The Role of the Federal Government in Advancing DM Science & Care: The NIH

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Agenda

• NIH 101
• Basic Data on NIH Funding
  – Research funding for muscular dystrophies
  – Wellstone Centers
  – Translational awards
• Therapeutic Development Principles and the NIH
  – Things fail—how to improve on that
  – Role of basic science
  – Leveraging NIH programs
  – Partnering is essential
  – Importance of trial readiness
• Questions
NIH 101 (Basics)

• NIH: 27 institutes and centers (ICs) (1° DM ICs: NINDS & NIAMS)
• IC Program Directors are the interface point (filter & facilitate)
• Most NIH grants are investigator-initiated & reviewed by non-gov scientists with decisions based on peer review
• Our “pay line” is based on funds available (budget) & approach is to fund the most meritorious science (NINDS FY2014: 14th percentile)
• NIH institutes that are current funders of DM: NIAMS, NINDS, NIGMS, & NHLBI
NIH 101 (Processes)

National Institutes of Health

Center for Scientific Review

Assigns for Review

Study Section

IC

Evaluates for Program Relevance

IC National Advisory Council

IC Director

Recommends Action

Takes final action for NIH Director

School or Research Center

Allocates Funds

Conducts Research

Submits Application

Initiates Research Idea

Research Grant Application

Research Idea

NIH Initiates

Process
NIH Funding Data

Factors in $$s Awarded for any Disease:

1. Numbers of Applications We Receive (applicants; numbers increasing)
2. NIH Budget Appropriation (Congress; budget decreasing)
3. NIH success rates now < 20%
NIH Funding for Muscular Dystrophy

NIH RePORTER
(grant lists by disease; Google ‘NIH disease dollars’)

Fiscal Year

$M

0 10 20 30 40 50 60 70 80 90 100


MD  DMD/BMD  DM  FSHD

ARRA

Action Plan
# NIH Funding Since MDCC Action Plan*

<table>
<thead>
<tr>
<th>RCDC Category</th>
<th>NIH Funding Since 2006 Launch of Action Plan ($$s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscular Dystrophy (parent category)</td>
<td>$538M</td>
</tr>
<tr>
<td>Congenital</td>
<td>New code in FY2014</td>
</tr>
<tr>
<td>Duchenne/Becker</td>
<td>$233M</td>
</tr>
<tr>
<td>Facioscapulohumeral</td>
<td>$36M</td>
</tr>
<tr>
<td>Myotonic Dystrophy</td>
<td>$78M</td>
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</tbody>
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*Data from NIH RePORTER, FY2006-13; bulk are investigator-initiated awards (R01)
Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers

- Program started 2003
- Six active Centers, 5 yrs funding each at ~$1M direct costs/year
- Active Centers (focus)
  - Nationwide Children’s (DMD) *
  - U. Iowa (CMD/LGMD) *
  - U. Massachusetts (FSHD)
  - U. Pennsylvania (DMD) *
  - U. Rochester (DM)
  - U. Washington (DMD/FSHD)

*Re-competing in 2014-15
Therapeutic Development Principles and the NIH
Bridging the ‘Valley of Death’

Lost in Translation

Basic Science

Clinical Application
Thing Fail!

- 6,000 rare diseases; ~200 have a therapy
- Combined, only ~5-6 approved therapies for neuromuscular diseases
- About 30-40 novel drugs approved by FDA/yr; phase 2 failure rate as high as 80%
- Credit model (“I cured DM”) simply won’t work—no one has all the needed resources
- Collaboration among all stakeholders is the only solution and even then...
First, It’s About the Basic Biology

• For DM therapies, need to know the disease mechanisms—e.g., how CTG/CCTG repeat expansion leads to muscle wasting & weakness
• NIH R01 is at the crux of basic science advances (“gold standard” for investigators)
• Mechanisms yield targets for drug discovery
• No mechanism = no target = no therapy
Basic Biology: Understanding the CNS in DM

• CNS next research frontier for DM
• Program Projects (P01) support synergistic team science
• Ranum P01 (Florida/Stanford/Minnesota)
  – Ranum: molecular mechanisms—RAN translation in CNS
  – Swanson: molecular mechanisms—toxic RNA in the CNS
  – Day: clinical consequences—structural & functional changes in DM CNS
• Strong basic-clinical collaboration
• Essential mechanistic data for CNS therapy development
Next, Optimizing for Success

• Why/when do candidates fail? Safety &/or efficacy in phase 2 trials
• Solutions? Obvious, but hard: understand & try to control the variables
• What’s not under control, but controllable?
  – Mechanistic knowledge
  – Strength of preclinical rationale
  – Natural history
  – Clinical sites
A call for transparent reporting to optimize the predictive value of preclinical research

Grant applications & publications should report on core parameters of randomization, blinding, sample-size estimation, & handling of data.

Better reporting will raise awareness rigorous study design.
Tools: Leveraging NIH Programs for Therapeutics

- NINDS NeuroNEXT trial network (ph 2 trial support)
- NCATS
  - TRND
  - BrDGS
  - ORDR programs (RDCRN, R13, etc.)
- NINDS translational programs
NIH Translational Initiatives & DM

• PAR-06-043 & PAR-08-228: Translational R21 Program in MD & NMD
  – 16 awards: CMD (Girgenrath), DM (Armstrong, Melander, Miller, Reddy, Thornton), DMD (Burkin (2), Chao, Duan (2), Fallon, Froehner, Samulski), FSHD (Kyba), LGMD (Khurana), pan-MD (Lee)
• NINDS “Generic” Translational R21 program
  – 3 awards: DMD/BMD (Bertoni, Selsby); FSHD (Wagner); DM (Gottesfeld, pending)
• PAR-06-044 & PAR-08-229: Translational U01 Program in MD & NMD
  – 4 awards: DMD (Fallon, Guttridge, Lu, & Stedman)
• NINDS “Generic” Translational U Program
  – U54: DMD (Sweeney & Mendell); U44: DMD (McPhee); U24: DMD (Kornegay); U01: DM (Thornton)
Example from Duchenne MD

Negotiating the Valley of Death with an Innovative Public – Private Partnership

Funding Recipient
- Brown University
- Tivorsan Pharmaceuticals, Inc.

Funding Source
- ACS: American Cancer Society
- MDA: Muscular Dystrophy Association
- NIH: National Institutes of Health
- PPMD: Parent Project Muscular Dystrophy
- QTDP: IRS Qualifying Therapeutic Discovery Project grant
Avoid Roadblocks: Trial Readiness

- Find trial subjects (diagnostics & registries)
- Stratify trials/select trial endpoints (natural history)
- Ensure comparisons across multi-sites in trial are optimized (endpoint validity; standards of care)
- Detect meaningful changes during duration of trial (natural history & biomarkers, surrogate endpoints)
- Ensure lessons learned from all trials, even those failing to achieve primary outcome—sharing of data & best practices
- Therapeutic misconception (recognizing trial = experiment)
Public-Private Collaborations for Clinical Trial Readiness in DM

• Rochester Wellstone
  – Registry
  – Natural history
  – Validate clinical trial endpoints and biomarkers
  – DM-CRN

• Wellstone Partnering
  – NINDS
  – NHLBI
  – MDF
  – MDA
  – Marigold
  – Isis & Biogen Idec

Without the infrastructure, DM trials will fail; Participate when you can!
Facilitate!

• NIH plays a role in facilitation the understanding of DM and, based upon that understanding, the development of therapies

• But, therapies will not happen without the active collaboration of academics, advocacy, companies, governmental agencies, & patients and their families
Questions?