MDF Conference: 9/12/2014

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

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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

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NIH 101 (Processes)

Research Grant Application

Initiates Research Idea

Submits Application

School or Research Center

Conducts Research

Allocates Funds

National Institutes of Health

Center for Scientific Review

Assigns for Review

Study Section

Evaluates for Scientific Merit

IC

Evaluates for Program Relevance

IC National Advisory Council

Recommends Action

IC Director

Takes final action for NIH Director

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%

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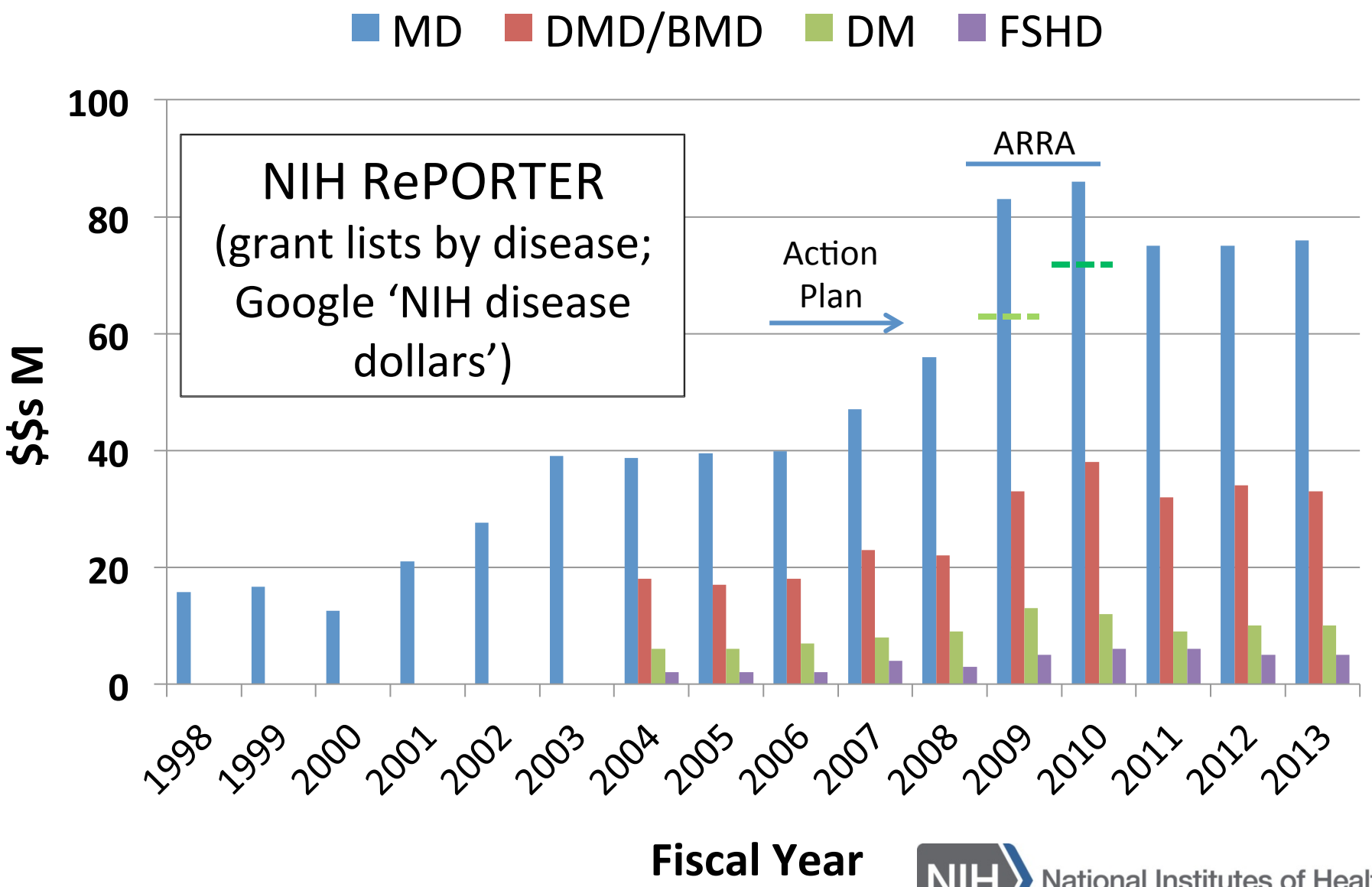
NIH Funding for Muscular Dystrophy



National Institutes of Health

NIH Funding Since MDCC Action Plan*

RCDC Category	NIH Funding Since 2006 Launch of Action Plan ($$s)
Muscular Dystrophy (parent category)	$538M
Congenital	New code in FY2014
Duchenne/Becker	$233M
Facioscapulohumeral	$36M
Myotonic Dystrophy	$78M

*Data from NIH RePORTER, FY2006-13; bulk are investigator-initiated awards (R01)

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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

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Therapeutic Development Principles and the NIH

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Bridging the 'Valley of Death'

Basic Science

Clinical Application

Lost in Translation

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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

PERSPECTIVE

Landis et al., *Nature* 490: 187-91, 2012

doi:10.1038/nature11556

A call for transparent reporting to optimize the predictive value of preclinical research

Story C. Landis[1], Susan G. Amara[2], Khusru Asadullah[3], Chris P. Austin[4], Robi Blumenstein[5], Eileen W. Bradley[6], Ronald G. Crystal[7], Robert B. Darnell[8], Robert J. Ferrante[9], Howard Fillit[10], Robert Finkelstein[1], Marc Fisher[11], Howard E. Gendelman[12], Robert Golub[13], John L. Goudreau[14], Robert A. Gross[15], Amelie K. Gubitz[1], Sharon E. Hesterlee[16], David W. Howells[17], John Huguenard[18], Katrina Kelner[19], Walter Koroshetz[1], Dimitri Krainc[20], Stanley E. Lazic[21], Michael S. Levine[22], Malcolm Macleod[23], John M. McCall[24], Richard T. Moxley III[25], Kalyani Narasimhan[26], Linda J. Noble[27], Steve Perrin[28], John D. Porter[1], Oswald Steward[29], Ellis Unger[30], Ursula Utz[1] & Shai D. Silberberg[1]

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)

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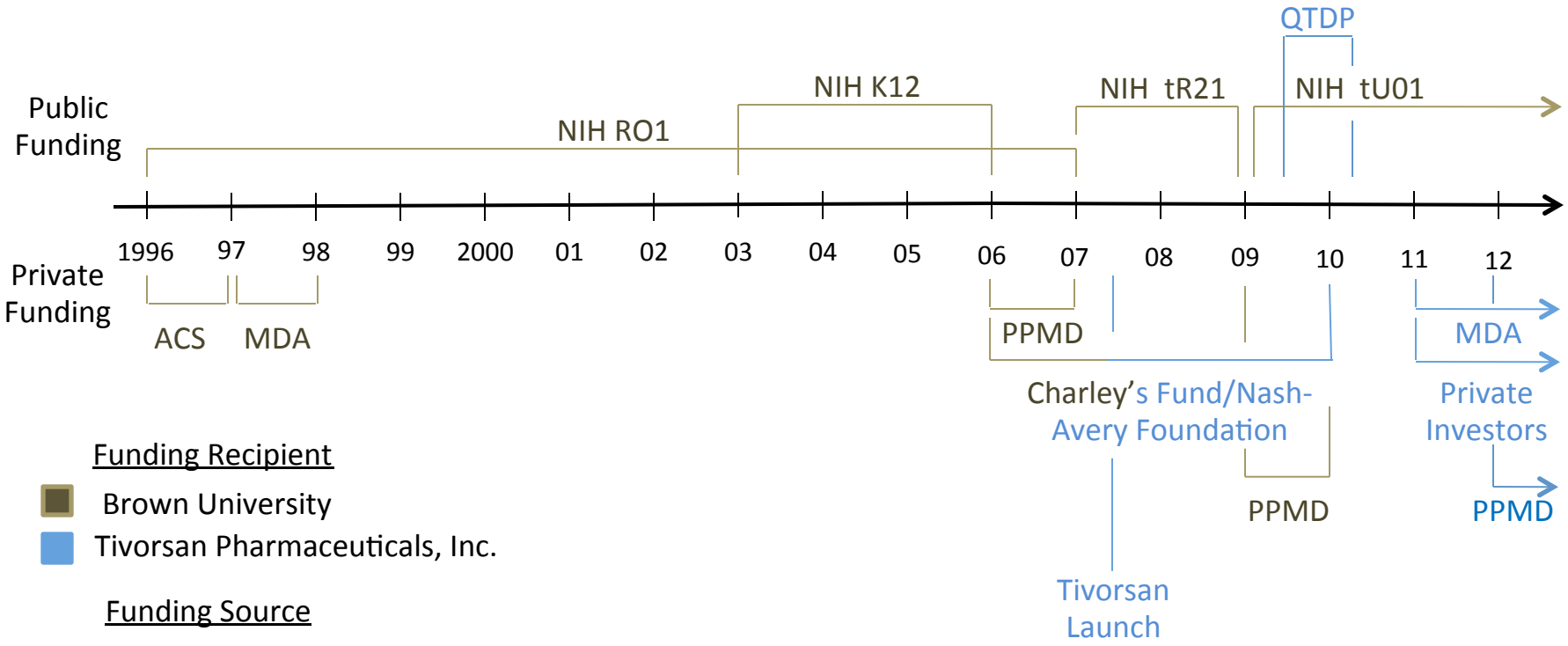
Example from Duchenne MD

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

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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!

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Facilitate!

- NIH plays a role in *facilitating* 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?