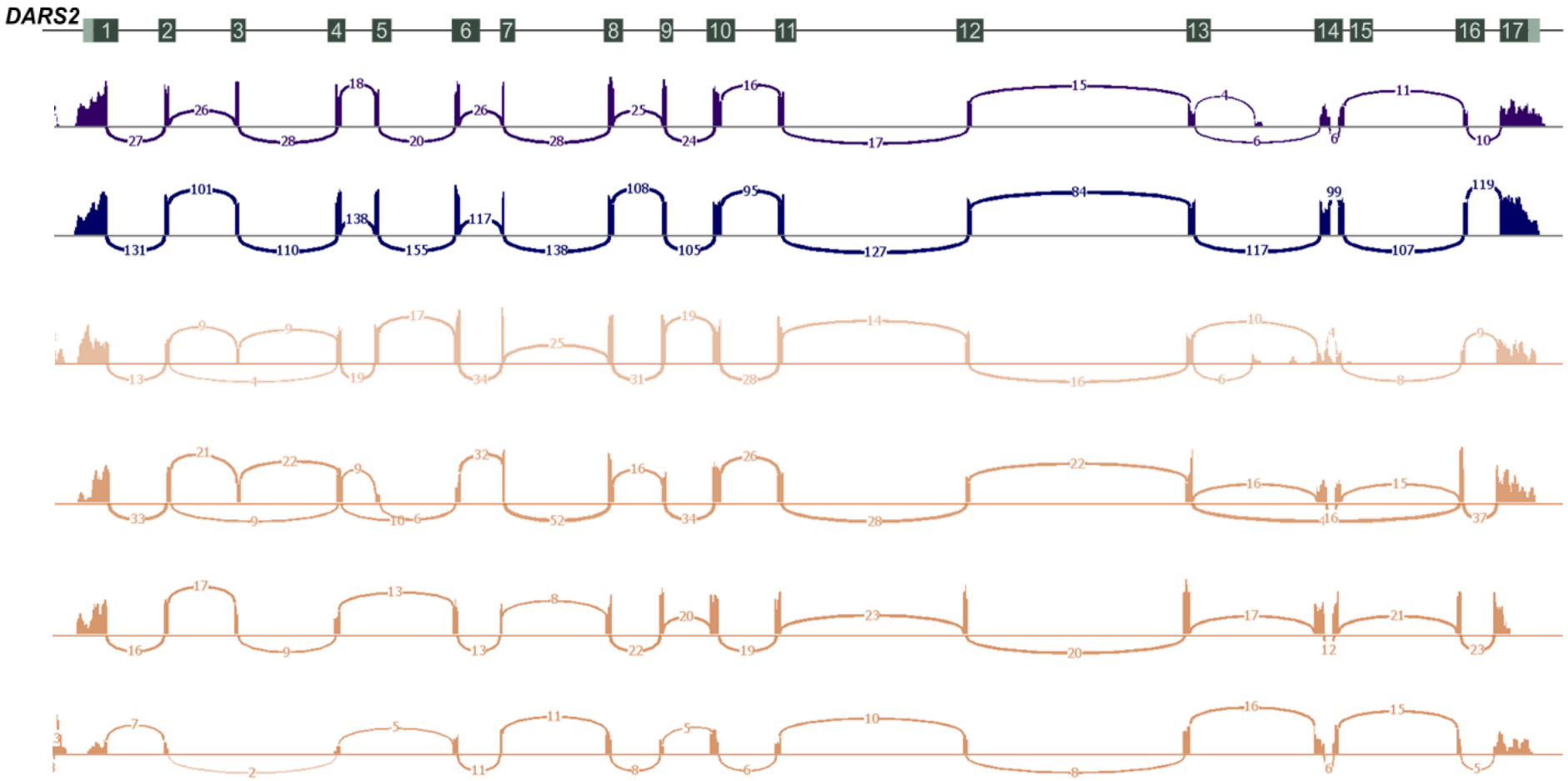


protein coding

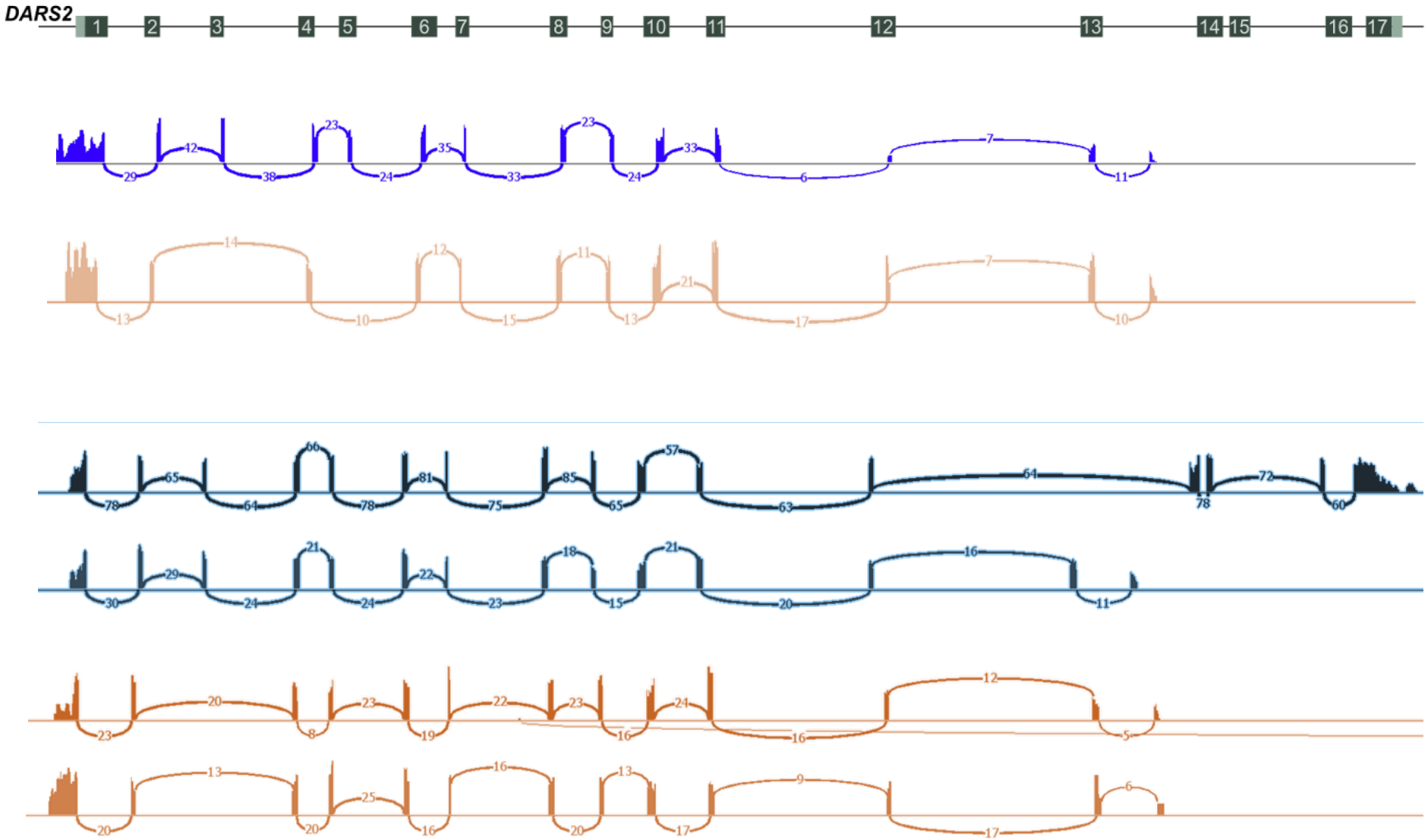
Full length, 17 exons

Nonsense mediated decay

DARS2 splice variants in control vs LBSL



Neuroepithelial Cells

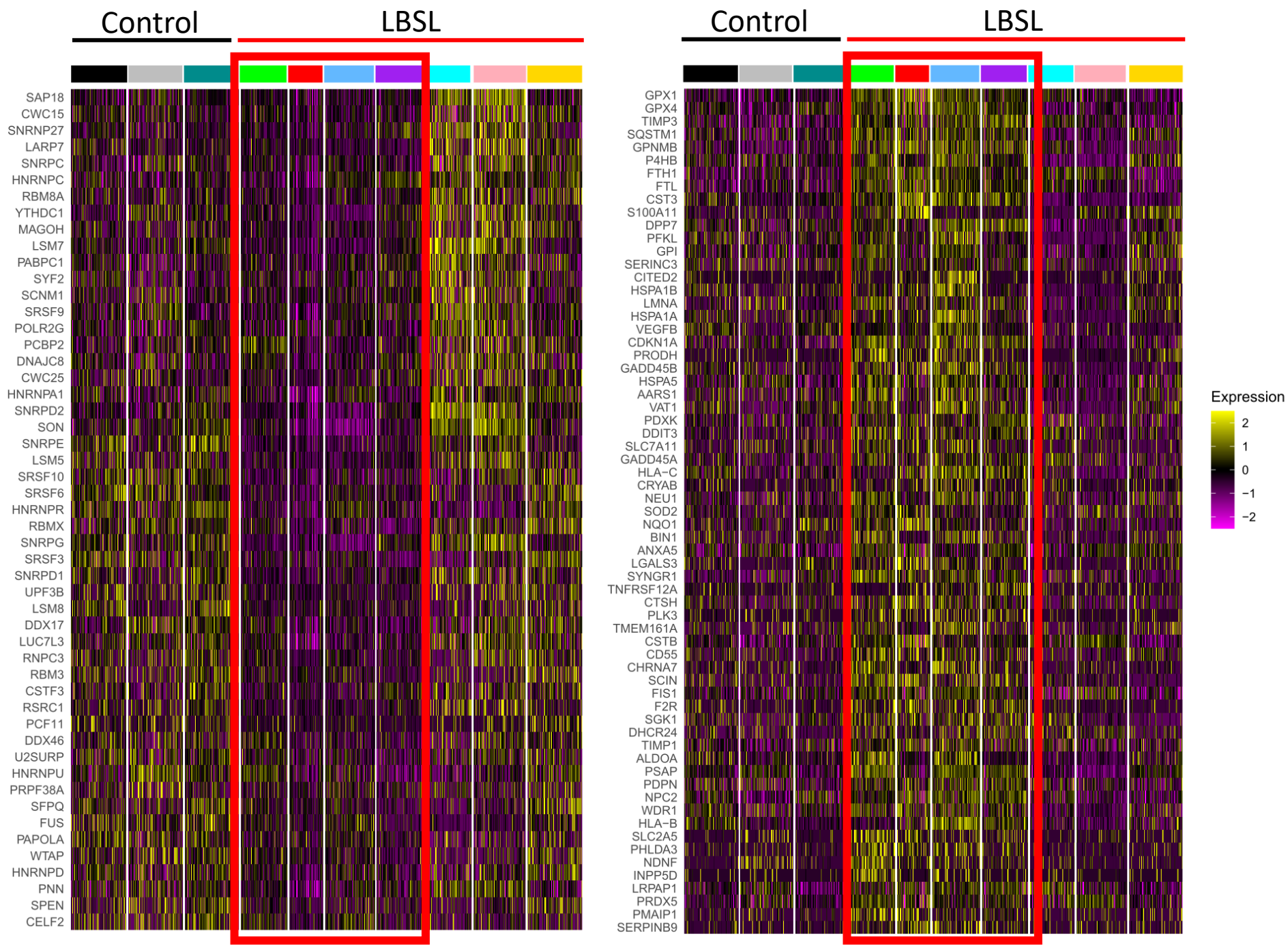


Radial Glia

Cortical Neurons

Discoveries

- DARS2, as we know it, functions normally
- **The “versions” or transcripts of DARS2 that LBSL cells produce is different than control cells and results in different amounts of protein**


Control
LBSL
SAP18
CWC15
SNRNP27
LARP7
SNRPC
HNRNPC
RBM8A
YTHDC1
MAGOH
LSM7
PABPC1
SYF2
SCNM1
SRSF9
POLR2G
PCBP2
DNAJC8
CWC25
HNRNPA1
SNRPD2
SON
SNRPE
LSM5
SRSF10
SRSF6
HNRNPR
RBMX
SNRPG
SRSF3
SNRPD1
UPF3B
LSM8
DDX17
LUC7L3
RNPC3
RBM3
CSTF3
RSRC1
PCF11
DDX46
U2SURP
HNRNPU
PRPF38A
SFPQ
FUS
PAPOLA
WTAP
HNRNPD
PNN
SPEN
CELF2
Control
LBSL
GPX1
GPX4
TIMP3
SQSTM1
GPNMB
P4HB
FTH1
FTL
CST3
S100A11
DPP7
PFKL
GPI
SERINC3
CITED2
HSPA1B
LMNA
HSPA1A
VEGFB
CDKN1A
PRODH
GADD45B
HSPA5
AARS1
VAT1
PDXK
DDIT3
SLC7A11
GADD45A
HLA-C
CRYAB
NEU1
SOD2
NQO1
BIN1
ANXA5
LGALS3
SYNGR1
TNFRSF12A
CTSH
PLK3
TMEM161A
CSTB
CD55
CHRNA7
SCIN
FIS1
F2R
SGK1
DHCR24
TIMP1
ALDOA
PSAP
PDPN
NPC2
WDR1
HLA-B
SLC2A5
PHLDA3
NDNF
INPP5D
LRPAP1
PRDX5
PMAIP1
SERPINB9
Expression
2
1
0
−1
−2

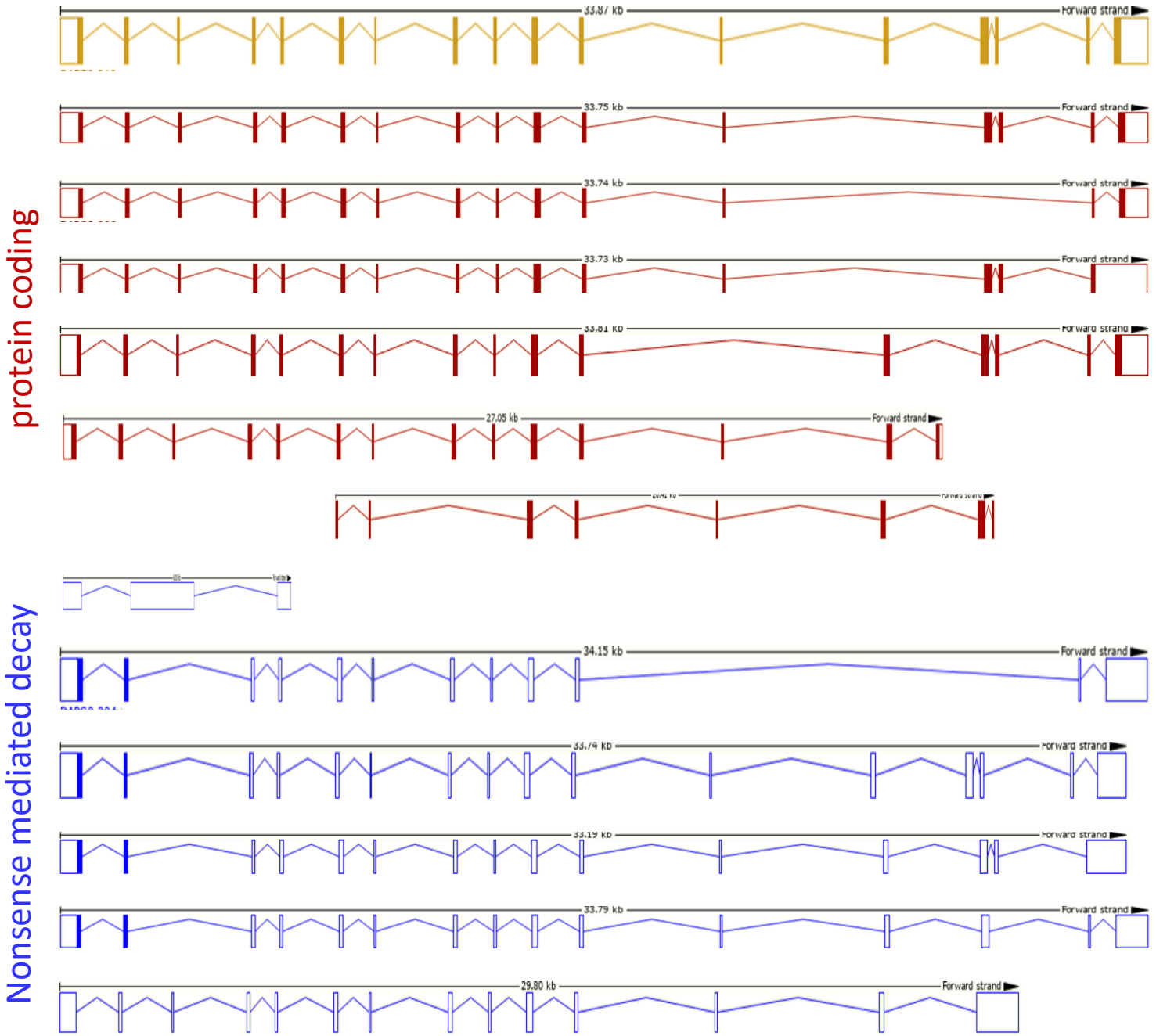
Types of patient mutations

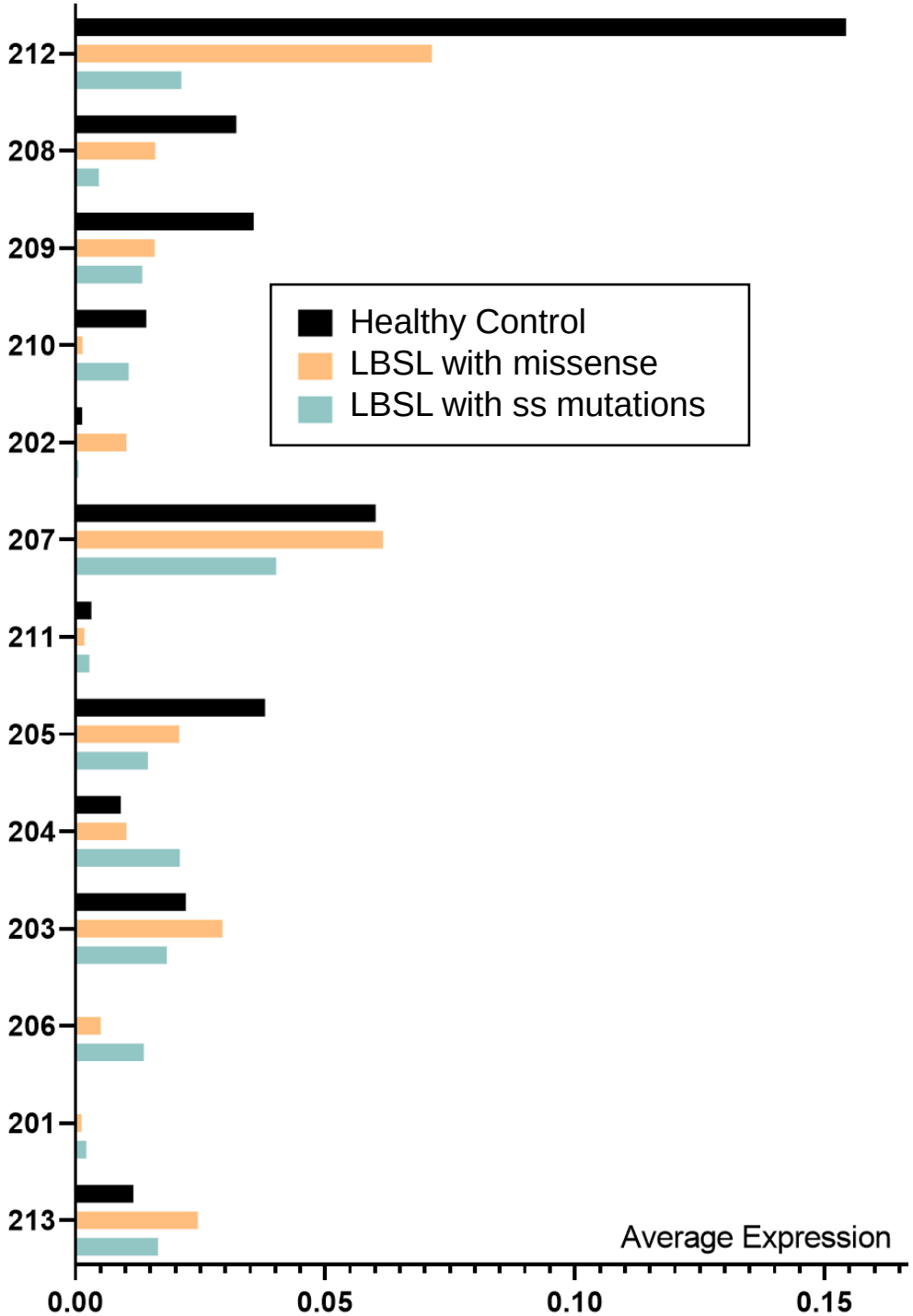
introns

exons

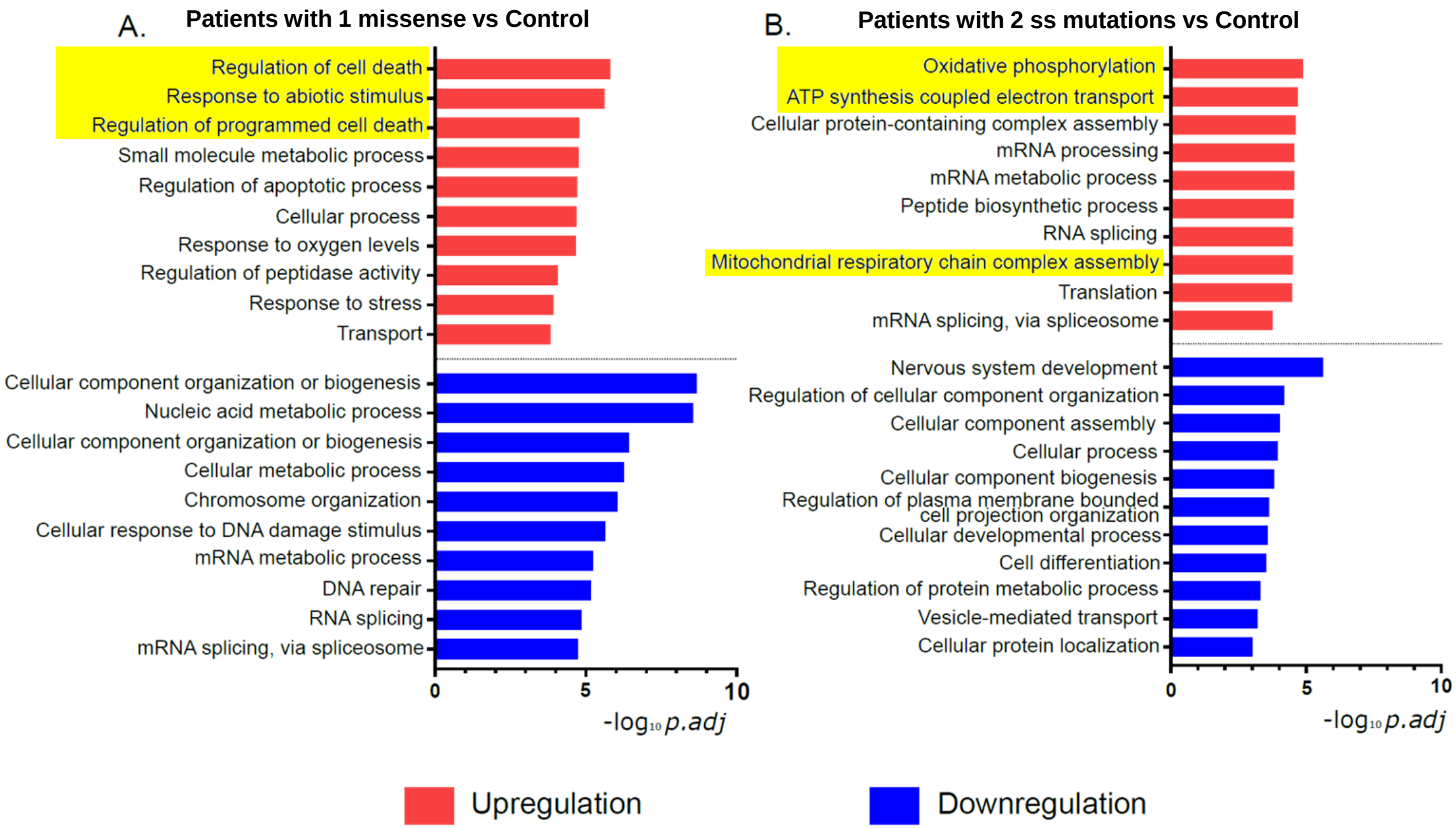
Splice site mutation would affect the presence/absence of exons (also referred to as *frame shift*)

Missense mutation would affect the protein sequence


protein coding
Nonsense mediated decay
33.75 kb
Forward strand
33.74 kb
33.73 kb
27.05 kb
34.15 kb
33.79 kb
29.80 kb


212
208
209
210
202
207
211
205
204
203
206
201
213
Healthy Control
LBSL with missense
LBSL with ss mutations
Average Expression
0.00
0.05
0.10
0.15

GO (Biological Process) Enrichment Analysis



Discoveries

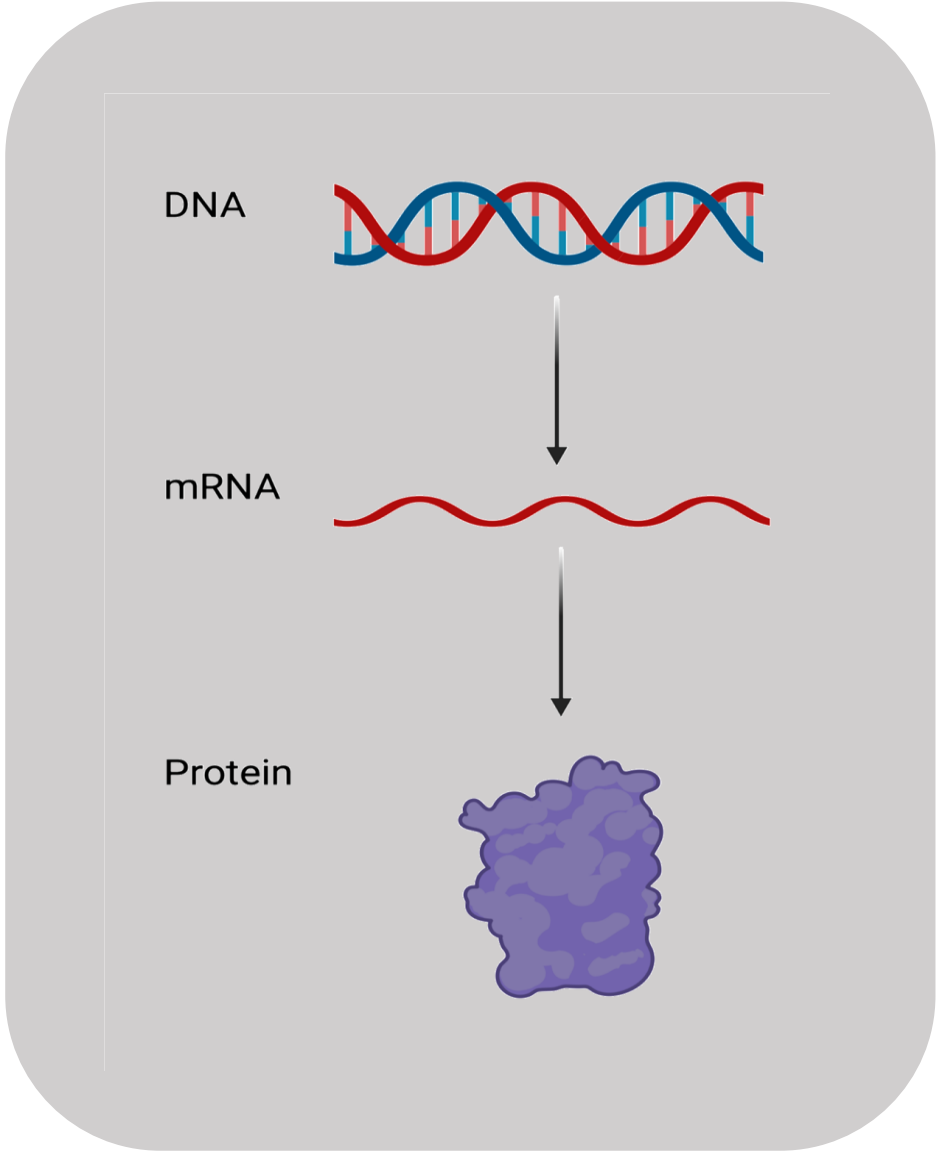
- DARS2, as we know it, functions normally
- The “versions” or transcripts of DARS2 that LBSL cells produce is different than control cells and results in different amounts of protein
- **Patient cells, depending on their mutations, have a different gene signature**

Gene Therapies

AAV9 Gene Therapy as a Potential Therapeutic Approach for LBSL

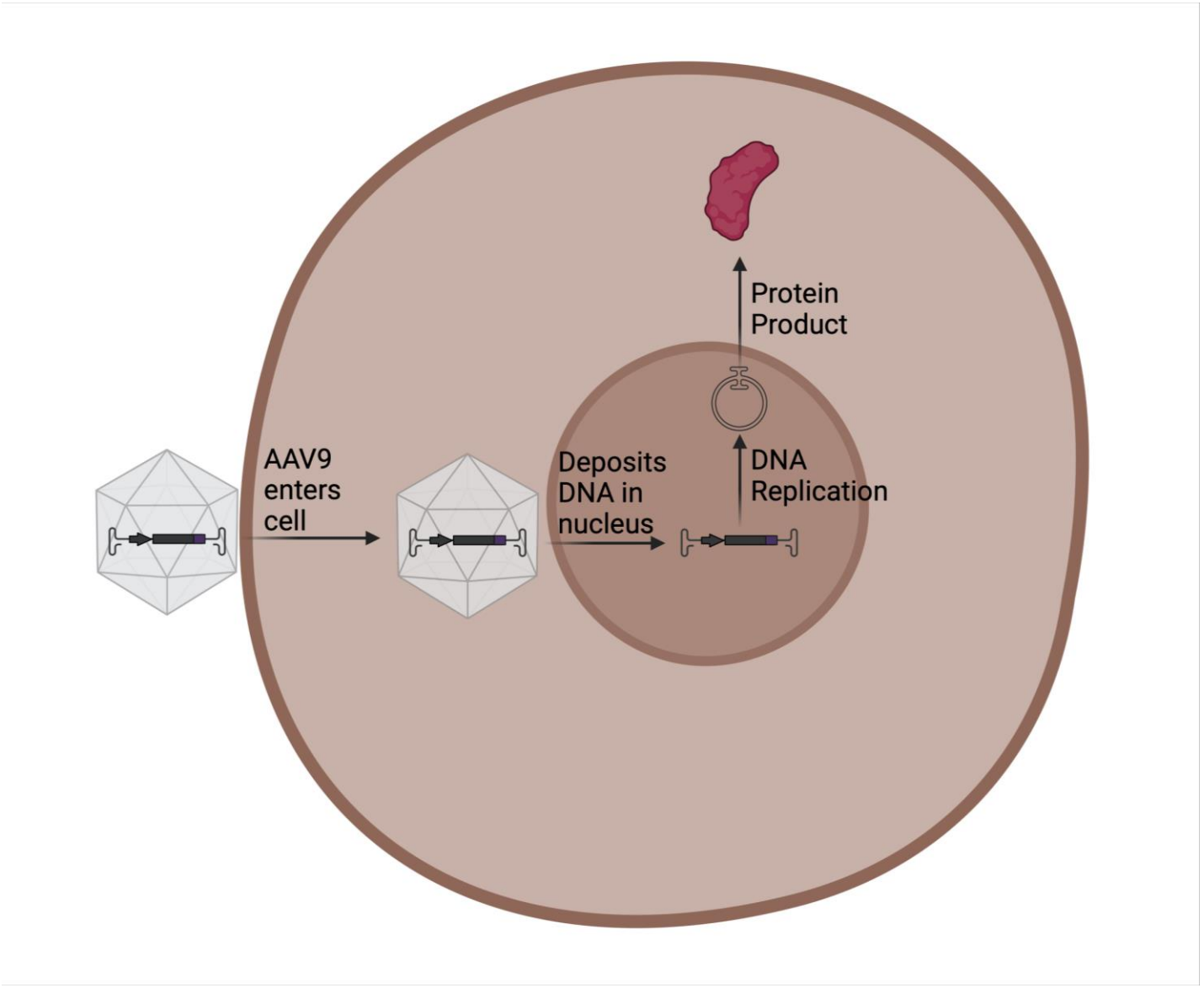
Adam Ratajczak

Quick Review



AAV9 Basics

- Relatively safe
- Cannot self-replicate
- Limited genomic integration
- High affinity for the nervous system
- Crosses Blood-Brain-Barrier

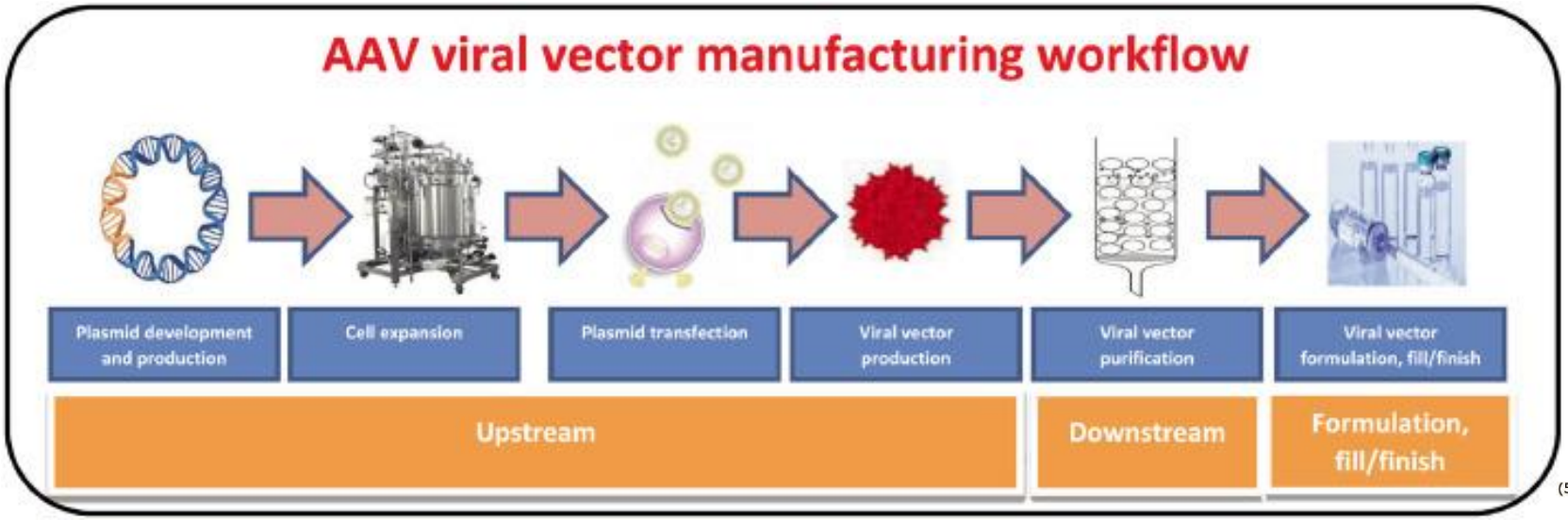


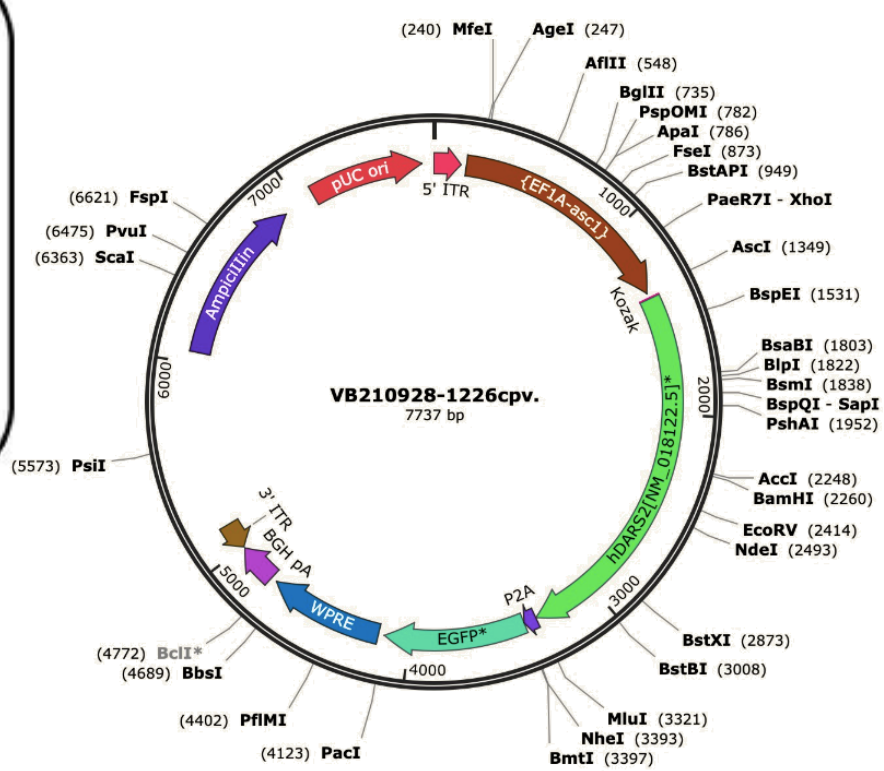
Clinical Trials

Approved AAV Treatments	
Condition	Drug Name
Inherited Retinal Disease (AAV2)	Luxturna
SMA (AAV9)	Zolgesma

Current AAV9 Trials	
Condition	Status
Batten's Disease	Phase I
Type I and Type II GM1 Gangliosidosis	Phase I/II
AMN	Phase I/II
Canavan Disease	Phase I/II
Krabbe Disease	Phase I/II

Development of AAV9 Vector for LBSL

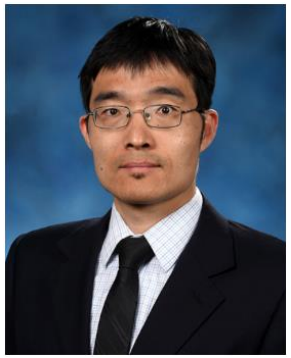




UNIVERSITY of MARYLAND
SCHOOL OF MEDICINE

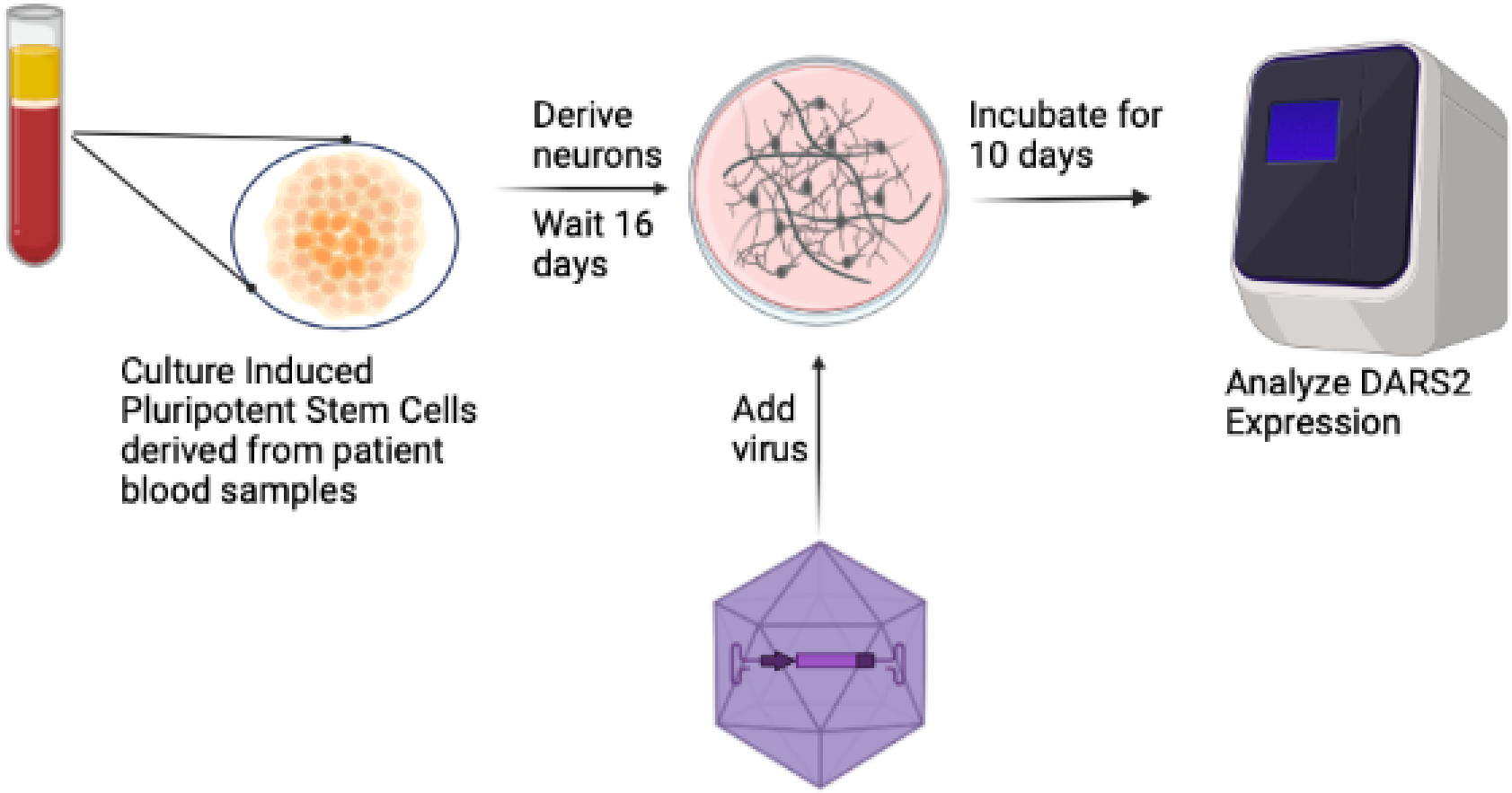
Piotr Walczak, MD, PhD

Miroslaw Janowski, MD, PhD

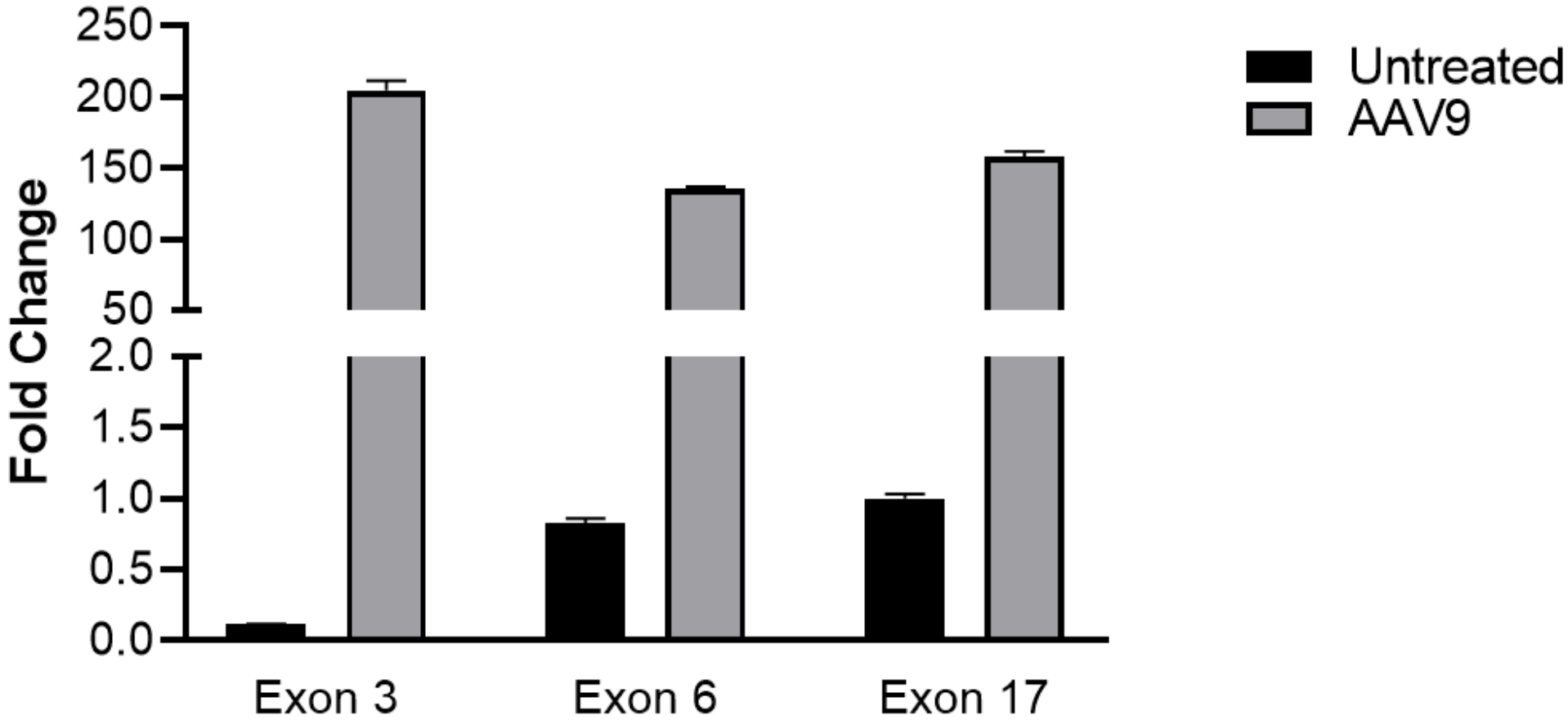


Yajie Liang, PhD

In-Vitro Study of AAV9 in LBSL



Current Data



Confirm in-vitro results via imaging and qPCR

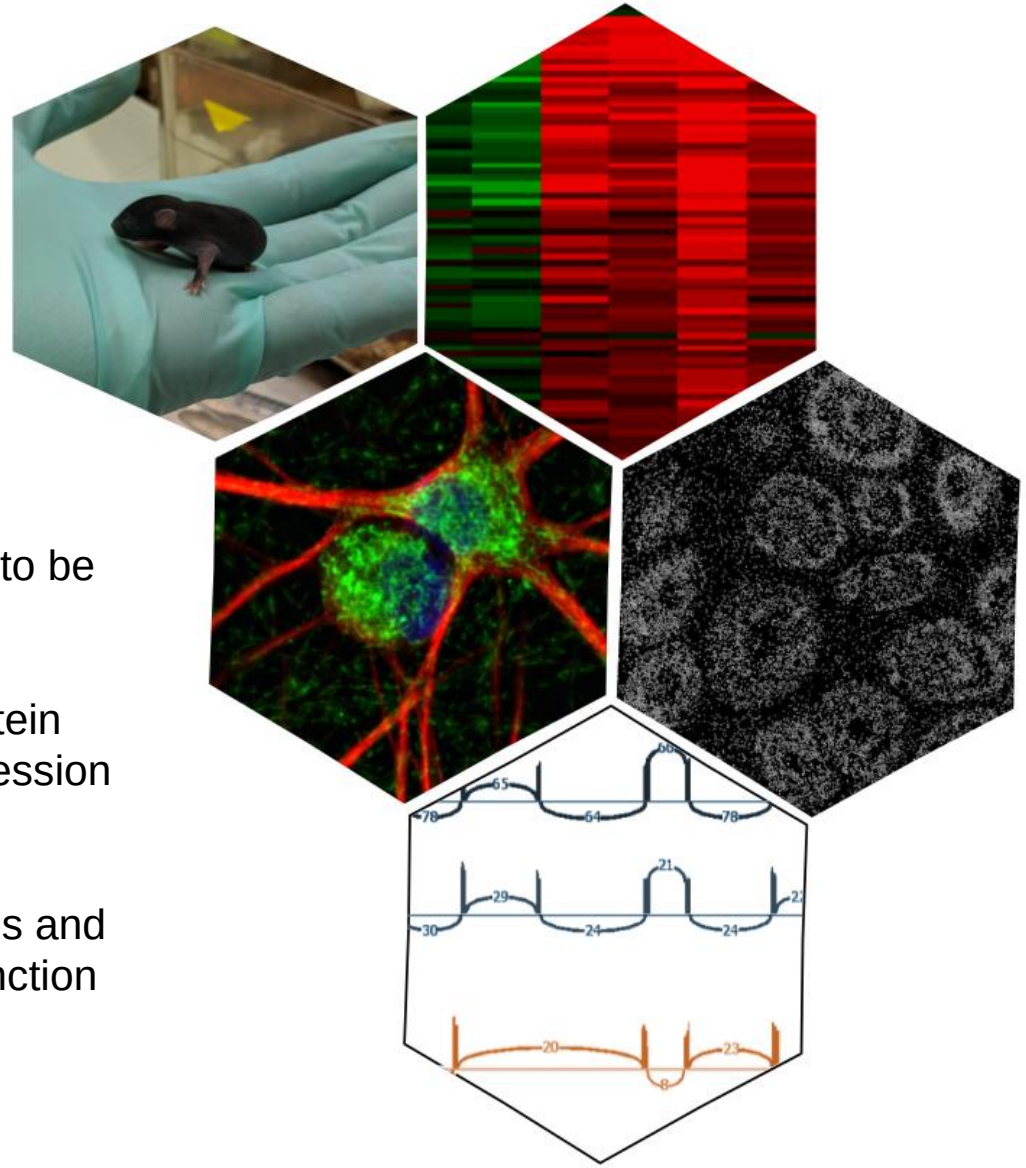
Analyze energetics in-vitro

In-vivo studies in mice and larger animals

Manou slides

Conclusions

- Thorough data on neuronal deletion of Dats2 in mice
- Developing two new mouse models for more accurate phenotyping
- Patient cells show deficits in function, yet Dars2 seems to be fulfilling translational role
- Mini brain work has revealed different production of protein based on cell type, and unique signatures of gene expression based on the patient mutation
- These models will all be useful for testing gene therapies and for further investigation into mechanism of Dars2 dysfunction



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Yajie Liang, PhD (University of Maryland)
Aleksandra Trifunovic, PhD (CECAD, Cologne Germany)
Stephen Fried, PhD (JHU, Chemistry)
Cedars Sinai Induced Pluripotent Stem Cell Core
Kennedy Krieger Institute IDDRC

A Cure for Ellie.org

Moser Center for Leukodystrophies
at Kennedy Krieger Institute

JOHNS HOPKINS
MEDICINE

Fairlington 5K, Arlington VA, May 2022

Fatemi Lab, December 2019

LBSL Patient Conference, April 2018

Dars2 deletion in CamKIIα leads to progressive increased activity

Experimental Neurology 326 (2020) 113164

Contents lists available at ScienceDirect

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journal homepage: www.elsevier.com/locate/yexnr

Research Paper

Neuronal ablation of mt-AspRS in mice induces immune pathway activation prior to severe and progressive cortical and behavioral disruption

Christina L. Nemeth[a], Sophia N. Tomlinson[a], Melissa Rosen[a], Brett M. O'Brien[a], Oscar Larraza[a], Mahim Jain[b], Connor F. Murray[a], Joel S. Marx[a], Michael Delannoy[c], Amena S. Fine[a,d], Dan Wu[e], Aleksandra Trifunovic[f], Ali Fatemi[a,g,*]

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ARTICLE INFO

Keywords:
LBSL
Leukodystrophy
Leukoencephalopathy
Mitochondria
DARS2
tRNA synthetase

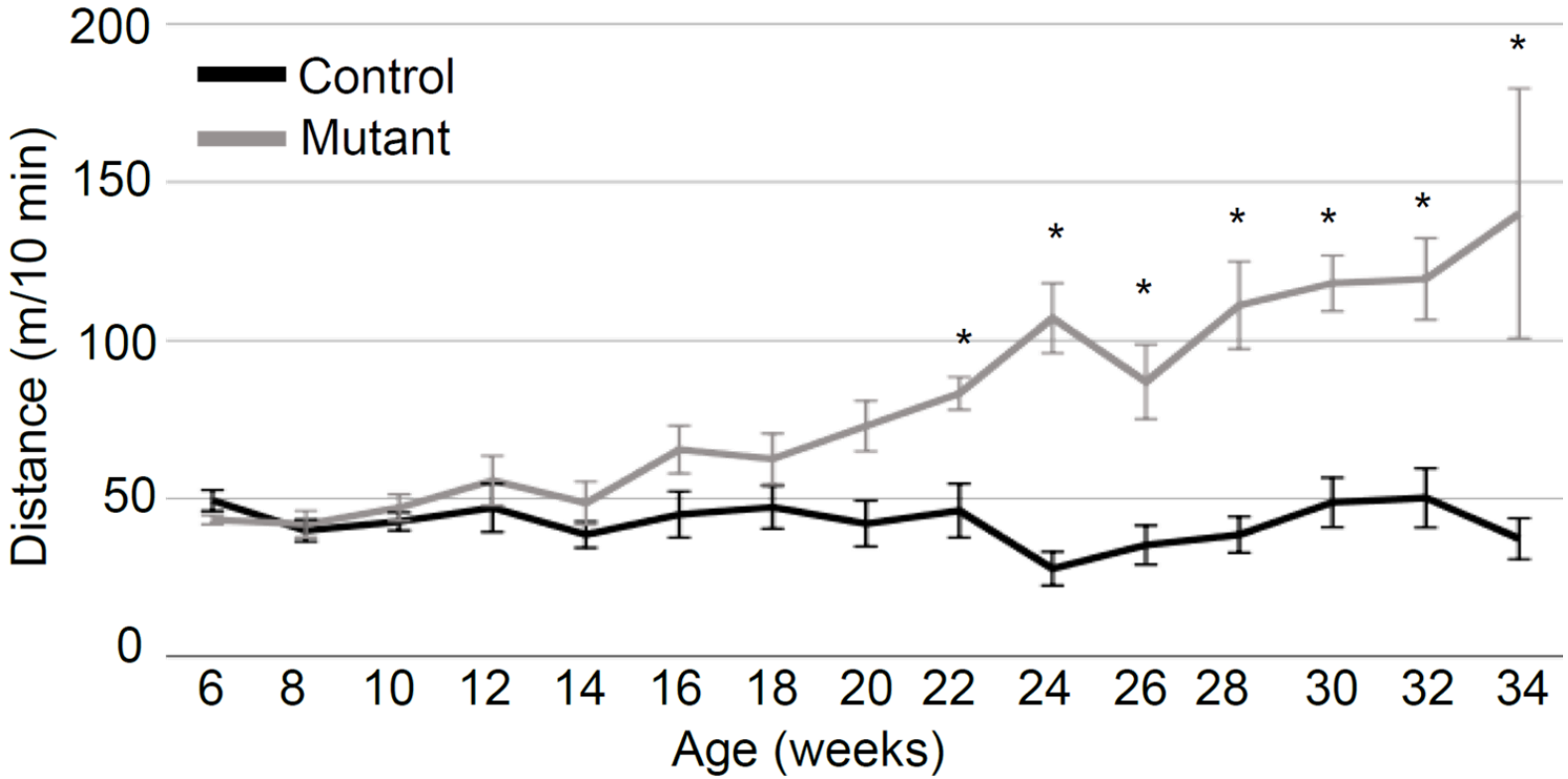
ABSTRACT

Leukoencephalopathy with brainstem and spinal cord involvement and lactate elevation (LBSL) is a rare, slowly progressive white matter disease caused by mutations in the mitochondrial aspartyl-tRNA synthetase (mt-AspRS, or DARS2). While patients show characteristic MRI T2 signal abnormalities throughout the cerebral white matter, brainstem, and spinal cord, the phenotypic spectrum is broad and a multitude of gene variants have been associated with the disease. Here, *Dars2* disruption in CamKIIα-expressing cortical and hippocampal neurons results in slowly progressive increases in behavioral activity at five months, and culminating by nine months as severe brain atrophy, behavioral dysfunction, reduced corpus callosum thickness, and microglial morphology indicative of neuroinflammation. Interestingly, RNAseq based gene expression studies performed prior to the presentation of this severe phenotype reveal the upregulation of several pathways involved in immune activation, cytokine production and signaling, and defense response regulation. RNA transcript analysis demonstrates that activation of immune and cell stress pathways are initiated in advance of a behavioral phenotype and cerebral deficits. An understanding of these pathways and their contribution to significant neuronal loss in CamKII-*Dars2* deficient mice may aid in deciphering mechanisms of LBSL pathology.

1. Introduction

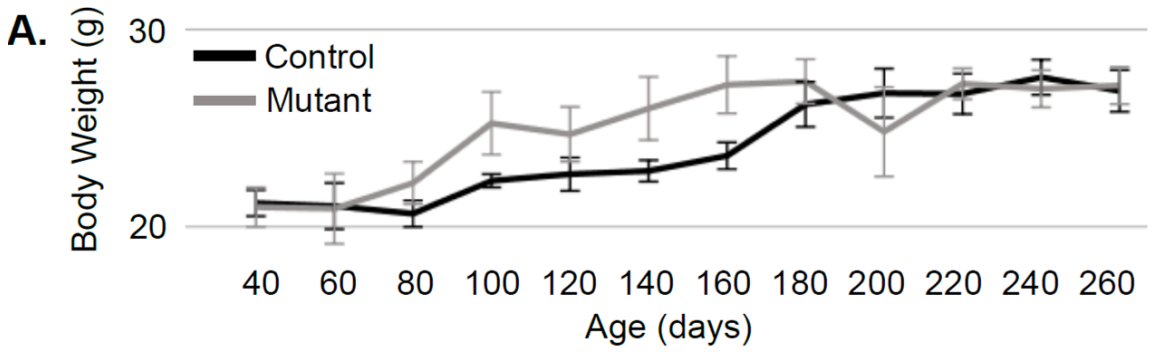
Leukoencephalopathy with brainstem and spinal cord involvement and lactate elevation (LBSL) is a rare, autosomal recessive disorder characterized by slowly progressive spasticity, ataxia, proprioceptive deficits, and in some cases, cognitive decline. Most patients harbor compound heterozygous mutations in the *DARS2* gene (Tzoulis et al., 2012) which encodes mitochondrial aspartyl-tRNA synthetase (mt-AspRS), a ubiquitously expressed enzyme which charges tRNA molecules with cognate amino acids essential for mitochondrial protein translation. Diagnosis of LBSL includes identification of pyramidal, spectroscopy (Scheper et al., 2007; van Berge et al., 2013). Age of onset and degree of disability vary widely with genotypic variation complicating a genotype-phenotype correlation (van Berge et al., 2014). With this said, more severe early infantile onset cases with seizures, microcephaly and global delay have also been reported (Sauter et al., 2015; Steenweg et al., 2012). Since the first descriptions of LBSL, human diseases have now been associated with each of the 19 mitochondrial tRNA synthetases, all presenting with diverse clinical symptoms (Sissler et al., 2017; Theisen et al., 2017).

Recapitulating *DARS2* deficiency and pathology in mouse or cell systems has proven difficult. Previous efforts to develop model animals

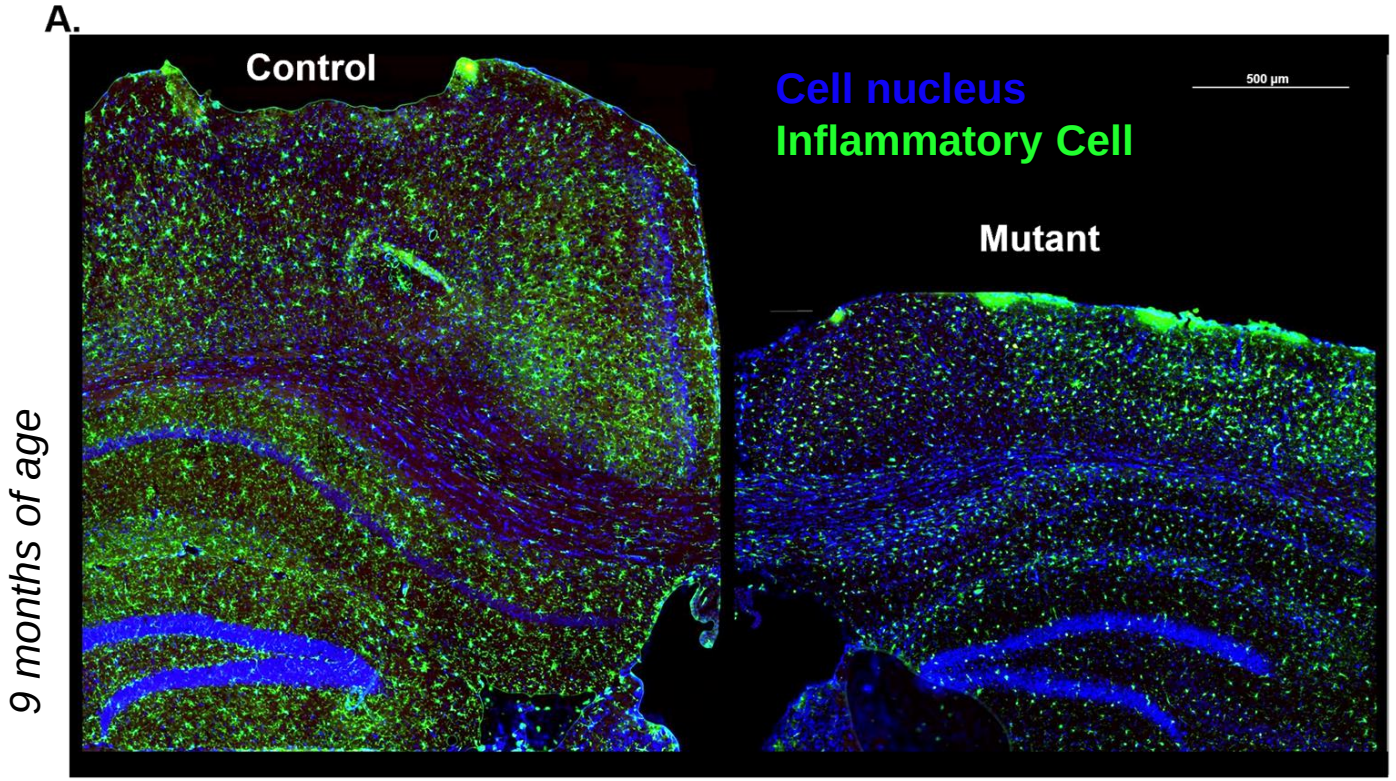


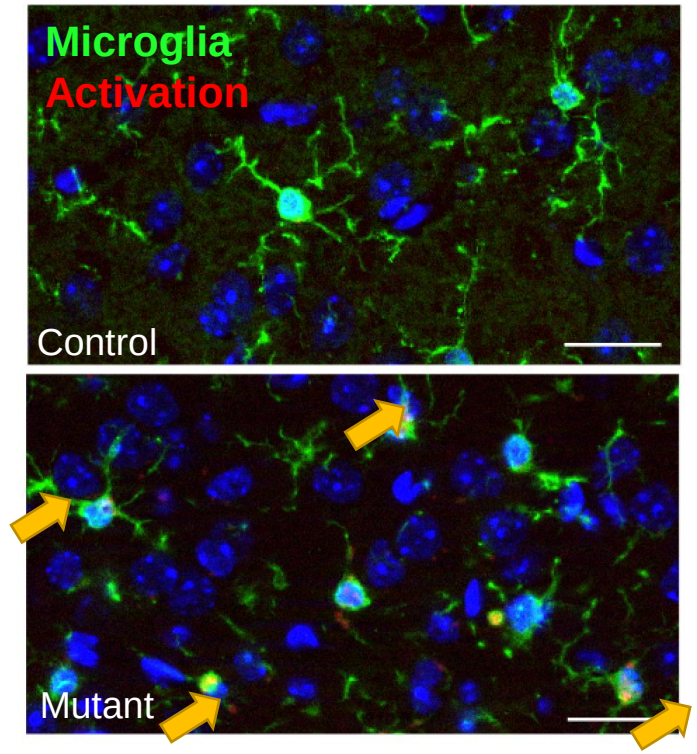
Nemeth et al., 2019

Dars2/CamKIIα show brain pathology beginning at 6 months



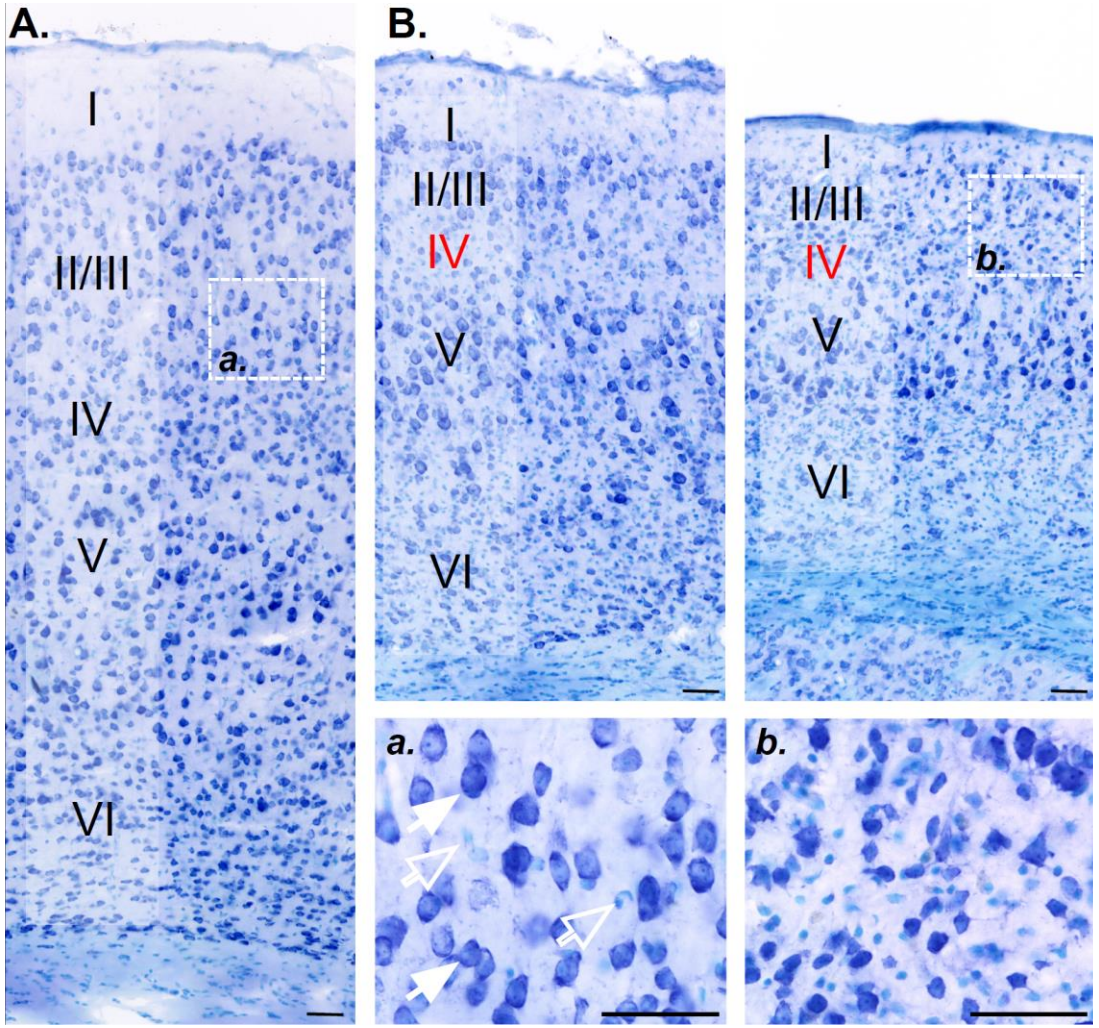
Dars2 deletion in CamKIIα leads to neuronal loss and inflammation

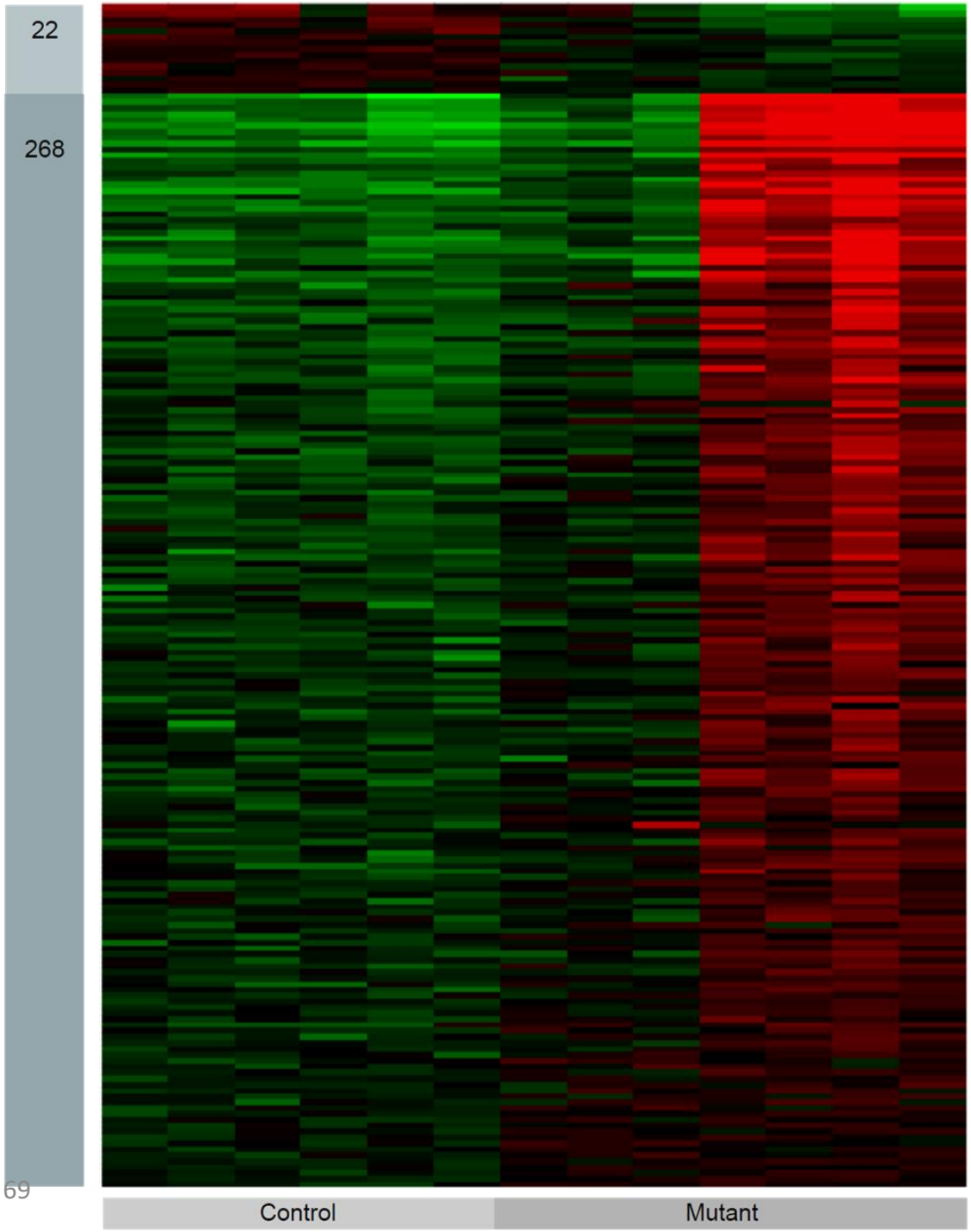




Nemeth et al., 2019

Dars2 deletion in CamKIIα leads to neuronal loss in the cortex





GO Biological Process	Adj *p*
Trans-synaptic signaling	1.7e-05
Chemical synaptic transmission	1.7e-05
Anterograde trans-synaptic signaling	1.7e-05
Synaptic signaling	1.7e-05
Synapse organization	3.2e-05
Immune response	3.9e-16
Response to biotic stimulus	1.0e-13
Innate immune response	1.8e-12
Immune effector process	1.1e-09
Reg of immune response	2.0e-08
Positive regulation of immune system process	1.5e-07
Cytokine production	1.9e-07
Inflammatory response	2.7e-07
Positive regulation of immune response	5.7e-07
Reg of cytokine production	5.7e-07
Response to cytokine	5.1e-07
Reg of defense response	2.8e-06
Adaptive immune response	6.4e-06
Leukocyte mediated immunity	8.8e-06
Defense resp to bacterium	4.1e-05
Response to virus	2.3e-05
Adaptive immune response based on somatic recombination of immune receptors built from immunoglobulin superfamily domains	3.6e-05
Lymphocyte mediated immunity	3.8e-05
Activation of immune response	2.8e-05
Cellular response to cytokine stimulus	1.9e-05

RNA Sequencing

Each row represents a gene's activity

Gene activity increased

Unchanged

Gene activity decreased

LBSL mice show strong increase in inflammatory genes

Nemeth et al., 2019

LBSL motor neurons show diminished mitochondrial activity