And Now For Something Completely Different

Standing up a new program that is waaay outside the box

Sharon Hesterlee, PhD
Chief Research Officer
The Muscular Dystrophy Association was founded in the 1950’s by concerned parents who wanted to develop treatments for their children who were living with neuromuscular disease.

MDA Research & Care

MDA Care Centers

- 150 Care Centers supported across the US
- 60,000 individuals seen annually

Research Grants

- $1B projects funded
- 7000 Individual investigators funded
- 2000 new investigators trained and supported

MOVR Clinical Database

- Over 4000 individuals enrolled
- 7 Disease areas
- 12,000 encounters documented

New Therapies

- 18 drugs approved for neuromuscular diseases
- 9 Drugs developed directly from MDA funding
# MDA Research Program Focused on “De-Risking” Drug Development

<table>
<thead>
<tr>
<th>Academic Institutions</th>
<th>Small Biotechnology Companies</th>
<th>Larger Companies</th>
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</thead>
<tbody>
<tr>
<td>Basic Research</td>
<td>Target Identification &amp; Drug Screening</td>
<td>“Proof-of-Concept” Testing</td>
</tr>
<tr>
<td>5-10 Years</td>
<td>2 Years</td>
<td>6 Years</td>
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<tr>
<td></td>
<td>2 Years</td>
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</table>

- 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
Needs Assessment

The Ultra-Rare Neuromuscular Disease Problem
7 major categories of NMDs in MDA’s Program = 330 individual diseases officially “covered” by MDA (partial list shown here)
Only 17 Diseases in MDA’s program likely affect over 1000 people each in the US

There are over 300 neuromuscular diseases individually defined by genetic cause (when applicable) covered in MDA’s program; The majority of people served by MDA (306,657) have one of these 17 diseases. The remaining 335 disorders may still impact between as many as 100,000 people collectively.

<table>
<thead>
<tr>
<th>Indication</th>
<th>% US Population</th>
<th>US Prevalence</th>
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<tbody>
<tr>
<td>1. CMT1A</td>
<td>0.02290</td>
<td>75,169</td>
</tr>
<tr>
<td>2. Myasthenia Gravis</td>
<td>0.02020</td>
<td>66,287</td>
</tr>
<tr>
<td>3. DM1/DM2*</td>
<td>0.01262</td>
<td>41,429</td>
</tr>
<tr>
<td>4. HNPP (CMT)</td>
<td>0.00885</td>
<td>29,033</td>
</tr>
<tr>
<td>5. Sporadic ALS</td>
<td>0.00473</td>
<td>15,511</td>
</tr>
<tr>
<td>6. FSHD</td>
<td>0.00454</td>
<td>14,914</td>
</tr>
<tr>
<td>7. DMD/BMD</td>
<td>0.00347</td>
<td>11,375</td>
</tr>
<tr>
<td>8. SMA</td>
<td>0.00293</td>
<td>9,612</td>
</tr>
<tr>
<td>9. CMTX</td>
<td>0.00271</td>
<td>8,883</td>
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<th>US Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>10. FA</td>
<td>0.00252</td>
<td>8,286</td>
</tr>
<tr>
<td>11. CMT1B</td>
<td>0.00214</td>
<td>7,026</td>
</tr>
<tr>
<td>12. CMT2A2</td>
<td>0.00174</td>
<td>5,700</td>
</tr>
<tr>
<td>13. OPMD</td>
<td>0.00100</td>
<td>3,314</td>
</tr>
<tr>
<td>14. EDMD</td>
<td>0.00100</td>
<td>3,314</td>
</tr>
<tr>
<td>15. LGMD2A</td>
<td>0.00100</td>
<td>3,282</td>
</tr>
<tr>
<td>16. Leigh Syndrome</td>
<td>0.00075</td>
<td>2,462</td>
</tr>
<tr>
<td>(SURF1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>17. CMT4C</td>
<td>0.00032</td>
<td>1,060</td>
</tr>
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*Preliminary studies suggest that DM1 prevalence may be up to five times higher than this older estimate.
How do we De-Risk Ultra-Rare Drug Development?

**Issue:** Standard methods of de-risking aren’t adequate incentives for ultra-rare drug development

**Investment**
- Staff Time: Research, Advocacy, Marketing, Legal
- Funding: $1M for in-licensing IP, vendor contracts, software
- Vendor Budgets for to add MOVR Case Report Form
- Additional investments for longer term initiatives

**Strategies**
1. Initiate In-House Drug Development Program to Boost Projects Through Early Preclinical Phase (“Kick Start’)
2. Increase availability of patient data by adding ultra-rare case report form to our MOVR clinical database
3. Issue RFA focused on ultra-rare disease
4. Work through consortium to develop draft FDA Guidance for ultra-rare disease
5. Work towards legislation to fundamentally alter approval pathways for ultra-rare disease

**Outcomes-Impact**

**1 Year**
- One ultra-rare disease will undergo a constructive pre-IND meeting

**2-3 Years**
- Ultra-rare indication begins phase I trial
- Additional ultra-rare indications shepherded through pre-IND meeting
- New MOVR CRFs will be used to increase availability of natural history data for ultra-rare disease
- Changes in FDA approval policy are introduced via consortium activities

**5 Years**
- Increased rate of new approval for ultra-rare indications

**Increased rate of new approval for ultra-rare indications**
MDA Kickstart Is an In-House Incubator for Ultra-Rare Gene Therapy Projects

**Goal:** De-risk technically feasible ultra-rare projects by completing a constructive pre-IND meeting with FDA

**Initial Budget:** $1.12M

**Project Criteria:**
- AAV-based gene therapy approach for condition affecting less than 1000 people in the US
- No disease-modifying therapy available; high unmet medical need
- Straight-forward gene replacement strategy, technically feasible (high likelihood of success)
- Construct design completed
- Proof-of-concept data using in vitro or in vivo models available

**Sustainability--Multiple Paths:** equity stake, share of licensing revenue, share of pediatric voucher sales
Kickstart will Provide the Initial Data Package for Constructive Pre-IND Meeting

Kickstart Advisory Committee:
- Dan Levy – Pfizer
- Katherine Wagner – Roche
- Barry Byrne – U of Florida
- Petra Kaufman – Affinia
- John Day - Stanford

Kickstart Project Team:
- Project Lead – MDA Staff
- Project Manager
- Scientific Indication Advisors (2-3 KOLs)
- Regulatory Consultant

Discovery & Pre-clin | IND Filing | Phase I | Phase II | Phase III | NDA
---|---|---|---|---|---
Pre-IND Meeting | IND Submission, Phase I | Pivotal Study |

- MDA Kickstart
- NIH Bespoke GTX or URGENT
- Biotech

- Research or Good Laboratory Practice (GLP) grade AAV manufacturing and product quality
- Chemistry, Manufacturing and Controls (CMC) activities
- Dose-escalation and biodistribution preclinical studies
- Experimental (Animal) pharmacology / toxicology study

- Extended Proof-of-Concept (POC) studies
- Potency assay development
- Development of regulatory strategy and support for FDA filings
- Development of Quality Assurance strategy
- Medical chart review or other plan to acquire natural history data

Therapy is Available
Details

• Gaining Board Support:
  – Timing is everything
  – Clear explanation of the problem
  – Convincing solution
  – Generating excitement

• Key Questions:
  – How to scale?
  – How to manage risk?
  – How to manage project and project data?

• Fuzzy Challenges:
  – Comfort with ambiguity
  – OK with being opportunistic

• Advice:
  – Socialize idea thoroughly first with all stakeholders