Leading the Way with MDA

Research

Angela Lek Ph.D
VP of research

Muscular Dystrophy Association

MDA Portfolio

National Care Network
150+ Care Centers
40+ ALS Centers

Worldwide Research Network
Researchers & Clinicians

Advocacy
10,000+ advocates across all 50 states

Community Education
100,000+ reached thru educational materials:
online, on-demand

Summer Camp & Recreation
Provided at no cost to families:
in-person & virtual

Volunteerism
30,000+ volunteers engaged across the country

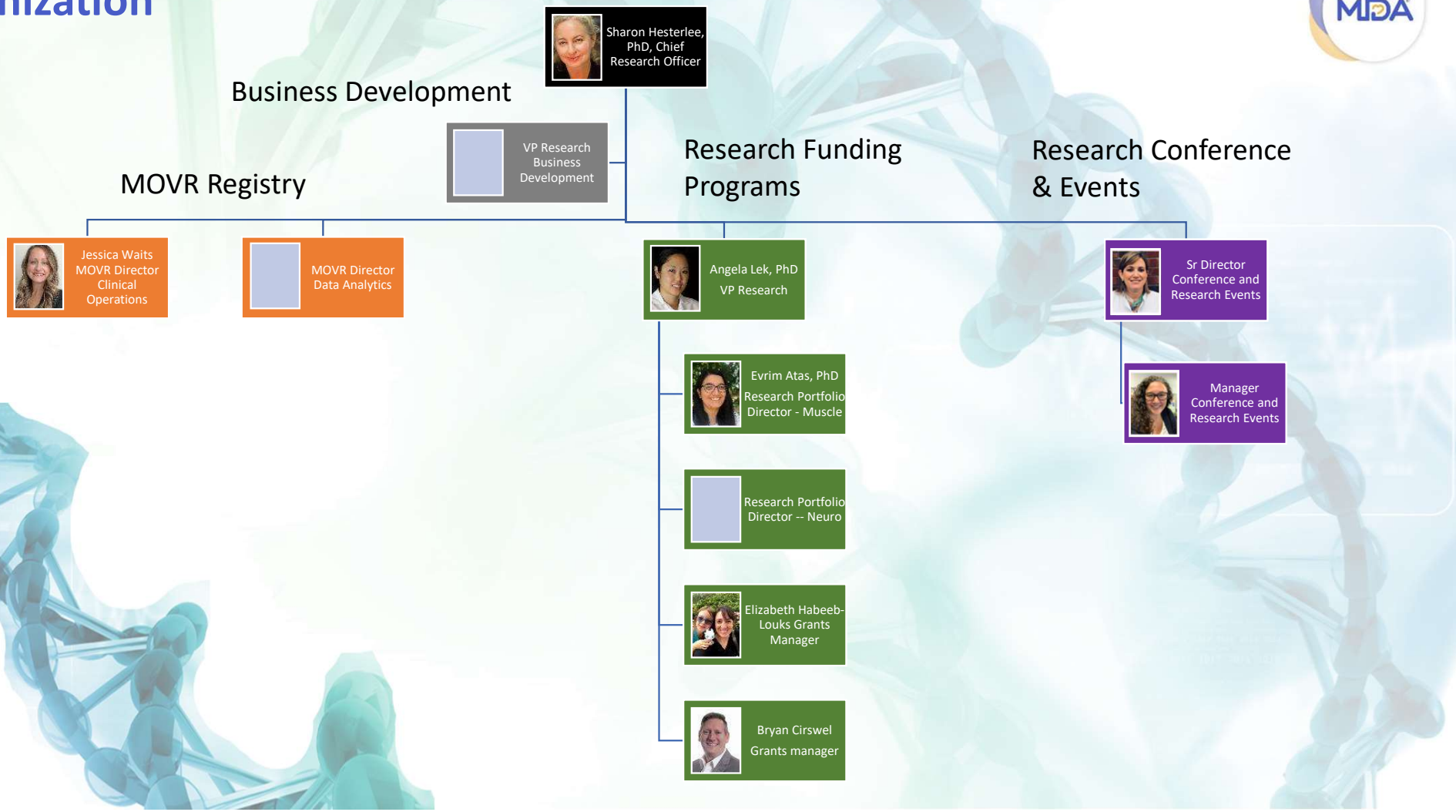
Events
Scientific Conference
Community Fundraisers
Marquee Events

Quest
Magazine
Newsletter
Podcast

Resource Center
20,000+ inquiries annually

Data Connections
Neuromuscular Disease Patient Registry &
MOVR Data Hub

Research Department Organization



Muscular dystrophies

The muscular dystrophies are a group of diseases that cause weakness and degeneration of the skeletal muscles.

Becker muscular dystrophy (BMD)

Congenital muscular dystrophies (CMD)

- Collagen VI CMDs (Bethlem, Ullrich)
- CMD, dynamin2-related
- CMD, telethonin-related
- CMDs with hypoglycosylation of dystroglycan
- CMDs with integrin deficiency
- Fukuyama CMD
- Lamin A/C/LMNA-related dystrophy
- Merosin/LAMA2-deficient CMD (MDC1A)
- Muscle-eye-brain diseases (MEBs)
- Rigid spine syndromes
- Walker-Warburg syndromes (WWS)

Duchenne muscular dystrophy (DMD)

Emery–Dreifuss muscular dystrophy (EDMD)

- Types 1-7

Facioscapulohumeral muscular dystrophy (FSHD)

- Types 1-2

Limb–girdle muscular dystrophies (LGMD)

- Types 1A-1F
- Types 2A-2Y

Myotonic dystrophy (DM)

- DM1
- DM2

Oculopharyngeal muscular dystrophy (OPMD)

Motor neuron diseases

In motor neuron disease, nerve cells called motor neurons progressively lose function, causing the muscles they control to become weak and then nonfunctional.

ALS (amyotrophic lateral sclerosis)

- Familial
- Sporadic

Spinal–bulbar muscular atrophy (SBMA)

Spinal muscular atrophy (SMA)

- Types 1-4
- Distal SMA

Ion channel diseases

Diseases associated with defects in proteins called ion channels typically are marked by muscular weakness, absent muscle tone, or episodic muscle paralysis.

Andersen–Tawil syndrome

Hyperkalemic periodic paralysis

Hypokalemic periodic paralysis

- HypoKPP Types 1-3
- Thyrotoxic HypoKPP

Myotonia congenita

- Thomsen myotonia
- Becker myotonia

Paramyotonia congenita

Potassium–aggravated myotonia

Mitochondrial diseases

Mitochondrial diseases occur when structures that produce energy for a cell malfunction.

Friedreich's ataxia (FA)

MDA covers all mitochondrial myopathies, including the following:

Mitochondrial myopathies

- Kearns-Sayre syndrome (KSS)
- Leigh syndrome (subacute necrotizing encephalomyopathy)
- Mitochondrial DNA depletion syndromes
- Mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS)
- Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE)
- Myoclonus epilepsy with ragged red fibers (MERRF)
- Neuropathy, ataxia and retinitis pigmentosa (NARP)
- Pearson syndrome
- Progressive external opthalmoplegia (PEO)

Myopathies

A myopathy is a disease of muscle in which the muscle fibers do not function properly, resulting in muscular weakness.

Congenital myopathies

- Cap myopathies
- Centronuclear myopathies
  - Centronuclear myopathy, BIN1-related
  - Centronuclear myopathy, DMN2-related
  - Centronuclear myopathy, RYR1-related
  - Centronuclear myopathy, TTN-related
- Congenital myopathies with fiber type disproportion
- Core myopathies
  - Central core disease
  - Multiminicore myopathies
- Myosin storage myopathies
- Myotubular myopathy
- Nemaline myopathies
  - NEM1-10

Distal myopathies

- Distal anoctaminopathy
- Distal myopathy with caveolin defect
- Distal myopathy with myotilin defect
- Distal myopathy with nebulin defect
- Distal myopathy with VCP defect
- Distal myopathy, alpha-B crystallin-related
- Distal myopathy, dynamin 2-related
- Distal myopathy, filamin C-related
- GNE myopathy/Nonaka myopathy/ hereditary inclusion-body myopathy (HIBM)
- Laing distal myopathy
- Markesbery-Griggs late-onset distal myopathy
- Miyoshi myopathy
- Udd myopathy/tibial muscular dystrophy
- Vocal cord and pharyngeal distal myopathy
- Welander distal myopathy

Endocrine myopathies

- Hyperthyroid myopathy
- Hypothyroid myopathy

Inflammatory myopathies

- Dermatomyositis
- Inclusion-body myositis
- Polymyositis

Metabolic myopathies

- Acid maltase deficiency (AMD, Pompe disease)
- Carnitine deficiency
- Carnitine palmitoyltransferase deficiency
- Debrancher enzyme deficiency (Cori disease, Forbes disease)
- Lactate dehydrogenase deficiency
- Myoadenylate deaminase deficiency
- Phosphofructokinase deficiency (Tarui disease)
- Phosphoglycerate kinase deficiency
- Phosphoglycerate mutase deficiency
- Phosphorylase deficiency (McArdle disease)

Myofibrillar myopathies (MFM)

- MFM, alpha-B crystallin-related
- MFM, BAG3-related
- MFM, desmin-related
- MFM, filamin C-related
- MFM, LDB3/ZASP-related
- MFM, myotilin-related
- MFM, SEPN-related
- Spheroid body myopathy

Scapuloperoneal myopathy

Neuromuscular junction diseases

Neuromuscular junction disorders result from the destruction, malfunction or absence of one or more key proteins involved in the transmission of signals between muscles and nerves.

Congenital myasthenic syndromes (CMS)

Lambert–Eaton myasthenic syndrome (LEMS)

Myasthenia gravis (MG)

Peripheral nerve diseases

In peripheral nerve diseases, the motor and sensory nerves that connect the brain and spinal cord to the rest of the body are affected, causing impaired sensation, movement or other functions.

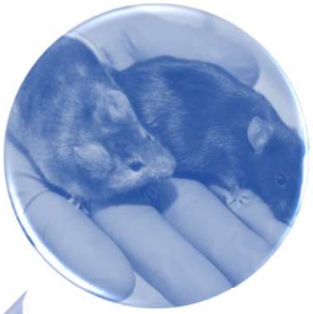
Charcot–Marie–Tooth disease (CMT)

- CMT-1
- CMT-2
- CMT-4
- CMT-X/X-linked CMT
- Dejerine-Sottas disease

Giant axonal neuropathy (GAN)

7 major categories of NMDs in MDA's Program = 330 individual diseases officially "covered" by MDA (partial list shown here)

MDA Research Activities



RESEARCH GRANTS

- Over $1B Invested
- 7000 individual investigators funded
- 2000 new investigators trained

MDA VENTURE PHILANTHROPY

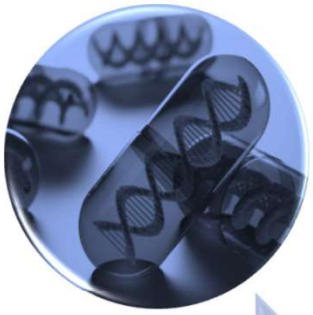
- 40 Investments since 2004
- $56M invested
- 2 NDAs submitted, one phase 3 and two phase 2

MOVR REGISTRY

- Clinic-entered
- 4000 participants
- 7 indications
- 2 publications

CONFERENCE & WORKSHOPS

- MDA Scientific and Clinical Conference: 1400 in-person attendees
- Challenges in Gene Therapy workshop



MDA KICKSTART

- In-house gene therapy for ultra-rare NMDs
- First indication is a congenital myasthenic syndrome

MDA Research Impact

Since the 1950's MDA has attracted the best and the brightest to the field of neuromuscular research, with funding levels only second to the Federal government

MDA has invested more than $1 billion in neuromuscular disease research to uncover new treatments.

- Over 7000 individual investigators funded
- Over 2200 fellowships to young investigators

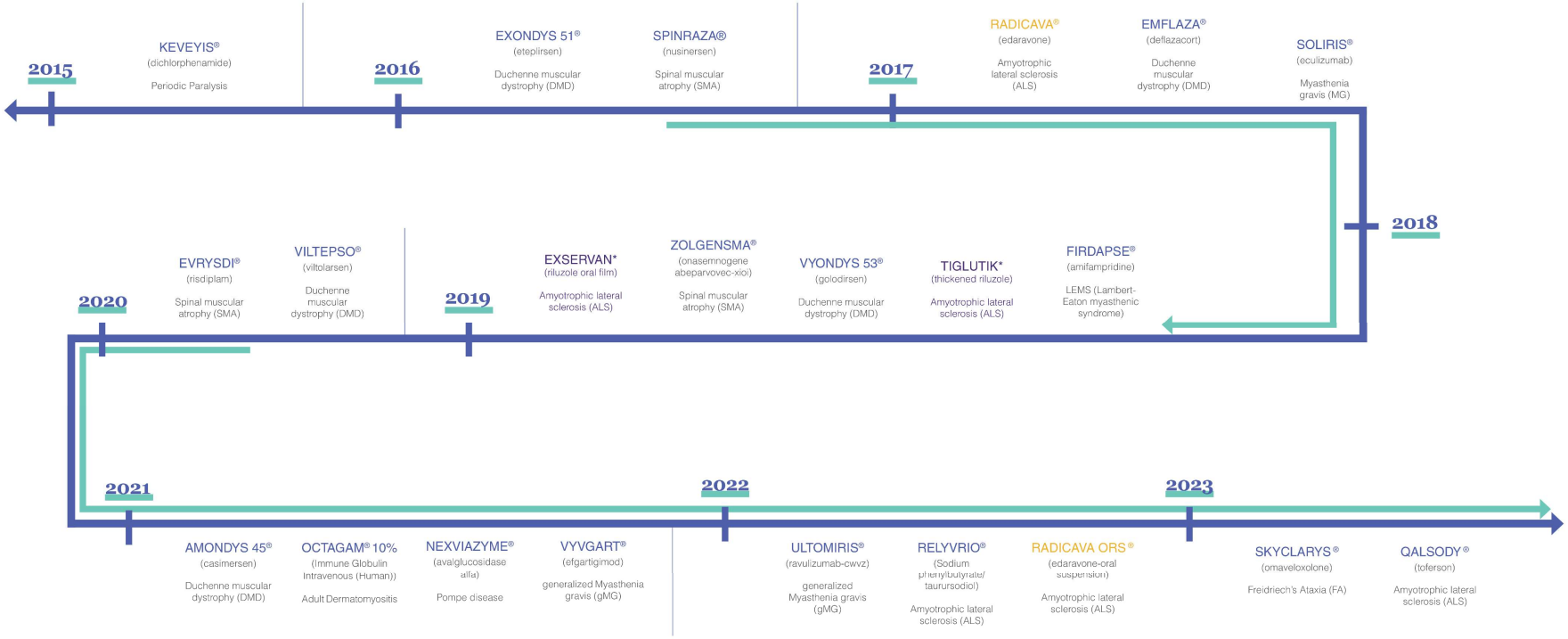
- 8 new drugs originating directly from MDA research
  - ALS: Rilutek
  - Pompe Disease: Myozyme
  - DMD: Exondys 51, Emflaza, Vyondys 53, Amondys 45
  - Periodic Paralysis: Keveyis
  - SMA: Spinraza

Treatments Approved for Neuromuscular Disease (2015 - Present)

Treatments approved prior to 2015 for neuromuscular disease (NMDs):
- 1995 Riglutek (ALS)
- 2006 Myozyme (Pompe)
- 2010 Lumizyme (Pompe)

As of April 2023, there are 19 FDA approved treatments for neuromuscular disease.

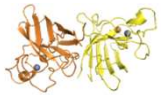
The chart above includes 22 FDA approved treatments due to different formulations of the same drug. **TIGULTIK** and **EXSERVAN** are brand names for different formulations of riluzole. Tiglutik is an oral suspension, Exservan is an oral film. **RADICAVA ORS** is another formulation for **RADICAVA (edavarone).**



MDA® Muscular Dystrophy Association

$170M investment by MDA has fueled critical breakthroughs in ALS

In the 1950's Eleanor Gehrig requested MDA's help in the fight against ALS



SOD1 Mutations identified
By Bob Brown and others with MDA funding

1993

Rilutek becomes the first FDA approved treatment for ALS"
MDA funding contributed to its development

1994

Development of SOD1 Mouse
By Teepu Siddique and others with MDA funding

1995

TDP 43 identified as key pathological protein in ALS

2005

Early safety data for oral sodium phenylbutyrate
Led to development of Amylyx drug

Start of $30M Investment in the ALS Therapy Development Institute

2006

2011

Discovery of C9ORF72 repeat expansions as the most common cause of familial ALS
Supported, in part, by MDA

Early efficacy of antisense oligos approach that is now tofersen
With substantial support from MDA

Radicava (edvaranone) becomes the second approved treatment for ALS by FDA

2017

2018

Phase I/II Trial evaluating T regulatory cells for ALS
MDA co-funding with advocacy partners to Stan Appel

First ever platform trial for ALS launched at Mass General Healey Center
MDA contributed funding via a grant to Sabrina Paganoni

2020

2021

MDA MOVR Patient Database records over 2000 participants
Fully supported by MDA

MOVR DATA HUB

MDA Research Grant Funding

Building the Foundation for Therapies

Angela Evrim Bryan Liz

Started: 1950

Total Grant Funding to date: Over $1 Billion

Number of grant categories: 7

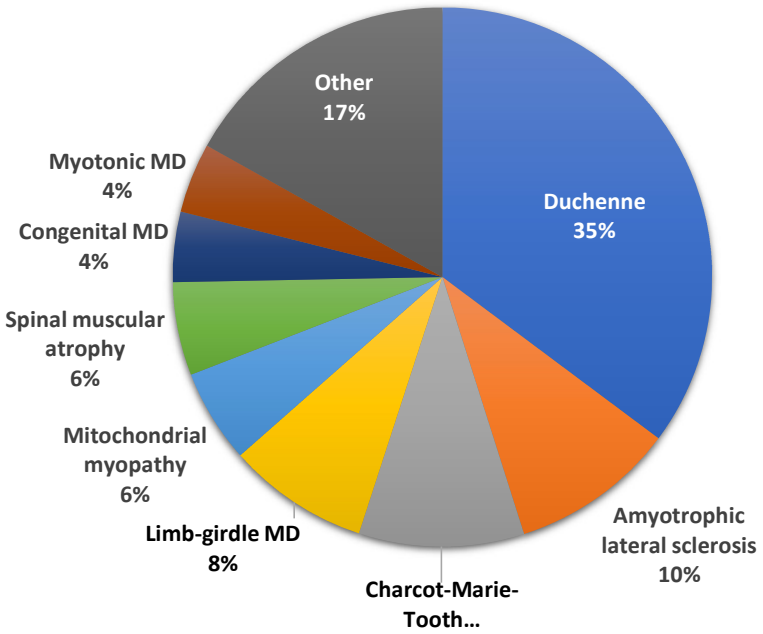
Investigators funded: 7000

New Investigators trained: 2000

2022 Funding: $17M committed, 80 new grants

Drugs approved for neuromuscular disease: >20

Active Grants by Indication



Process

1. Hundreds of investigators submit grant applications
2. The proposals are scrutinized and ranked by MDA's expert research advisory committee members
3. A subset with the highest review scores are selected for funding an approved by MDA's Board
4. MDA research staff monitor progress for each project and communicate with applicants
5. Funded investigators produce publications, receive bigger grants and develop new therapies

Grant review committee

- Impact for MDA's Mission
- Investigator
- Innovation
- Scientific Merit
- Rigor and Transparency

MDA grant categories

Academic Funding Opportunities

MDA Research Grants (RG)
The RG program supports independent, established investigators to accelerate progress toward understanding and treating neuromuscular disease..

MDA Idea Awards (IDEA)
The IDEA program seeks bold, innovative research ideas that can have an impact in the eld of neuromuscular disease. The idea should be supported by a strong scientic premise and include a feasible experimental plan.

MDA Development Grants (DG)
The DG program is meant to expand the number of scientists conducting neuromuscular disease research for postdoctoral investigators working in the laboratory of a senior investigator under whose guidance the researcher will be given exibility to work independently or as part of a collaborative effort.

MDA Clinical Research Grants (CRG)
The CRG program aids the development of therapeutic interventions for neuromuscular diseases.

MDA Clinical Research Network Grants (CRNG)
The CRNG program is meant to form a network to promote and accelerate clinical research helping support the infrastructure necessary to conduct research eciently through the collaborative activities of the network.

MDA Research Infrastructure Grants (RIG)
The RIG program is designed to support the development of tools, techniques, and services of need to the neuromuscular research community.

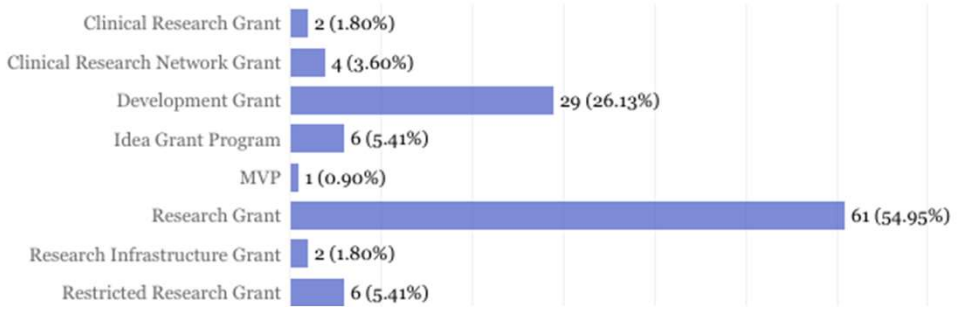
MDA Conference Grants (CG)
The CG program supports meetings and conferences focused on the muscular dystrophies and related diseases of the neuromuscular system.

Industry Funding Opportunities

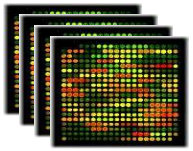
MDA Venture Philanthropy Program (MVP)

The MVP program targets investments in early-stage companies with promising technologies (drug or device) for neuromuscular diseases, serving to de-risk their platform and to help attract larger venture capital investments.

Breakdown of active grants in 2022



MDA De-Risking Tools Across Life Cycle of Drug Development

5-10 Years	2 Years	2 Years	2 Years	6 Years
Academic Institutions	↔ Small Biotechnology Companies		↔	Larger Companies
 Basic Research	 Target Identification & Drug Screening	 "Proof-of-Concept" Testing	 Translational Research	 Clinical Trials
• MDA Research Grant • MDA Development Grant • MDA Idea Award • Funding Conferences • Holding Conferences	• MDA Infrastructure Grant (tools, techniques and services) • MDA Research Grant	• MDA Research Grant • MDA Idea Award • MDA Development Grant	• MDA Venture Philanthropy • MOVR Registry	• MDA Clinical Trial Grants • MDA Clinical Research Network Grants • MDA Clinical Fellowship • MOVR Registry • MDA Care Center Network

De-Risking Mechanisms (Examples)

Research Grant (32) $9,417,271	Development Grant (13) $2,715,402	Clinical Trial Grant (2) $797,011	Clinical Research Network Grant (2) $1,715,502	Infrastructure Grant (1) $439,250	Idea Award (9) $450,000	MDA Venture Philanthropy (2) $1,200,000	MOVR Registry	MDA Care Center Network	MDA Conferences
Mobilizing Muscle Stem Cells to Treat DMD (Rudnicki, Michael) Ottawa Hospital Research Institute 	**ASM-AAV Gene Therapy as a Treatment for Limb Girdle Muscular Dystrophy 2B** (Bittel, Daniel) Children's National Medical Center 	Brett McCray, MD., Ph.D Johns Hopkins University School of Medicine, MD **Advancing clinical trial readiness in TRPV4 neuropathy** $497,011 	Jeffrey Statland, M.D. University of Kansas Medical Center Research Institute, Inc., KS **Muscular Dystrophy Clinical Trial Research Network** $1,517,502 	Michael Shy, M.D. The University of Iowa, IA **Inherited Neuropathy Consortium** $439,259 	**Ultrasound-induced access of therapeutics to peripheral nerves** (Kagiava, Alexia) The Cyprus Foundation for Muscular Dystrophy Research 	• Over $30M invested in small biotechs and start-ups over 10 years • First investment payouts potentially this year 	• Data for ALS, DMD, BMD, SMA, FSHD, LGMD, Pompe disease • Over 4000 participants • Clinic-entered, regulatory compliant data 	• 150 Care centers throughout US • 60,000 individuals seen annually • Over 90,000 visits • Care Center Directors convened 2X/year 	**Main Conference:** • 1200 in-person attendees • 120speakers • 32 sessions **GTx Workshop** • 50 attendees • Invitation only **Funding Support to Many External Conferences:** FSHD, LGMD, New Directions, NHC Myology Course

https://www.mda.org/science/grants-at-a-glance

2022 Grants at a Glance

MDA's research program awards grants to the world's best scientists investigating promising theories and therapies that may accelerate treatments and cures for families living with muscular dystrophy, ALS and related neuromuscular diseases. Here are the grants funded by the MDA in 2022.

Learn more about MDA funded research
See how we choose our grants
See past grants

Grantee | **Grant Type** | **Disease**

- Any -

Apply | Reset

Pathophysiology and Treatment of Tubular Aggregate Myopathy
Grantee: Robert Dirksen, Ph.D.
Funded: 9/1/2022 - 8/31/2025
Grant Type: Research Grant
Disease(s): Congenital muscular dystrophies (CMD)

Combining oxytocin with corticosteroid therapy in DMD patients
Grantee: Sabine De La Porte, HDR
Funded: 9/1/2022 - 8/31/2023
Grant Type: Idea Award
Disease(s): Duchenne muscular dystrophy (DMD), Becker muscular dystrophy (BMD)

Unraveling the contribution of local translation to ALS pathogenesis
Grantee: Sandrine Da Cruz, Ph.D.
Funded: 9/1/2022 - 8/31/2025
Grant Type: Research Grant
Disease(s): ALS (amyotrophic lateral sclerosis)

Therapeutic significance of FKRP's regulation of glycosylation within the Golgi
Grantee: Peter Currie, PhD
Funded: 9/1/2022 - 8/31/2025
Grant Type: Research Grant
Disease(s): Limb-girdle muscular dystrophies (LGMD)

Long-read genome sequencing to diagnose neuromuscular disorders
Grantee: Greg Cooper, Ph.D.

Investigating a link between ER stress and nucleocytoplasmic transport in ALS

Microdystrophin Design for the Treatment of Dystrophin-Deficient Cardiomyocytes

Currently, there are three clinical trials testing microdystrophin in Duchenne muscular dystrophy (DMD) patients. Microdystrophins have shown promise in improving skeletal muscle function; however, little is known about efficacy in the heart as animal models used in preclinical testing do not manifest dilated cardiomyopathy. This is a critical gap in our knowledge, as dilated cardiomyopathy is the leading cause of death in DMD patients. My project capitalizes on cardiomyocytes differentiated from human induced pluripotent stem cells harboring dystrophin mutations. I will compare how well microdystrophin variants rescue functional deficits exhibited by dystrophin-deficient cardiomyocytes against minidystrophin, comprised of more domains of dystrophin. The outcome of this study will yield design principles for transgenes that can improve the functional deficits of DMD cardiomyocytes. This study will evaluate the efficacy of existing microdystrophin variants in the context of cardiomyocyte function and will establish a platform for assessing functional rescue in human cells, accelerating the development of therapies to delay the onset of heart failure.

Grantee: Asuka Eguchi, Ph.D.
Grant type: Development Grant
Award total: $210,000
Institution: The Board of Trustees of the Leland Stanford Junior University

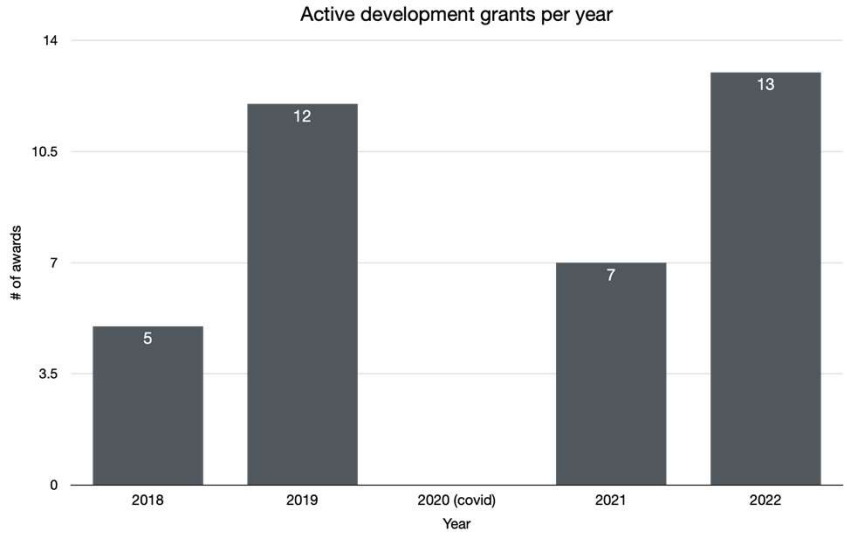
Identification of genetic modifiers for C9ORF72-ALS/FTD

A hexanucleotide repeat expansion in the C9ORF72 gene is the most common genetic cause of amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD), two adult-onset progressive neurodegenerative diseases. One of the major hypotheses for toxicity is the accumulation of dipeptide repeat (DPR) proteins produced by RNA repeats. There were many studies unraveling the toxicities by different DPRs. In particular, poly-GR is one of the most toxic DPRs and is found to correlate with neurodegeneration in C9ORF72-related ALS, implicating the contribution of poly-GR to the disease etiology. Therefore, we performed a genetic screening in human neurons to identify modifiers that regulate the poly-GR mediated toxicity. I identified and validated one candidate modifier, knockdown of which strongly improved the survival of the poly-GR expressing neurons. I now propose to further decipher the neuroprotection mechanism, and validate the rescue efficacy in both C9ORF72-ALS patient-derived neurons and the mouse model. This study will provide novel insights on disease mechanisms and potential therapeutic target.

Grantee: Zhe Zhang, Ph.D
Grant type: Development Grant
Award total: $210,000
Institution: Johns Hopkins University School of Medicine

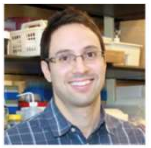
Funding the next generation leaders

- MDA awards research and clinical fellowships to trainees interested in pursuing a career in neuromuscular disorders.
- In 2022, MDA funded thirteen (13) post-doctoral fellows with the **Development Grant**, and two (2) clinicians with **clinical research fellowships**.




Alba Timon-Gomez, PhD
Oroboros Instruments


Ron Batra, PhD
Locana Bio


Justin Boyer, PhD
Canadian Gov't


Fatima Gasset-Rosa, PhD
Vividion Therapeutics


Monkol Lek, PhD
Yale University


Angela Lek, PhD
MDA


Jennifer Levy, PhD
Coalition to Cure Calpain 3


Dwi Kemaladewi, PhD
University of Pittsburgh

Diversity – Equity – Inclusion
Summer Internship in neuromuscular disease

Angela Bryan

One student will be selected from the following institutions, given a stipend of up to $10,000 and be paired with a mentor from MDA's Research Advisory Committee (RAC).

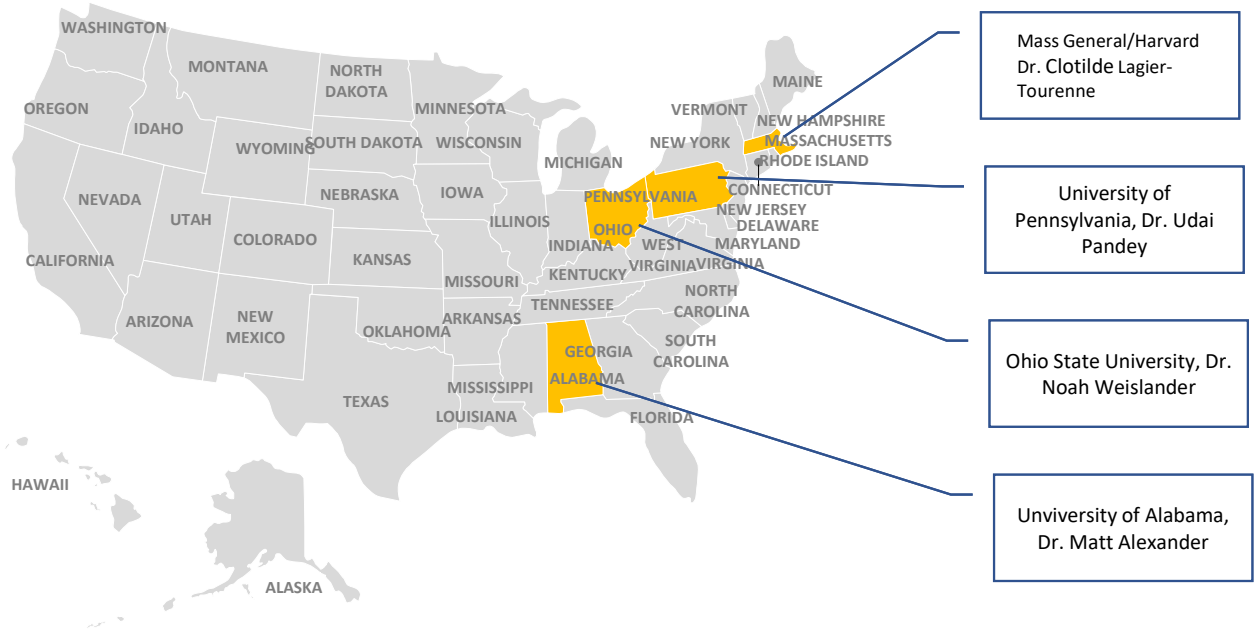
Started: 2023

Type of students supported: Diverse undergraduates

Diversity attributes considered: underrepresented racial and ethnic groups, individuals with disabilities, individuals from disadvantaged backgrounds

Total Students to Date: 4 the first year (not yet selected)

Number of Institutions involved: 4



MDA Venture Philanthropy

Investing in neuromuscular disease therapy development

Angela Evrim Bryan

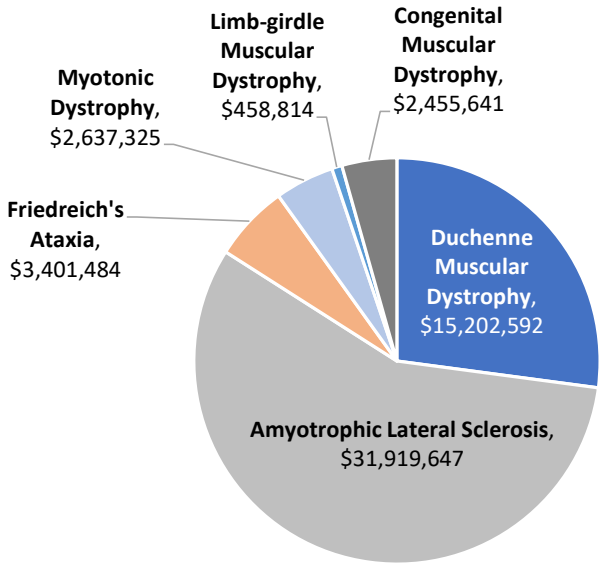
Started: 2004

Total Investments to Date: $58,316,543

Investments still in play: 22

Most interesting near term: Vamorolone: steroid alternative, Santhera, new drug application submitted -- FDA decision in Fall 2023

Most recent: Myosana (non-viral gene therapy for DMD) and Pathmaker Biosystems (device for ALS)



Process

20 minute "pitch decks" submitted and reviewed by MVP committee

2-3 Pitches selected for deeper diligence

Investment Memo submitted to MDA BOD

Royalty sharing or equity agreement negotiated

MVP Phase II Diligence

- Technology platform
- Pipeline
- Disease overview
- Epidemiology
- Natural history
- Pathology
- Rationale
- Target Product Profile
- Preclinical plan and timeline
- Screen strategy
- Preclinical Proof-of-Concept
- PK/PD (Pharmcokinetics and pharmacodynamics)
- ADME (Adsorption, distribution and mechanism of excretion)
- Toxicology plan/data
- Translational plan
- Overall clinical plan/timeline
- Biomarkers
- Endpoints
- Recruitment plan
- Clinical data summary
- Manufacturing plan and timelines
- Overall regulatory plan and timeline
- Regulatory – preclinical
- Regulatory -- clinical
- Patient advocacy landscape
- Goals for engagement with advocacy orgs
- Timeline for advocacy engagement
- eNPV and assumptions
- Competitive review
- Exit options
- Funding request
- Life of project budget
- Granular current budget
- Key budget assumptions
- Key management
- Board members
- Relevant external advisors
- Partnerships and collaborations
- Intellectual property
- Summary
- Closing

MVP Investments History

Translational Research Grant

MVP

Ended

In Play

*Equity Investment

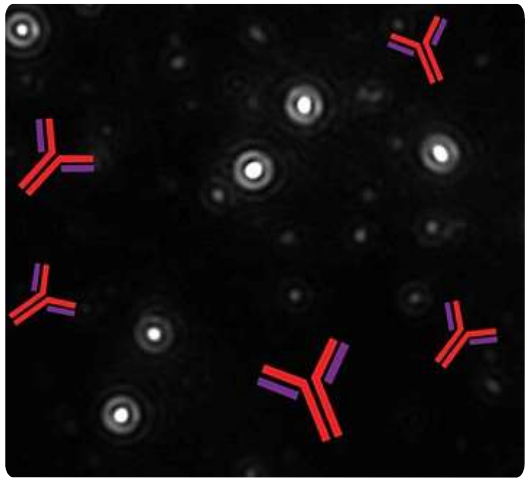
Year	Company	Indication	Amount	Status	Revenues
2004	Askbio	DMD	$1,621,172		
2005	PTC Therapeutics	DMD	$1,500,000	Clinical testing	
2006	TGEN	ALS	$652,056		
2006	Askbio	DMD	$2,403,367		
2007	Repligen	FA	$978,237		
2007	Insmed	DM1	$2,087,325		
2007	ALSTDI	ALS	$18,000,000	Clinical Testing	
2008	CA Stem Cell	ALS	$200,000		
2009	Repligen	DM1	$731,534		
2009	Catabasis	DMD	$150,000		
2010	ALSTDI	ALS	$3,355,600	Clinical testing	
2010	PTC Therapeutics	DMD	$1,000,000	Clinical testing	
2010	Validus/Reveragen	DMD	$360,000	Near Approval	
2010	Nationwide	LGMD2D	$458,814	Clinical testing	$40,000
2010	4S3 Bioscience Inc	MTM	$260,291		
2010	Acceleron	DMD	$1,500,000		
2010	UCLA	DMD	$513,665		
2010	Giglogix	ALS	$268,000		
2010	Repligen	FA	$1,423,247		
2011	ALS Biopharma	ALS	$250,000		

Year	Company	Indication	Amount	Status	Revenues
2011	Tivorsan	DMD	$1,000,000		
2011	ALSTDI	ALS	$3,200,000	Clinical Testing	
2011	ALSTDI	ALS	$278,850	Clinical testing	
2011	Summit	DMD	$750,000		$800,000
2012	ALSTDI	ALS	$2,000,000	Clinical testing	
2012	Reveragen	DMD	$1,549,725	Near Approval	
2013	ALSTDI	ALS	$3,200,000	Clinical testing	
2013	Armgo Pharma	RYR1	$999,588	Clinical testing	
2013	Valerion	MTM	$1,195,762		
2013	Akashi	DMD	$500,000		
2014	Reveragen	DMD	$1,015,200	Near Approval	
2017	Izumi	ALS	$96,360	Pre-Clin	
2017	Iron Horse Diag.	ALS	$205,287	Near Approval	
2018	AcuraStem	ALS	$300,000	Pre-Clin	
2019	Locana	DM1	$550,000	Pre-Clin	
2019	UCLA	DMD	$389,463	Pre-Clin	
2019	Aavanti*	FA	$1,000,000	Pre-Clin	
2021	Myogene*	DMD	$150,000	Pre-Clin	
2022	Myosana*	DMD	$650,000	Pre-Clin	
2022	PathMaker Neuro*	ALS	$600,000	Clinical	

Myosana Therapeutics

The Myosana Investment: $650,000

- We have developed a *Platform Technology* with key features to address the problems posed by AAV administration



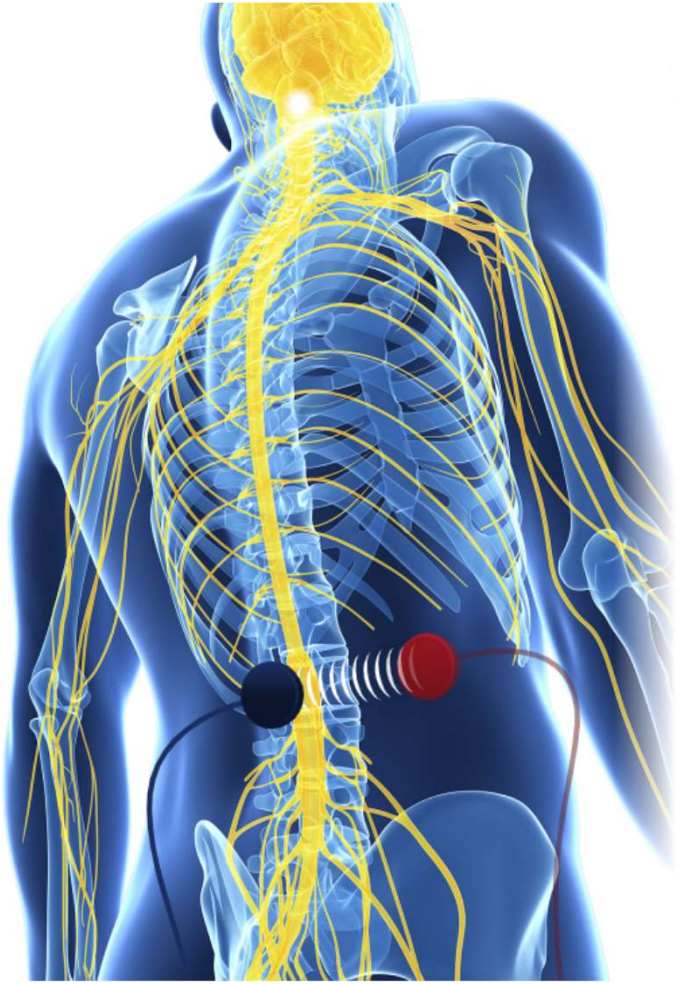
Stan Froehner

Nick Whitehead

- Our technology does not use viruses to deliver genes to the cells.
- A Non-Viral delivery method is much less likely to elicit an immune response, enabling repeated dosing over months or years.
- We are able to directly target the muscle cells.
- We have developed antibodies to a specific muscle protein, which binds to the cell and delivers the appropriate gene into skeletal & cardiac muscle. This unique technology has application to a wide range of genetic diseases affecting skeletal and/or cardiac muscle.
- Importantly, our platform is *Not Restricted By Gene Size*

PathMaker Neurosystems Investment: $600,000

- **PathMaker Neurosystems** is a near-commercial stage neuromodulation company founded to commercialize recent advances in the development of non-invasive devices for neuronal hyperexcitability suppression that enable the treatment of patients with serious neurological disorders. We are focused on rapidly bringing to market revolutionary products for non-invasively treating Spasticity and ALS (amyotrophic lateral sclerosis). Based on extensive pre-clinical animal studies, recent elucidation of molecular mechanisms and published human clinical results, the Company is advancing an entirely novel treatment paradigm based on multi-site direct current stimulation (Multi-Site DCS). Our proprietary technology is able to non-invasively restore neural pathways damaged by stroke, ALS and other neurological disorders by normalizing pathway overactivity



MDA Kickstart

Enabling drug development for ultra-rare disease

Angela Evrim Liz

Started: 2022

Total Investments to Date: $1M committed

Projects started: 1

Current Project: Gene therapy for congenital myasthenic syndrome

- Affects <300 people in US, primarily infants, children and adolescents
- Collaboration with UC Davis – Ricardo Maselli
- Symptoms: muscle weakness, potentially fatal apnia (breathlessness)

Kickstart is an in-house drug development program for MDA's ultra-rare diseases that are amenable to a gene therapy approach

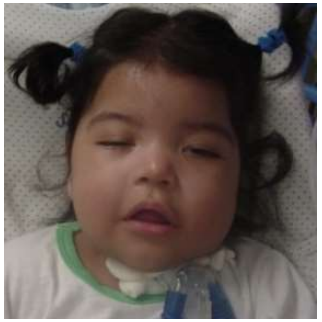
Goals:

1. To develop treatments for ultra-rare diseases in MDA's program that lend themselves well to gene therapy and for which there are currently no other effective treatments
2. To demonstrate that it is possible to de-risk these assets in such a way that they can be partnered through an approval
3. To document roadblocks and lessons learned to benefit advocacy efforts around ultra-rare disease

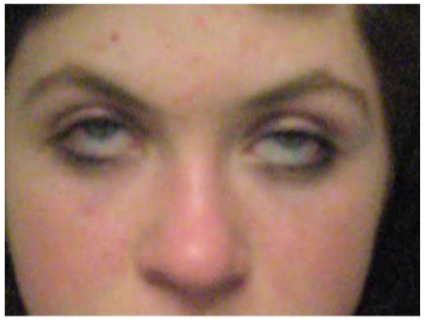
Congenital myasthenic syndrome with episodic apnoea (CMS-EA) is an ultra-rare disease but potentially treatable

CMS-EA is most commonly caused by mutations in CHAT (single gene) resulted in life-threatening events in infancy.

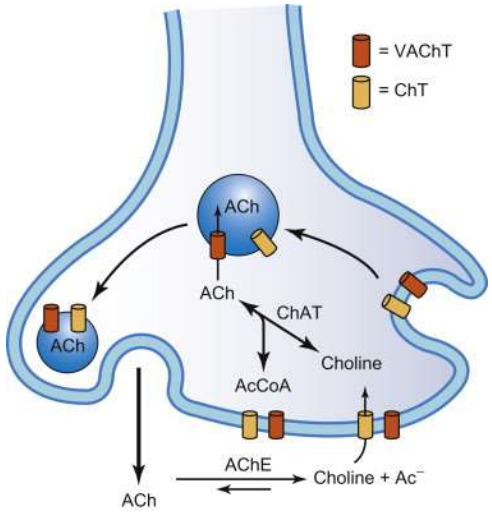
- Enzyme: choline acetyltransferase (ChAT).
- Function: ChAT resynthesizes ACh at nerve terminals.
- Translation: Spinal motor neurons, central and autonomic neurons
- Two variants of the disease: neonatal form (severe with cognitive developmental delay) and childhood/adult form (moderate but with sudden apneas).
- Treatment: Pyridostigmine, albuterol and 3,4 DAP (all ineffective).



Neonatal form

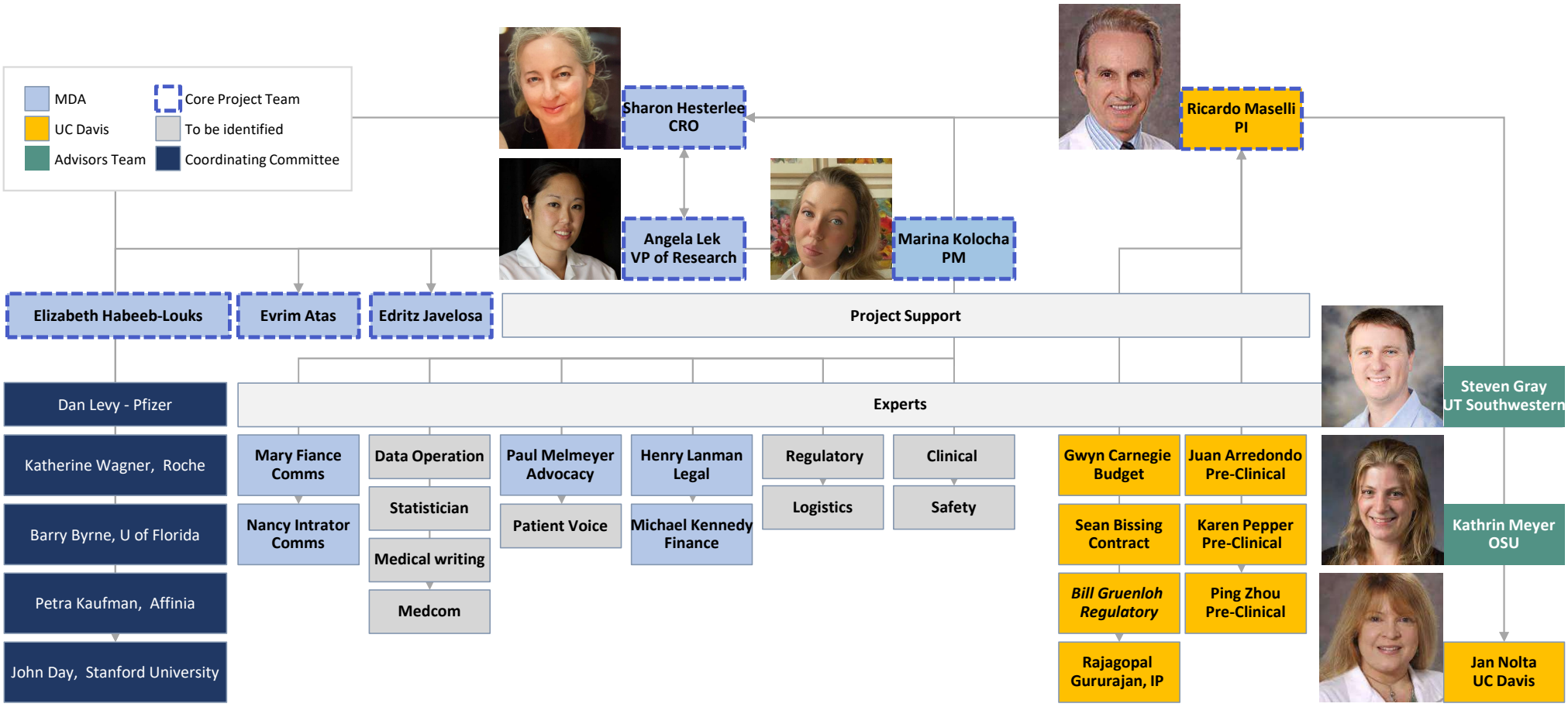


Childhood form



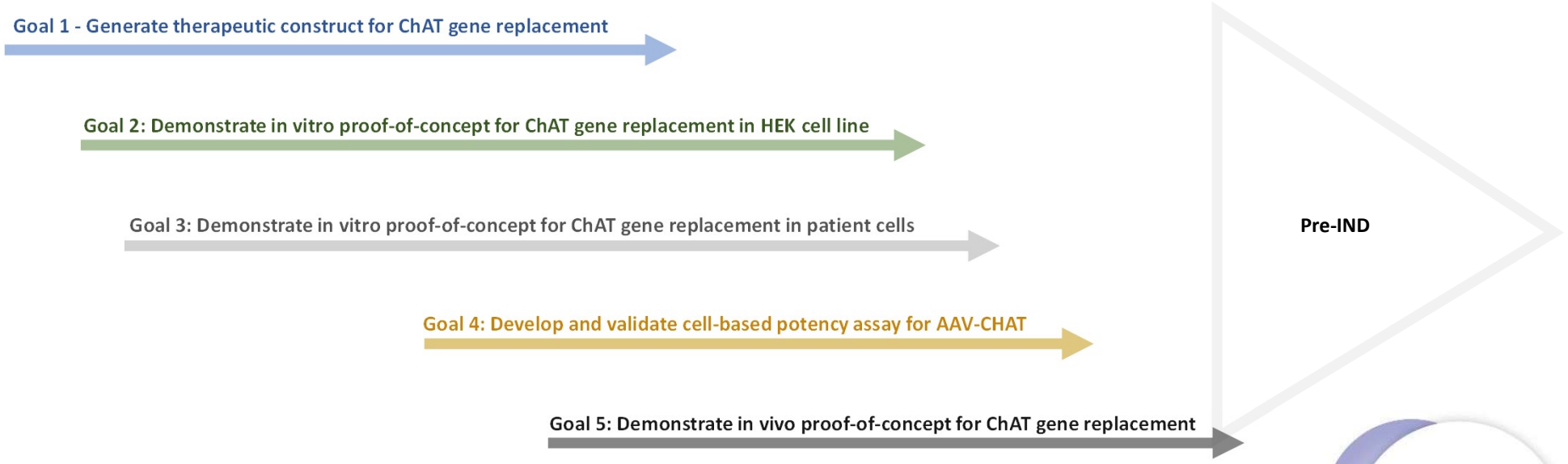
ChAT Function

Our Expert Team



Pre-Clinical Plan: for Pre-IND submission we designed the pre-clinical research plan to meet the requirements, expectations and needs

We plan to work on five goals with our multi-expert team; consult and review our progress regularly with advisors



- Transgene expression
- Infectivity of the carrier
- Transcription and translation of transgene
- Modifications
- Western blot (WB)
- Enzyme-linked immunosorbent assay (ELISA)
- Flow cytometry (FCM)
- Real time PCR
- Transcription
- Protein levels
- Proper localization
- Therapeutic efficacy
- Mouse models

MDA's $125M Commitment to the Development of Gene Therapy

Now:

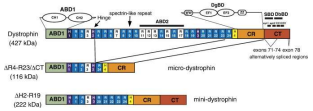
- Zolgensma approved for SMA
- Human trials taken place or underway in LGMD2D, LGMD2E, LGMD2i/R9, Pompe Disease, DMD, XLMTM

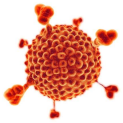
First MDA gene therapy grant:
"Direct in vivo gene therapy of Duchenne muscular dystrophy"

1990

1991

Shrinking the dystrophin gene
"Dystrophin mini-genes for gene therapy"





Using Adenoviruses
"Optimization of dystrophin-expressing adenovirus vectors"

1994

1998

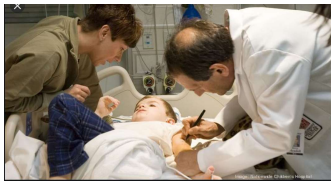
Using adeno-associated viruses
"Adeno-associated virus (AAV)-mediated therapy for acid maltase deficiency"

First human trial
"Alpha-sarcoglycan gene therapy for limb-girdle muscular dystrophy (LGMD)"

1999

2004

First DMD Study
"Phase I/II Study of mini-dystrophin gene in AAV vector"



Systemic gene therapy in Dog
"Systemic AAV gene therapy in a Duchenne Dog Model"

2008

2013

DMD Gene Editing
"Genetic correction of Duchenne muscular dystrophy with engineered nucleases"

RNA-targeting
"Reversal of myotonic dystrophy 1 using RNA-targeting Cas9 technology"

2018

2019

Large dystrophin genes
"Generation of large dystrophins in muscle via AAV gene therapy"

MDA Holds Summit to Address Challenges in Gene Therapy

Chairs: Dr Carsten Bönnemann (NIH)
Dr Barry Bryne (University of Florida)
2022 and 2023

- ➔ **RFA on important issue(s) raised**
- ➔ **Publish Meeting Report: 'Safety and challenges in gene transfer therapy'**

MDA Muscular Dystrophy Association

MDA achievements from last year's meeting:

- Meeting report published in Journal of Neuromuscular Diseases

Meeting Report: 2022 Muscular Dystrophy Association Summit on 'Safety and Challenges in Gene Transfer Therapy' Cite

Article type: Meeting Report

Authors: Lek, Angela[a,*] | Atas, Evrim[a] | Hesterlee, Sharon E.[a] | Byrne, Barry J.[b] | Bönnemann, Carsten G.[c]

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DOI: 10.3233/JND-221639

Journal: Journal of Neuromuscular Diseases, vol. Pre-press, no. Pre-press, pp. 1-10, 2023

Published: 11 February 2023

- Fundraised for grant RFA:

'transgene-triggered safety concerns in DMD gene therapy'

- Awarded two 2-year project grants:

Jeffrey Chamberlain, PhD

University of Washington

"Expression of enhanced dystrophins via AAV"

Carrie M. Miceli, PhD

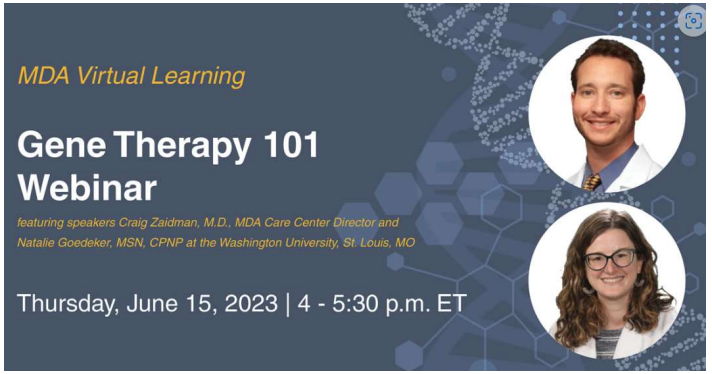
University of California, Los Angeles

"Single cell transcriptomics to assess transgene related responses in DMD"

Muscular Dystrophy Association Announces Gene Therapy Support Network for Families Living with Neuromuscular Disease

MDA Gene Therapy Support Network offers guidance on MDA Care Centers, resources, and educational programming beginning with MDA Virtual Learning: Gene Therapy 101 webinar to be held Thursday, June 15, 4-5:30pm ET

NEW YORK, May 22, 2023 -- Muscular Dystrophy Association (MDA) announced today the launch of the MDA Gene Therapy Support Network (GTx), ahead of a pending FDA approval for the first gene therapy for Duchenne muscular dystrophy (DMD). The expanded nationally renowned MDA Resource Center offers nationwide one-on-one expert support and guidance for newly approved gene therapy treatments for people living with neuromuscular diseases (NMDs). FDA approvals for gene therapies in NMDs include treatment for spinal muscular atrophy (SMA) and amyotrophic lateral sclerosis (ALS). Families may contact MDA Resource Center Gene Therapy Specialists for information, guidance and help facilitating access to novel therapies, by phone at 1-833-ASK-MDA1 (1-833-275-6321) or via email at ResourceCenter@mdausa.org. Virtual appointments may also be scheduled at: GTx Support Specialist Meeting.



MDA ObserVational Research database (MOVR)

Maximizing the potential of clinical data

Sharon Jessica

Started: 2013

Total Participants: >4000

Disease covered: 7

- ALS
- DMD
- BMD
- LGMD
- FSHD
- Pompe
- SMA

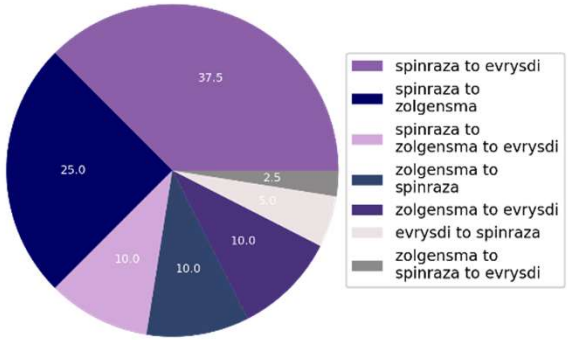
MOVR sites: 55

55 Care Center sites are also MOVR sites

What kinds of things can we learn?

- Understanding Demographics
- Designing Trials – Understanding Disease Progression
- Recruitment for Clinical Trials
- Understanding variability in care across sites
- Tracking therapy uptake and change over time

For example, we know in what order people are trying different SMA treatments



SMA Approved Treatments

- Almost 40% of SMA participants who have switched drugs have gone from Spinraza to Evrysdi
- Some people have tried all three approved SMA drugs

Summary of Data Elements for ALS

Demographics Form
Enrollment
Disease type*
Enrollment date*
Demographics
Gender*
DOB*
Race*
Ethnicity*
Insurance
Type of health insurance*
Primary care physician status
Education
Student status
Education level
Employment
Employment status

ALS Diagnosis Form
Diagnosis
Date / age of diagnosis*
Date / age of symptom onset*
Body region(s) first affected*
Genetic Diagnosis
Gene mutation*
Revised El Escorial Criteria
Revised El Escorial Criteria value
Family History
Any family members diagnosed with ALS or FTD*
If yes, select relative affected and their diagnosis (either ALS or FTD)

ALS Encounter Form (1/2)
Patient Information
Encounter date*
Method of encounter
Height / method of measurement*
Weight*
Clinical trial participation status
Falls & Hospitalizations
Approx. # of falls over past 3 months*
Reason for hospitalization / ICD-10 Code / admission and discharge dates
ALSFRS-R
Was ALSFRS-R done?*
Date / administration method / person who responded to ALSFRS-R
Questionnaire values (1-R3) and Total Score
Mental Status
Screened for cognitive and behavioral impairment?*
Mental status/cognitive scale performed status / scale used / score*
Medications
Disease-modifying therapy discussed*

ALS Encounter Form (2/2)
Symptomatic therapy discussed*
Medication name / start date / end date
Disease Progression
Clinical milestone (ambulation, speech, gastrostomy, NIV, tracheostomy) / date*
Assistive device / orthosis device / communication device log
Nutritional & GI Therapies
Screened by clinician for dysphagia, weight loss or impaired nutrition*
Medical nutritional supplementation status*
Feeding route*
Pulmonary
Symptoms of respiratory insufficiency / treatment options discussed*
Non-invasive ventilation status*
Tracheostomy status*
Pulmonary function testing / date of test / type of test performed / results*
Pulmonary device log
Visit Summary
End of life issues discussion status*
Multidisciplinary care plan status*
Patient seen by and referred to*

Discontinuation Form
Discontinuation
Cause of discontinuation*
Date of lost to follow up*
Date withdrew consent*
Reason for study withdrawal*
Date of death*
Primary cause of death / ICD-10*
Secondary cause of death / ICD-10*

*Indicates core data elements (mandatory), all other items are supplemental

- *Demographics and Diagnosis forms are filled one time upon enrollment into registry (updated if data changed)*
- *Encounter form is filled out for every clinic visit*

“ALS Go Digital” Study with Mitsubishi Tanabe Pharma

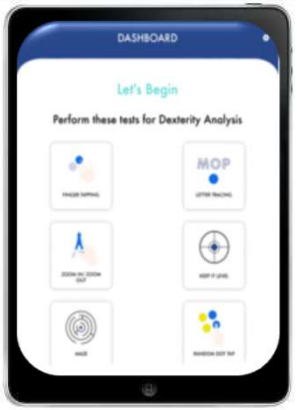
- **12-month Observational Study**
- **75 Adult MOVR Participants with ALS**

Objectives

1. **Assess feasibility of collecting data at home**
2. **Determine whether data collected by Digital Health Technologies (DHT’s) can be used to accurately capture changes in ALS progression**
3. **Determine the correlation between data collected at home and gold standard outcome assessments such as the ALSFRS-R and the ROADS**

Mitsubishi Tanabe Pharma

“ALS Go Digital” Remote Data Collection Overview

Monthly	Monthly	Continuously
		
ALS Health Surveys Patient Smartphone	**Fine Motor Assessments/Hand Dexterity Provisioned iPad**	**Activity & Sleep**

Mitsubishi Tanabe Pharma

MDA Clinical & Scientific Conference

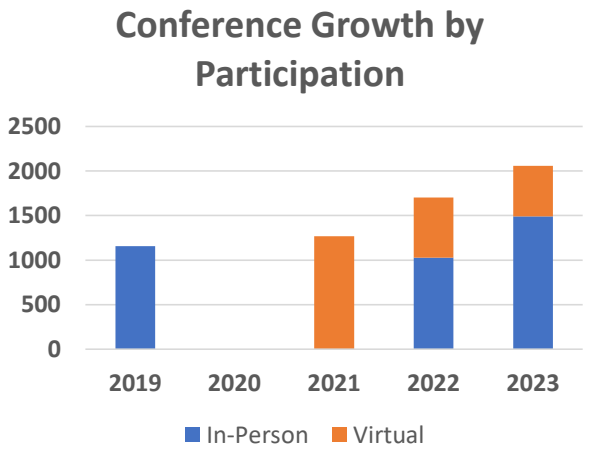
The largest meeting of its kind in the neuromuscular space

Pam Cortney

2023

- Back to full size, Dallas, TX
- 1492 in person attendees, 567 virtual attendees, 33 sessions, 160 speakers, 55 exhibitors, 14 PAP
- Net revenue pending close to $1.4M

Attendee Type	In-Person	Virtual	Overall
Physician/Researcher (MD and/or PhD)	429	191	**620**
Allied Health (RN, NP, SW, GC, PT, OT, etc.)	111	49	**160**
Non-Profit Organizations	46	9	**51**
Patient/Caregivers	10	86	**96**
Industry	740	104	**844**
Other (Investor, Press, BoD, Staff, etc.)	178	128	**284**
TOTAL REGISTERED	**1491**	**567**	**2056**



Thank you for your support !

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- YouTube: YouTube.com/MDA
- TikTok: @mdaorg
- Twitch: MDA_LetsPlay
- Discord: MDA Let's Play