

NATURAL HISTORY OF MYOTONIC DYSTROPHY

“Discovery of the Genes Provides New Opportunities To Define the Natural History and To Develop Therapeutic Trials”

- **Myotonic Dystrophy Type 1 (DM1)**
[Steinert’s Disease]
[Brook et al. Cell 68, 799-808, 1992;
Fu et al. Science 255, 1256-1258, 1992;
Mahadevanetal. Science 255, 1253-1255, 1992]
- **Myotonic Dystrophy Type 2 (DM2)**
[Liquori, et.al. Science 293, 864-867,2001;
Day, et al. Neurology 60, 657-664, 2003]

NATURAL HISTORY OF MYOTONIC DYSTROPHY

“Broad Challenges”

- **To define the natural history of the complete spectrum of impairments in DM1 and DM2**
[weakness, myotonia, pain, cataracts, cardiac, respiratory, central nervous system, gastrointestinal, endocrine]; and,
- **To determine the effect of these disease manifestations over time in causing functional limitations and disability**

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“Some Specific Challenges”

- **What measures of strength, muscle function, and myotonia are best suited to evaluate (both short and long-term) treatment in:**
 - a) ambulatory adults (or children)?**
 - b) non-ambulatory adults (or children)?**
- **What different pattern of measurements, for example, MMT, or QMT, or timed function testing, do we recommend, if any, to evaluate DM1 compared to DM2 patients?**

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“Other Specific Challenges”

- What “endpoints” or “life events” do patients feel are most important to assess changes in:
 - Arm (or leg) function (or strength)?
 - Sleep (or breathing)?
 - Cardiac function?
 - Muscular Pain?
 - Cognitive function?
 - Other systems?

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“Other Specific Challenges”

- What instruments (measures) are most appropriate to assess quality of life for certain stages in the natural history of DM1 and DM2?
- What laboratory measures are best suited to evaluate short and/or long term changes in:
 - Muscle mass, strength, function?
 - Myotonia?
 - Endocrine dysfunction (gonadal, insulin resistance)?

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“Opportunities for Treatment that Benefit From Knowledge of Natural History”

Examples of Potential Future Trials

- **Muscle weakness and wasting**
 - IGF-1 complexed with IGF binding protein-3
 - Inhibitor of myostatin
- **Myotonia**
 - Long-term (> 6 months) trial of mexiletine



NATURAL HISTORY OF DM

CHALLENGE

- Define natural history of DM1 & DM2 over several years to evaluate:
 - Weakness pattern and relation to function
 - Myotonia and its relation to function and musculoskeletal pain

OPPORTUNITY

- Develop protocols and assess major disease manifestations by:
 - Organizing multicenter collaborative protocols
 - Developing “user friendly” methods to monitor myotonia, function, pain

NATURAL HISTORY OF DM

CHALLENGE

- Identify “optimal patients” to perform treatment trials to assess therapy for:
 - Leg and hand weakness
 - Myotonia
 - Respiratory/sleep disturbance
 - Musculoskeletal pain
 - Cognitive dysfunction

OPPORTUNITY

- Develop protocols to examine a spectrum of patients to establish those measures to assess efficacy
 - In short-term < 4 months
 - In long-term > 6 months

NATURAL HISTORY OF DM

CHALLENGE

- **Identify multisystem problems most suitable to monitor long-term, such as:**
 - **Respiratory muscle weakness**
 - **Cardiac conduction disturbance**
 - **Sleep disorders**
 - **Cognitive dysfunction**
 - **Endocrine disturbances**

OPPORTUNITY

- **Establish methodology feasible for use in treatment trials to assess these multisystem problems, such as**
 - **Standardized procedures for each**
 - **Guidelines for time intervals between assessments**

NATURAL HISTORY OF DM

CHALLENGE

- **Develop measures of quality of life and burden of disease at different stages in the natural history**
- **Identify measures that patients feel best describe response to treatment.**

OPPORTUNITY

- **Use existing patient registries and clinical populations to evaluate existing QoL instruments and to develop better instruments.**
- **Partner with existing government and private groups to develop patient-based assessment methodology.**

NATURAL HISTORY OF DM RECOMMENDATIONS

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