Leveraging Natural History Knowledge to Design Informative Clinical Trials

FDA Workshop
Developing Therapies for Primary Mitochondrial Diseases:
Bridging the Gaps
Silver Spring, MD
September 6, 2019

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Financial Disclosures
Michio Hirano, MD

- **Site investigator for Stealth Biotherapeutics, Inc. SPIMM-300 and SPIMM-301 studies**
- **Research funding from Entrada**
- **Co-inventor of a pending patent for deoxynucleoside therapy for mtDNA depletion syndrome.**
- **Columbia University has licensed the pending patent to Modis Therapeutics**
- **Consultant for Modis (formerly Meves) Pharmaceuticals Inc.**

Leveraging Natural History Knowledge to Design Informative Clinical Trials

Natural History Studies:

How does the disease begin and progress?

“Begin with the goal in mind”

Leveraging Natural History Knowledge

“Begin with the goal in mind”

Goal:

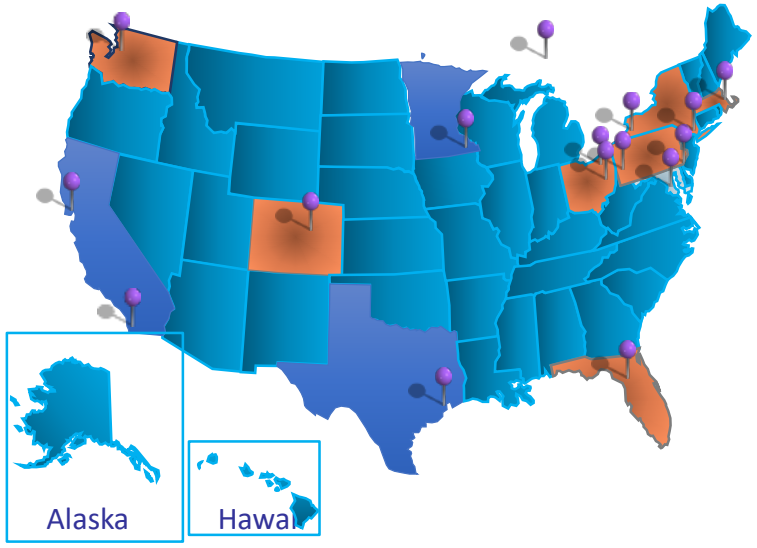
To design informative clinical trials that will demonstrate ”clinical benefit” by proving that a drug or other intervention has a ”real effect on how a patient survives, feels, or functions.”

Obstacles:

- Mitochondrial diseases are clinically, biochemically, and genetically heterogeneous.
- Mitochondrial diseases are rare and most are ultra-rare.
- The onset and progression of most mitochondrial diseases are not well-characterized.
- Few outcome measures have been assessed in mitochondrial diseases.
- No single outcome measure will fit all mitochondrial diseases.
- Few funding opportunities for natural history studies.

NAMDC

the north american mitochondrial disease consortium

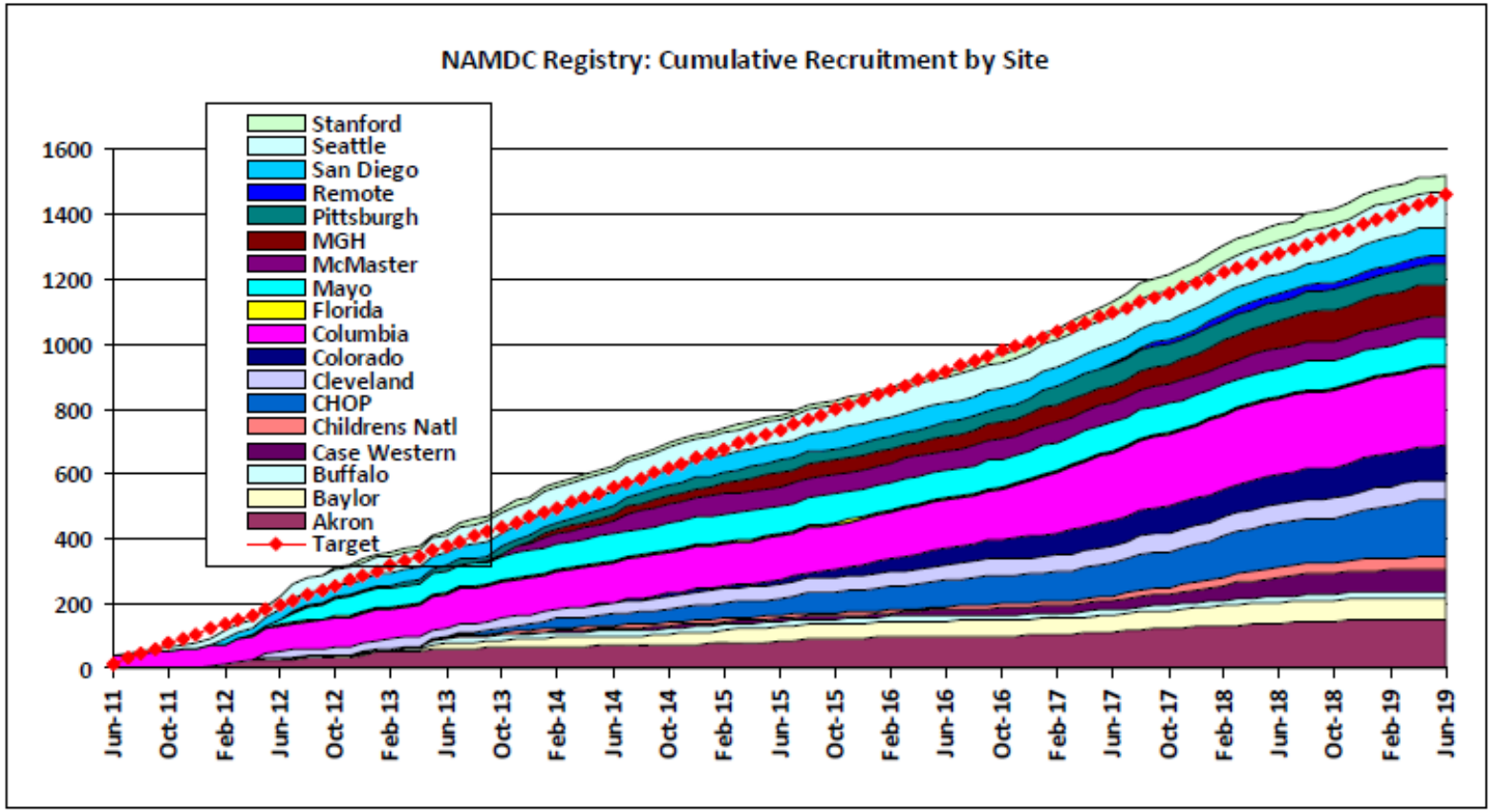


- Columbia University Medical Center
- Akron Children's Hospital
- Baylor College of Medicine
- Boston Children's Hospital
- Case Western Reserve University School of Medicine
- Children's Hospital of Colorado
- Children's Hospital of Philadelphia
- Children's National Medical Center
- Cleveland Clinic Foundation
- Hamilton Health Sciences
- Massachusetts General Hospital
- Mayo Clinic
- Seattle Children's Hospital
- Stanford University
- University of California San Diego Medical Center
- University of Pittsburgh

- Affiliated sites:
- University of Florida College of Medicine
- Buffalo General Hospital

Rare Diseases Clinical Research Network, National Institutes of Health
NIH National Institute of Neurological Disorders and Stroke
NIH Eunice Kennedy Shriver National Institute of Child Health and Human Development
NIH National Institutes of Health Office of Dietary Supplements
United Mitochondrial Disease Foundation. HOPE. ENERGY. LIFE.

NAMDC Registry: Cumulative Recruitment by Site



Total recruitment number represents (#) of patients with data entry completed at the time of the report.

NAMDC
the north american mitochondrial disease consortium

N= **1562*** as of August 1st, 2019
(Previous month = 1543)

NAMDC
the north american mitochondrial disease consortium

NAMDC Prospective Natural History Studies

Alpers Syndrome
Mitochondrial NeuroGastroIntestinal Encephalopathy (MNGIE)
Pyruvate dehydrogenase complex deficiency
Pearson-CPEO-Kearns Sayre Syndrome

Prospective natural history studies for rare diseases are ideal but can be expensive and labor intensive.

NIH National Institute of Neurological Disorders and Stroke
NIH Eunice Kennedy Shriver National Institute of Child Health and Human Development
NIH National Institutes of Health Office of Dietary Supplements

Developing deoxynucleos(t)ide therapy for Thymidine Kinase 2 deficiency (TK2d)

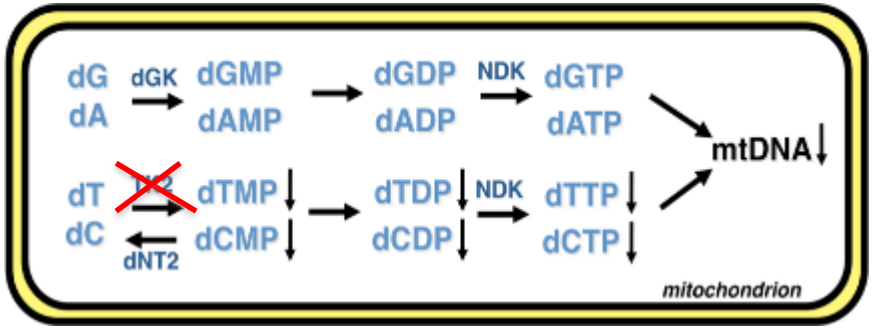
Mutant mitochondrial thymidine kinase in mitochondrial DNA depletion myopathy

Ann Saada[1*], Avraham Shaag[1*], Hanna Mandel[2], Yoram Nevo[3], Staffan Eriksson[4] & Orly Elpeleg[1]

nature genetics • volume 29 • november 2001

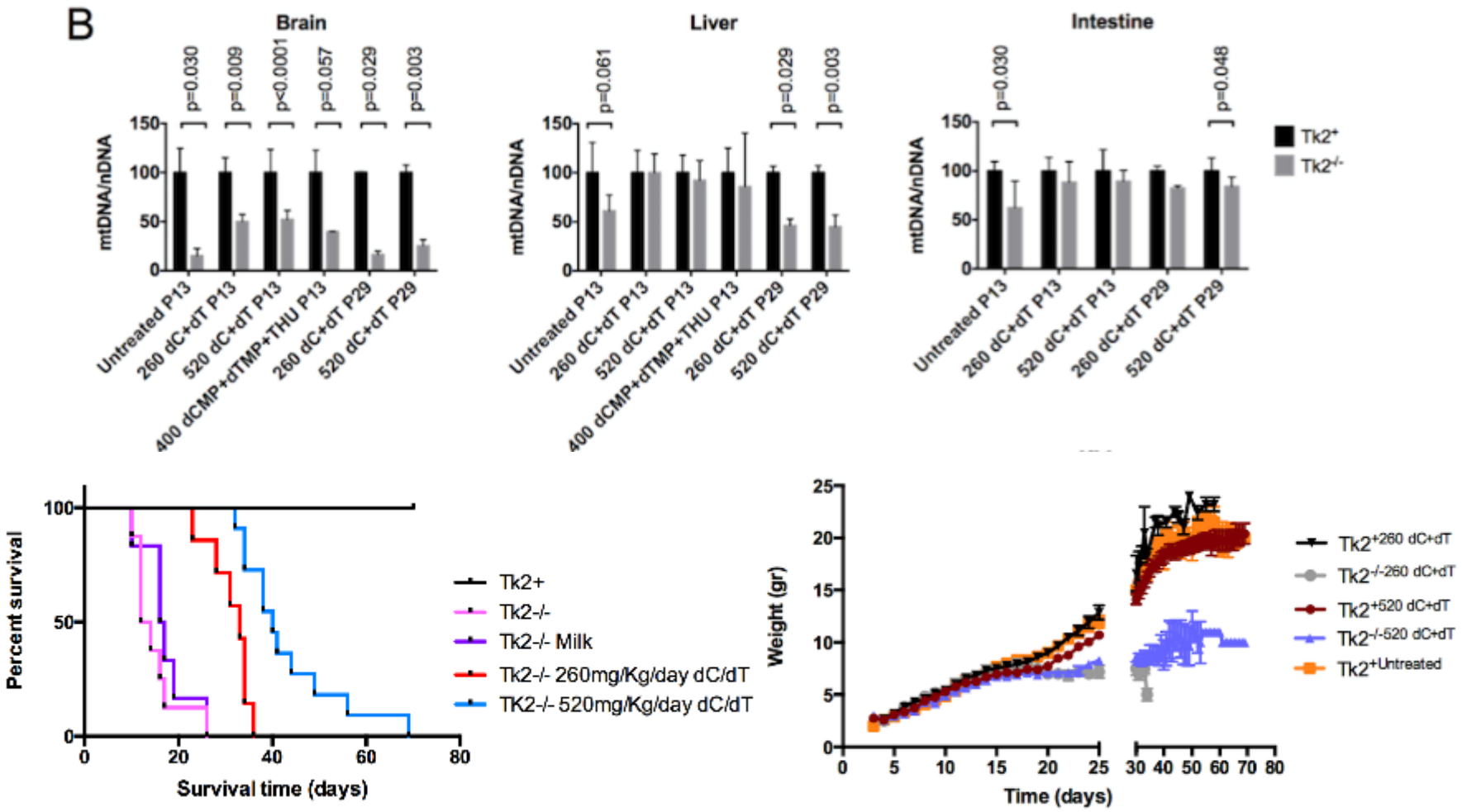
Table 2 • The activity of thymidine kinase 2 in muscle mitochondria

Sample	Substrate	
	[^{3}H]dThd	[^{3}H]dCyt
patient 1	3.42±0.38	1.80±0.06
patient 2	1.03±0.31	0.71±0.59
patient 4	1.76±0.42	0.68±0.08
controls (range)	7.55±1.45 (5.40–10.51)	5.65±1.89 (4.55–7.59)



- Early onset: from birth to 30 months
- Progressive weakness of skeletal and respiratory muscles
- Elevated CK and lactic acid
- Mean age of death: 2.6 years

dC+dT ameliorates mtDNA depletion and improves growth and survival of $Tk2^{-/-}$ mice

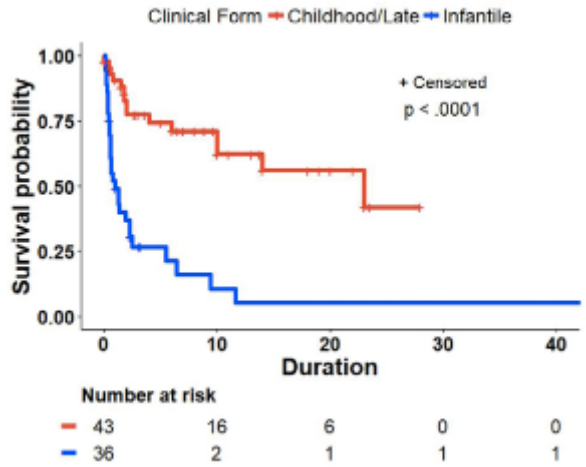


C. Lopéz et al. Ann Neurol 2017

Retrospective Natural History of Thymidine Kinase 2 Deficiency

Garone et al. J Med Genet 2018

Disease Spectrum of 92 TK2-deficient Patients			
	Infantile-onset myopathy 39 (42.4%)	**Childhood-onset myopathy** 37 (40.2%)	**Late-onset myopathy** 16 **(**17.4%)
Onset	≤12 months	>1-<12 years-old	≥12 years-old
Symptoms	Diffuse muscle weakness, early respiratory failure	Proximal muscle weakness, areflexia	Muscle weakness
EMG	Myogenic +/- neuropathic pattern	Myogenic +/- neuopathic pattern	Myogenic pattern
CK	↑↑↑	↑↑↑	normal-↑↑
mtDNA depletion	+++	+++	+/-
mtDNA deletions	–	–	+++
Other signs & symptoms	seizures 7, encephalopathy 5, cognitive dysfunction 3, ptosis 4, facial diplegia 3, dysphagia 3, multiple bone fractures 2, nephropathy 1, rigid spine 1, coma episodes 1, cardiomyopathy 1, bi-ventricular hypertrophy 1, arrhythmia 1 and esophageal atresia 1	facial diplegia 11, ptosis 9, PEO 3, hearing loss 2, cognitive decline 1, encephalopathy 1, prolonged QT 1, arrhythmia 1, multiple bone fractures 1, renal tubulopathy 1, and gynecomastia 1	ptosis 9, PEO 8, dysphagia 6, respiratory insufficiency 5, dysarthria 3, cardiomyopathy 2, gynecomastia 1, Neuropathy 1, Hearing loss 1



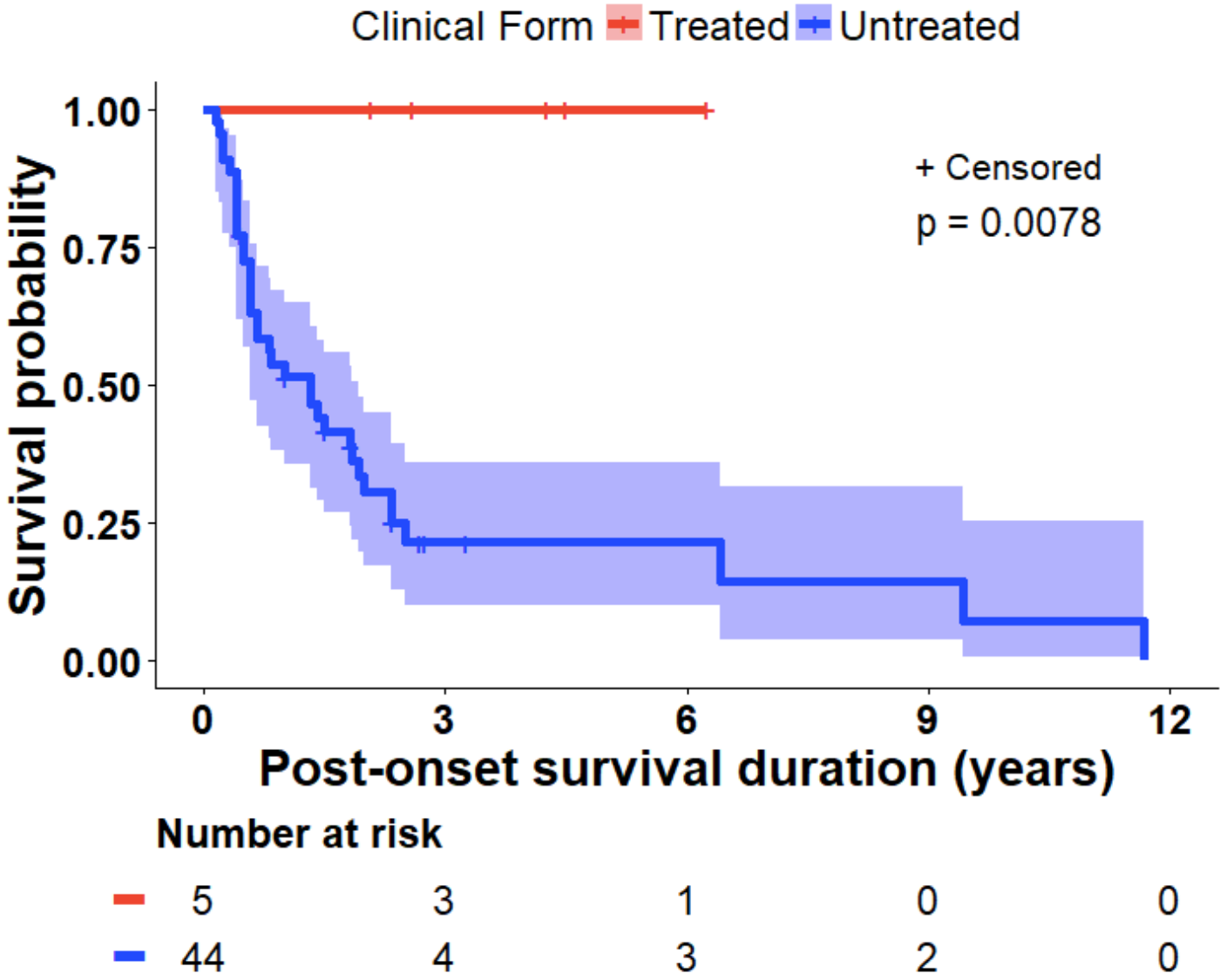
Compassionate use deoxynucleos(t)ide therapy

- **Completed analysis of the first 16 patients treated with dTMP+dCMP (1), dT+dC (10), or both sequentially (5).**
- **4 infantile-onset; 8 childhood-onset; 4 late-onset**
- **Ages at initiation of therapy: 1.33-60 years-old**
- **Current ages: 3.33-61 years-old**

26 additional patients have received deoxynucleoside therapy.

Dominguez Gonzales et al Ann Neurol 2019

Survival of TK2-deficient patients with early onset and severe myopathy



Acknowledgements

Columbia University Medical Center
Billi DiMauro, MD
John (Seamus) Thompson, PhD
Caterina Garone, MD, PhD
Emanuele Barca, MD, PhD
Valentina Emmanuele, MD, PhD
Kris Engelstad, MS
Andres Berardo, MD
Xiomara Rosales, MD
Richard Buchsbaum
Yuelin Long, MS
Johnston Grier, MS
Alexandra Sanford, MS
Joshua Kriger, MS
Taylor Bracken, MS
Bruce Levin, PhD

Modis Therapeutics
Peter Barber
Daniel DiPietro, PhD

United Mitochondrial Disease Foundation
Phil Yeske, PhD
Brian Harman

NIH
Adam Hartman, MD, NINDS
Danuta Krotoski, PhD, NICHD
Kathryn Camp, PhD, ODS

Funding
FUNDISMUN Foundation
MDA
NIH
Estopinan Columbia TK2 Research