MDF 3.0: Accelerating Drug Development

Care and a Cure

September 2016
MDF 3.0: Impact

**CARE & A CURE**
- Improved clinical care landscape
- More accurate clinical trial design
- Improved capacity to evaluate drug efficacy
- Better understanding of disease course

**R & D**
- More dynamic and growing DM research field
- Increased efficiency of research output
- More reliable research findings
- More populated drug development pipeline

**DRUG DEV**
- Optimal drug review time
- Improved trial processes
- Improved clinical trial readiness
- More pharma investment, exploration
- Reduced trial risk

**ADVOCACY**
- More industry engagement in DM drug development
- Enhanced case for reimbursement
- Influence over pricing/access

**PAYORS & ACCESS**
- More industry engagement in DM drug development
- Public & private payers reimburse DM family members for approved therapies
- Approved therapies pricing more community friendly
MDF 3.0: Progress at a Glance

2015 – 2017 $5,000,000

CLINICAL CARE
- Care Considerations
- Care Landscape Analysis and SWOT

RESEARCH
- Fund-a-Fellow Expansion
- Mouse Model Creation
- Biobank and Cell Line Library Expansion
- Mouse SOPs
- SAC Expansion and Development

DRUG DEV
- Clinical Research Network Expansion
- Biomarkers and Endpoint Development
- Industry Drug Screening Grants
- Regulatory Advocacy
- Clinical Coordinators Recognition Program
- Registry Expansion

ADVOCACY
- Muscular Dystrophy Coordinating Committee
- Federal agency advocacy for research funding
- DM Prevalence Study

PAYORS & ACCESS
- Burden of Disease Study
- Meeting with Social Security Administration & presentations at MDF conference
DRUG DEVELOPMENT: Targets

TREAT DM

- Modulate DNA Base Excision Repair
- Prevent Repeat Expansion
- Symptomatic Relief (options need improvement)
- Gut Motility Issues
- Behavioral and Cognitive Therapies
- Delivered follistatin gene therapy
- Rebuilding Muscle Mass
- Block Myostatin
- Enhancing/Blocking Modifiers
- Gene therapy, small molecules, AONs, other
- Upregulating MBNL1
- Blocking CELF
- AONS to correct splicing
- Gene Therapy

- Gene Therapy
- Neutralizing Toxic RNA
- Normalize CUG Binding Proteins
- Normalize Mis-Regulated Downstream Gene Expression
- Deliver follistatin gene therapy
- Block Myostatin
- Gene therapy, small molecules, AONs, other

- Myotonia
- Daytime Sleepiness
- Insulin Resistance
- Cardiac Conduction Abnormalities
- Myostatin
- Muscle Mass
- Neutralizing Toxins RNA
- Block Myostatin
RESEARCH: MDF Fellowship Program

• 25 Fellows funded since 2009; fellows posters at Conference
• A 2014 evaluation:
  • >70% remained in DM research
  • 60% raised additional funding totaling over $2.5M
• Four MDF Fellows have gone to receive faculty positions and in several cases, NIH and other agency funding

Eric Wang, Ph.D.
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Professor- Molecular Genetics &Microbiology
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Asst. Professor
Pharmacy Practice and Pharmaceutical Sciences
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Asst. Professor of Biochemistry and Medical Biochemistry
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University of Illinois

Nicholas Johnson, M.D.
Neurology – Asst. Professor
University of Utah
Why do we need another mouse model?

- Genetic stability
- Better symptom profile (e.g., cognitive effects)
- Better access
- Avoiding licensing/reach-through issues
- Funding: Cat Lutz (JAX) BAC transgenic DM1 model
Why do we need new cell lines?

- Deriving specific cell types for screen
- Improving flexibility and availability through iPSCs housed at an NIH source
- Avoid licensing and reach-through issues
- Funding: NHCDR/NINDS, 4 DM1 & 4 DM2 lines
ENDPOINTS RFA:

• Develop new or refine existing endpoints for DM
• $150,000, 1 yr award
• Funding: Donovon Lott (UFL) for skeletal muscle MRI
• Upper & lower extremity; correlate with variety of functional measures
• 25 subjects
• Strong MRI track record at UFL, inc. initiating qualification process for DMD
• Project requires FDA consultation
DRUG DEVELOPMENT: Biomarkers

BIOMARKER RFA:

- Development of a biomarker for a specific drug program or a biomarker of general utility; should be a path to regulatory qualification
- $150,000, 1 yr award
- Taking recommendation for funding to Board
DRUG DEVELOPMENT: PHENO-DM1

PHENO-DM1 Study:

- Leverage existing NIHR (UK) grant to Newcastle
- $120,000, 18 month award
- Funding: Hanns Lochmuller, to extend 1 yr natural history study in 200-400 subjects to 2 yrs
- Upper & lower extremity; correlate with variety of functional measures
- 25 subjects
- 20 measures (inc. MRC strength, 10MWT, nine-hole peg, DM1Activ, FVC/FEV, MDHI, Mini Mental)
CRITICAL REGULATORY QUESTION:

• Does drug’s clinical benefit outweigh risk?
  • Improving, halting or slowing muscle weakness = greatest benefit to study participants
  • Reducing fatigue = least benefit
  • Loss of appetite was the best tolerated risk
  • 1:1000 chance of liver damage was the least tolerated
REGULATORY ADVOCACY

• All-day FDA workshop at MDF conference 2015
  • Moderator: former FDA Deputy Commissioner Dr. Stephen Spielberg
  • Topics:
    • Patient-Focused Drug Development
    • Endpoint Validation Group
    • Neurology Review Division
    • Biomarkers Validation Group
    • >70 attendees from industry, academia, NIH
    • Publication submitted August 2016

• Patient Focused Drug Development Meeting at MDF conference 2016
  • Significant participation confirmed from FDA leadership
  • First formally approved Externally-Led PFDD for FDA
  • Will include testimony from MDF conference attendees on burden of disease and input on desired impacts of treatments
  • Proceeds to inform FDA Neurology Review Division via regulatory framework

• Outreach to European Medicines Agency ongoing
**REIMBURSEMENT & ACCESS: Burden of Disease Study**

**GOAL:** DOCUMENT ANNUAL MEDICAL COSTS OF DM DIAGNOSIS

**TARGET AUDIENCE:** PAYERS & POLICY MAKERS

**PARTNERS:** MAYO CLINIC & OPTUM LABS

- REACH: >100M CLAIMS & 300K MATCHED MEDICAL RECORDS

**STATUS:** PRELIMINARY FINDINGS DUE FALL 2016

**NEXT STEPS:** CMS DATA FOR EMPLOYMENT, EDUCATION & QOL
**GOAL:** Define mutation and pre-mutation load in US population

**TACTIC:** Two-phased project
- Phase I: develop and validate a scalable, inexpensive methodology
  - Award to Nick Johnson, UUT 2015
  - Assay complete
- Phase II: measure the frequency of DM1 and DM2 expansions in the general population via +/- 70,000 newborn blood spots
  - One application received
  - Phase II RFA review November 2016
DRUG DEVELOPMENT: Network & Natural History Data Expansion Project

GOAL:
- National network of study & trial sites
- Increase natural history data collection

IMPACT:
- Improved trial infrastructure
- Drive study & trial efficiencies
- Capture more natural history data
- Create centralized, accessible database

TACTICS:
- Annual multi-site grants based on milestones

ONGOING $700,000
Drug Development: DM Advantages

DM is Tractable

- Prevalence: about 30K in the US, likely significantly understated
- Compelling and well-understood disease mechanism
- Preclinical POC established for different targets in the pathogenic cascade
- Ability to get rapid molecular readout (splicing) of target engagement/modulation in early stage clinical trials
- Ability to use molecular readout in dose ranging studies
- Ability to get physiological readout of disease modification in early stage clinical trials
- Concerted effort on endpoints, including efforts to coordinate endpoint SOPs internationally
- Existing registries provide data, patient location and trial facilitation
- Patient care considerations being disseminated internationally
- Centers of excellence program in the US (DMCRN) & effort to establish & coordinate with EU
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