MYOTONIC DYSTROPHY FOUNDATION

Care and a Cure

2018
MDF ANNUAL CONFERENCE
September 14-15, 2018
Nashville, TN

UPDATE ON IONIS-DMPK$_{RX}$ PROGRAM

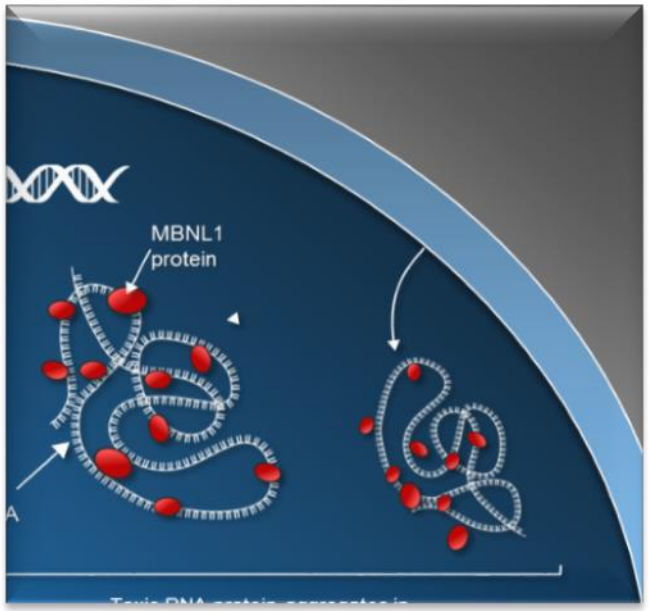
Laurence Mignon, PhD; Ionis Pharmaceuticals, Inc

The Search for a Treatment for Myotonic Dystrophy

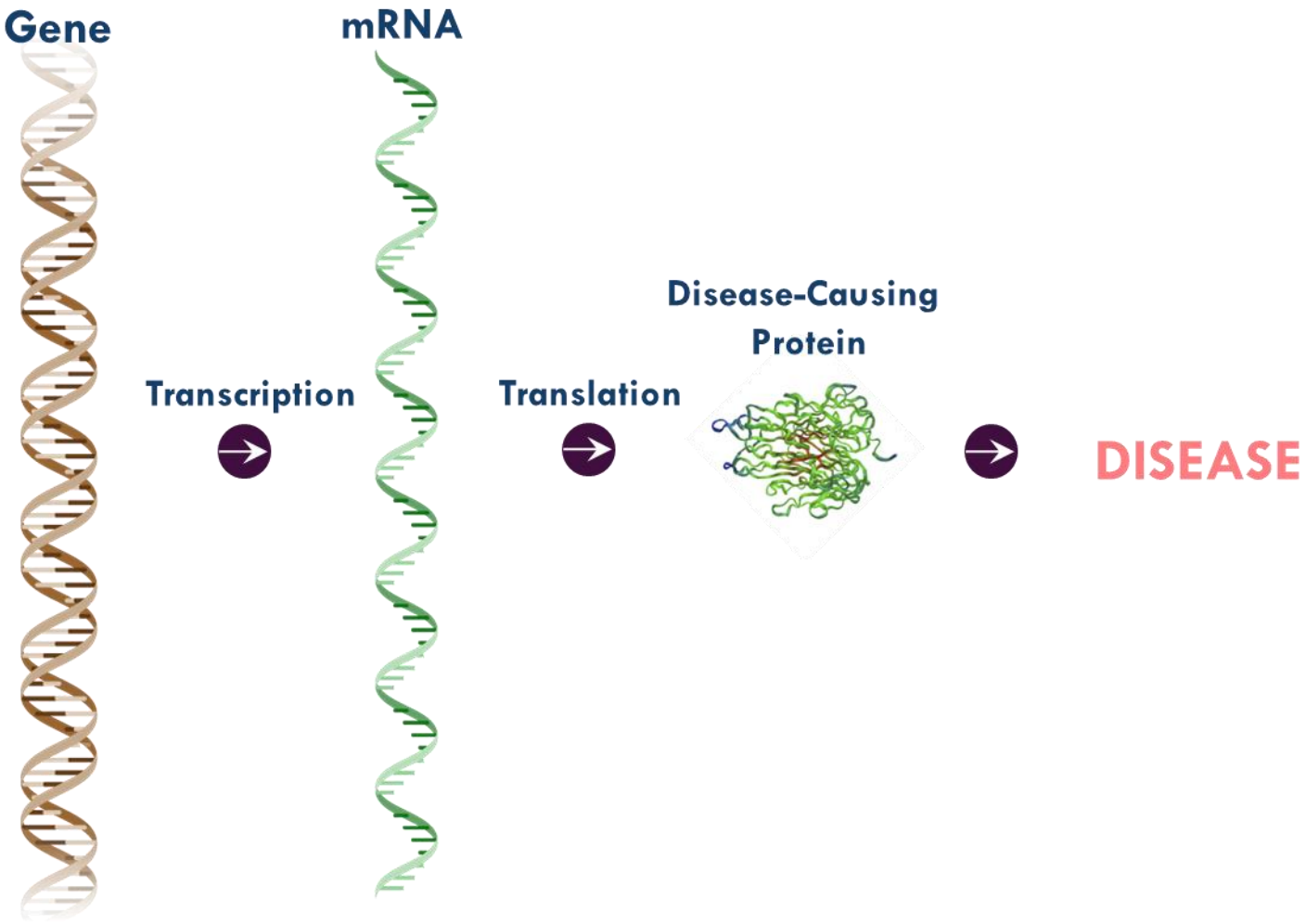
- Myotonic Dystrophy Type 1 (DM1) – A toxic gain-of-function RNA
- Triplet Repeat Disease – expanded CUG repeats in the DMPK gene results in the formation of long "toxic" RNAs
- Disease severity and age of onset are correlated with number of repeats (higher # repeats = more severe disease)
- Broad spectrum of symptoms, including muscle dysfunction, GI tract issues, CNS issues
- Juvenile and adult forms of DM1

Why IONIS became interested in DM1

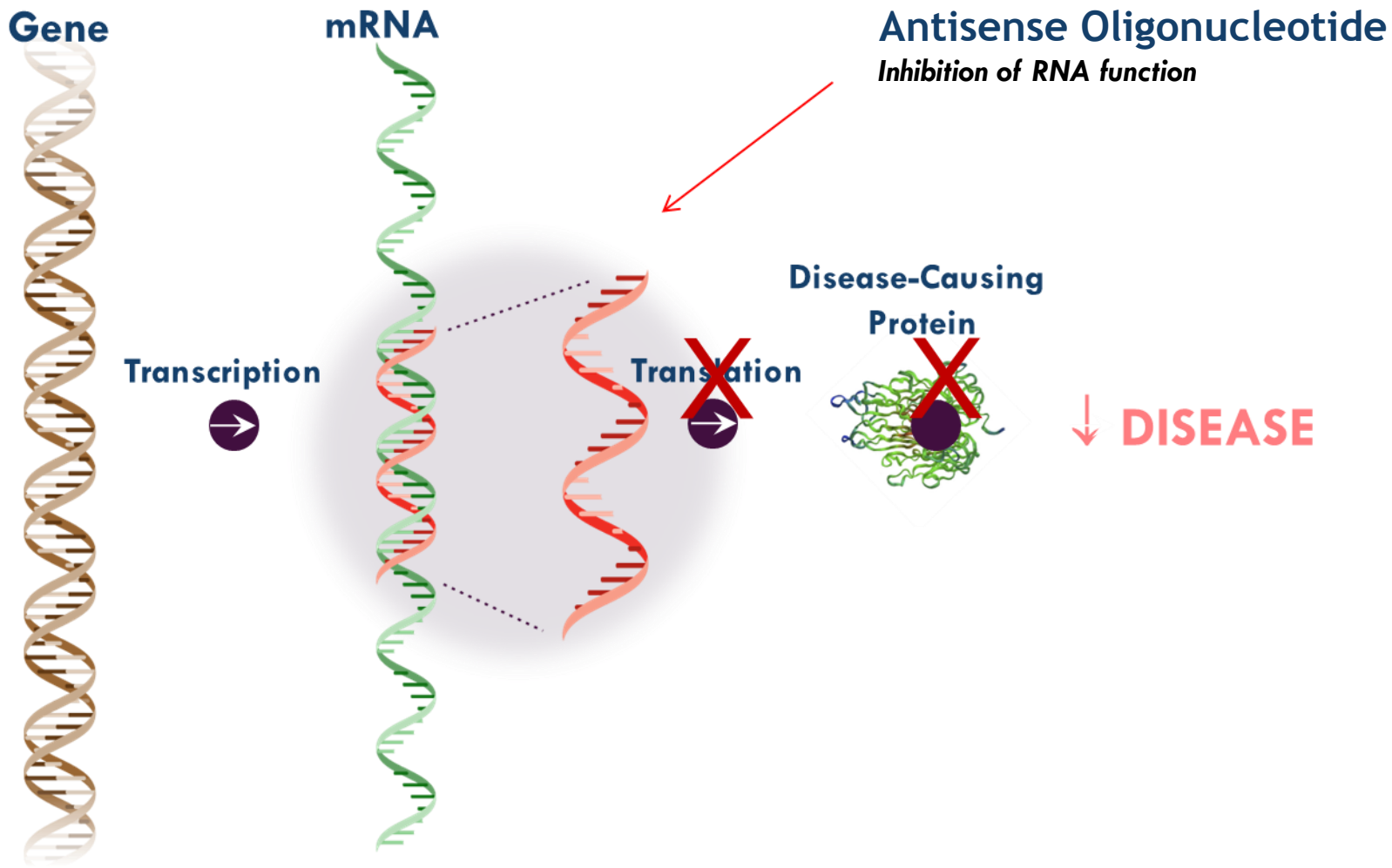
- Targeting toxic RNA, uniquely possible through ASO technology
- Potential to treat multiple aspects of the disease
- This is a rare autosomal dominant genetic disease with no treatment
- No approved treatment to stop or slow the progression of DM1



How Genetic Information Flows From DNA → Protein
The "Central Dogma" of Molecular Biology

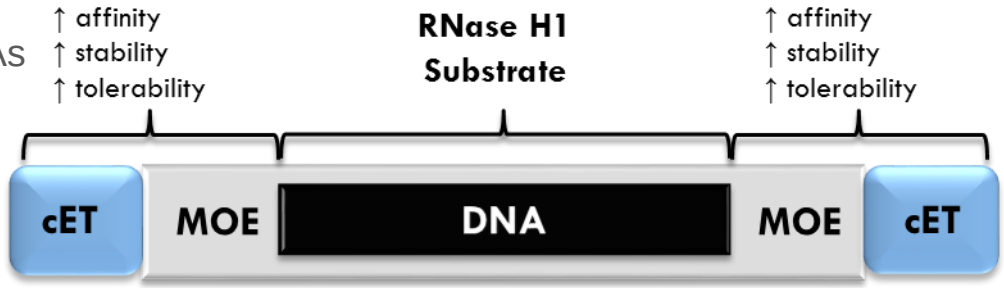


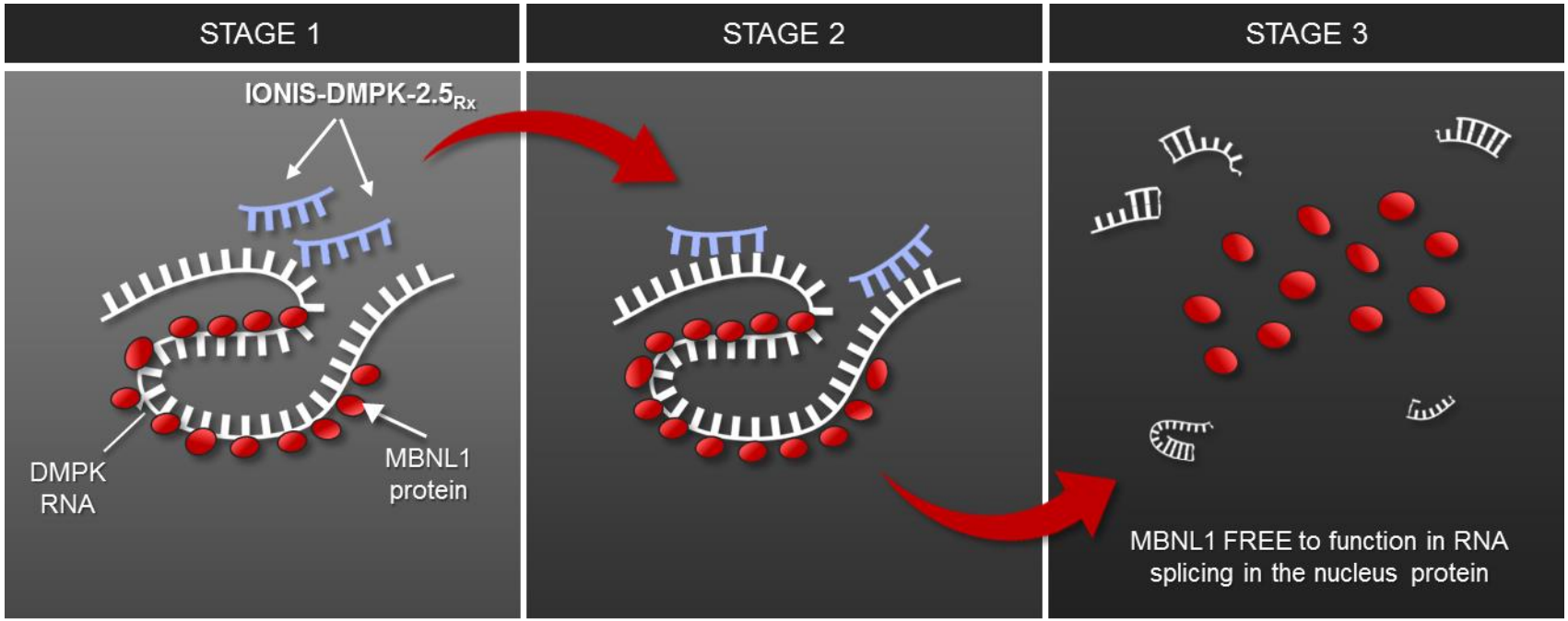
Antisense Drugs Target RNA, Not Proteins



IONIS-DMPK-2.5Rx: a Gen 2.5 Antisense Drug Designed to Reduce Toxic RNA Levels

- First muscle target
- IONIS-DMPK-2.5$_{Rx}$ targets toxic DMPK RNAs in multiple tissues
- RNase H1-mediated degradation of DMPK RNA releases sequestered proteins and restores normal cellular function

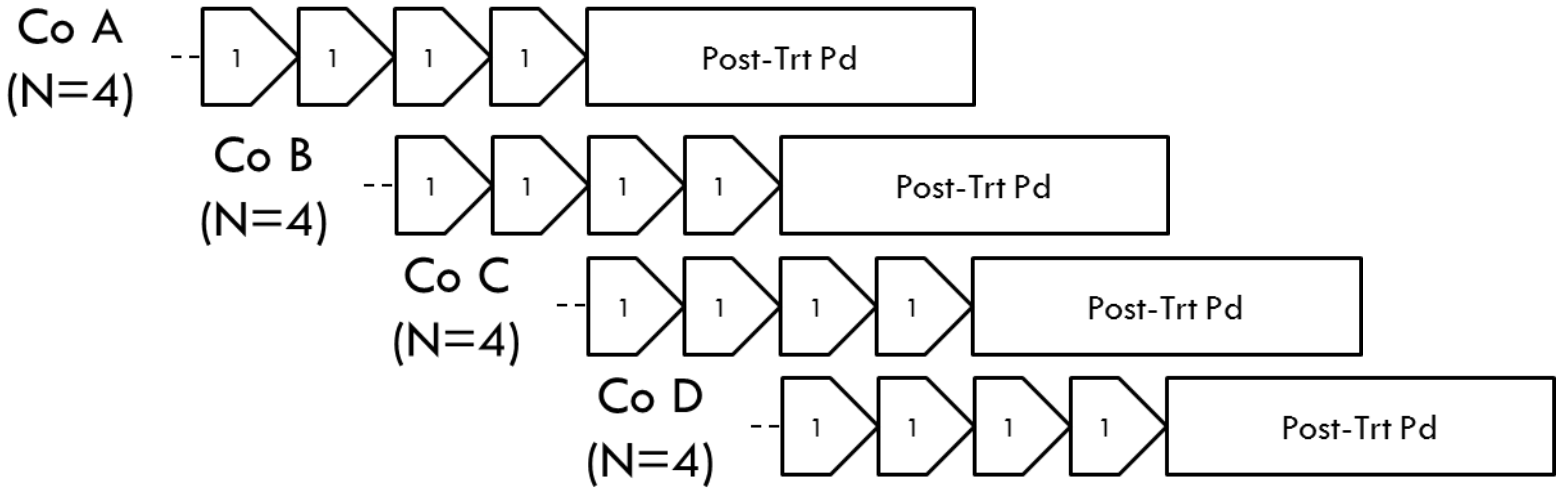




Cooper, T.. (2009) *Science*. 325:272-273

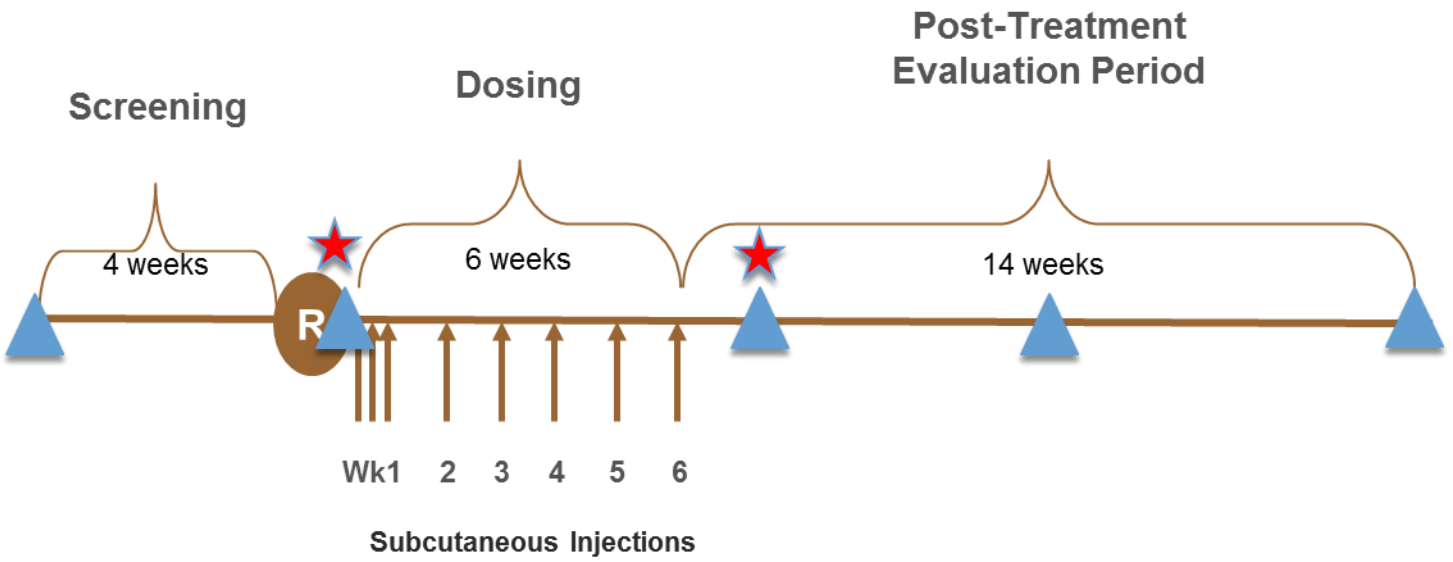
IONIS-DMPK-2.5_{Rx}:
Phase 1 Clinical Trial

- Phase 1 single-ascending dose study in healthy volunteers
  - Safety and Tolerability Study
    - 4 different dose levels tested; each subject receives only one dose; subjects followed for 28 days
    - Subcutaneous injections
    - Completed in 2014 in the UK in healthy volunteers
    - IONIS-$DMPK_{Rx}$-2.5 was well-tolerated



IONIS-DMPK-2.5$_{Rx}$:
Phase 2 Clinical Trial

- Phase 1/2a multiple ascending dose study in DM1 patients
  - Safety and Tolerability Study
    - 5 dose levels tested: 100mg, 200mg, 300mg, 400mg, 600mg
    - Short 6-week treatment; weekly doses
    - Subcutaneous injections
    - Multi-center study, including 8 sites across the US
    - Study included muscle biopsies of tibia pre-drug and 2 weeks after the last dose



IONIS-DMPRKx-CS2 Study:

Objectives

- Primary Objective
  - **safety** and **tolerability**

- Lab values
- ECGs
- How are injections tolerated

- Secondary Objectives
  - blood and urine **pharmacokinetics**
  - **muscle tissue effects**

- How fast the body breaks down the drug
- How the drug distributes throughout the body
- Splicing changes in muscle

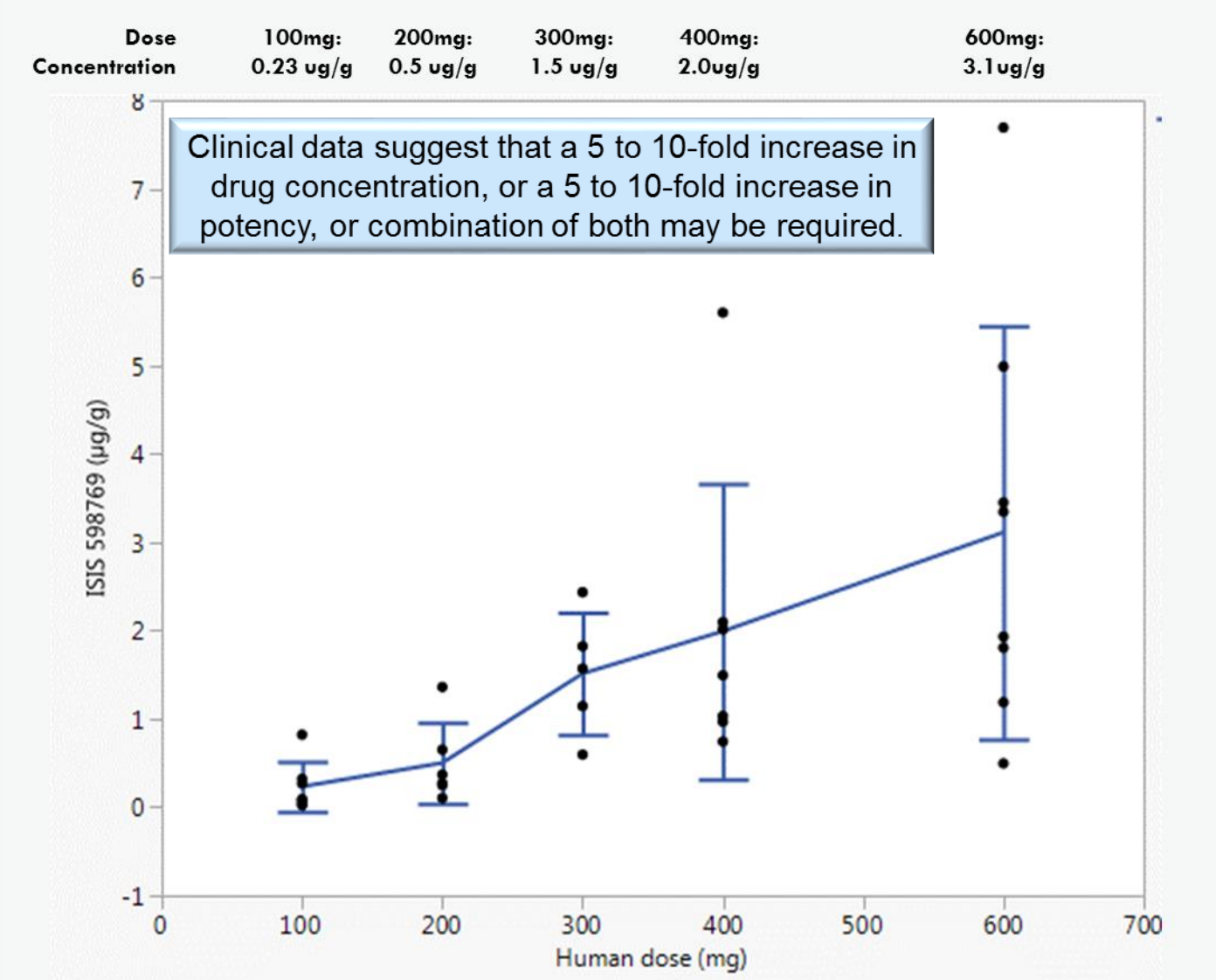
- Exploratory Objectives
  - **biomarkers** and **clinical outcomes**

- Myotonic tests
- Strength tests
- Functional tests
- Patient-reported outcomes

IONIS-DMPK-2.5$_{Rx}$ Did Not Reach Target Concentration of ~10 ug/gm in the Muscle

Target tissue concentration was determined to be 10-15 ug/gm to get ~50% KD in muscle

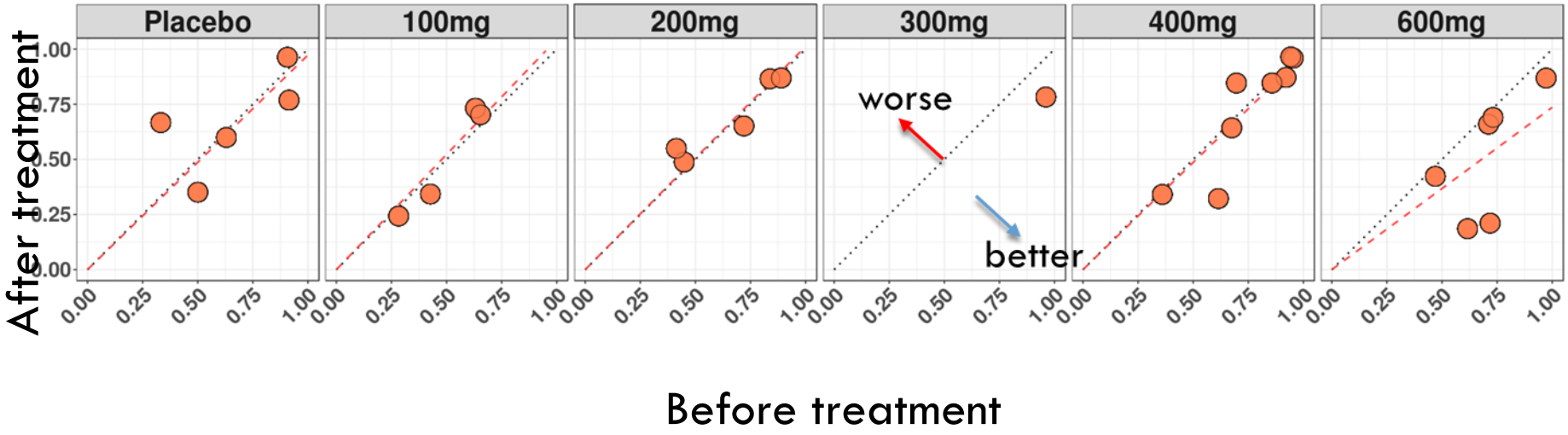
Drug levels were based on estimated ED50 (25 mg/kg) and on muscle concentrations in mouse from GLP study



Splicing Biomarkers in Tibialis Anterior Muscle Biopsy of DM1 Patients: Small Biomarker Changes at Highest Dose

Targeted RNA sequencing of 22 splice events in 29 patients

6 weeks of treatment with Ionis-DMPK$_{Rx}$ or placebo



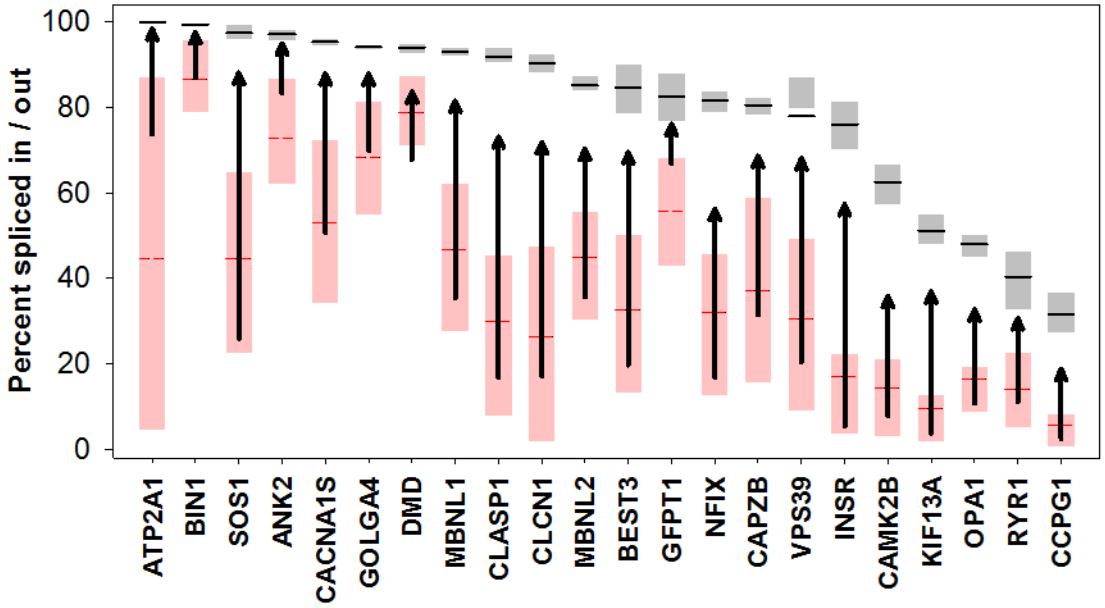
- Overall splicing index provides information on before versus after treatment change
  - 0 is normal, 1 is severely affected

Matt Tanner

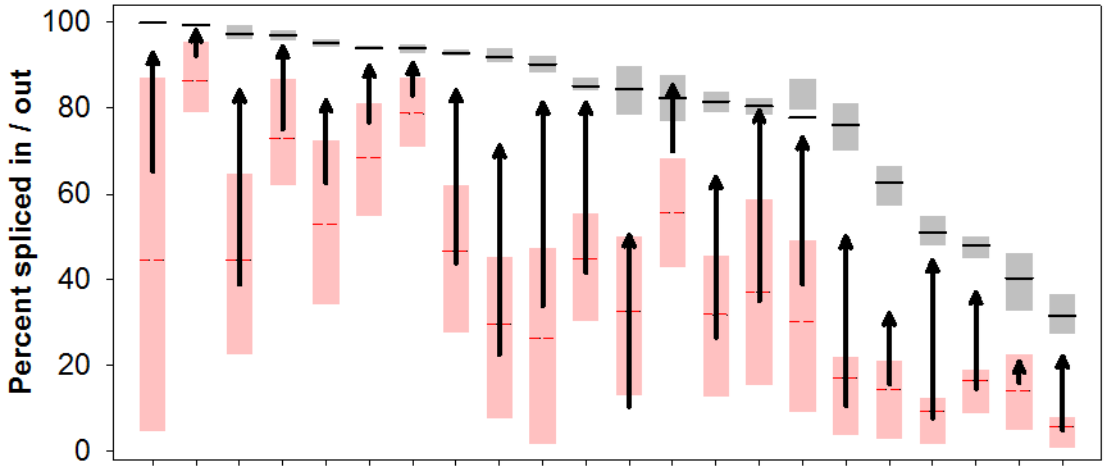
Effect of IONIS-DMPK$_{Rx}$ on Individual Splice Events in Two Patients

Range of splicing profile in group of healthy people

Range of splicing profile in group of DM1 patients



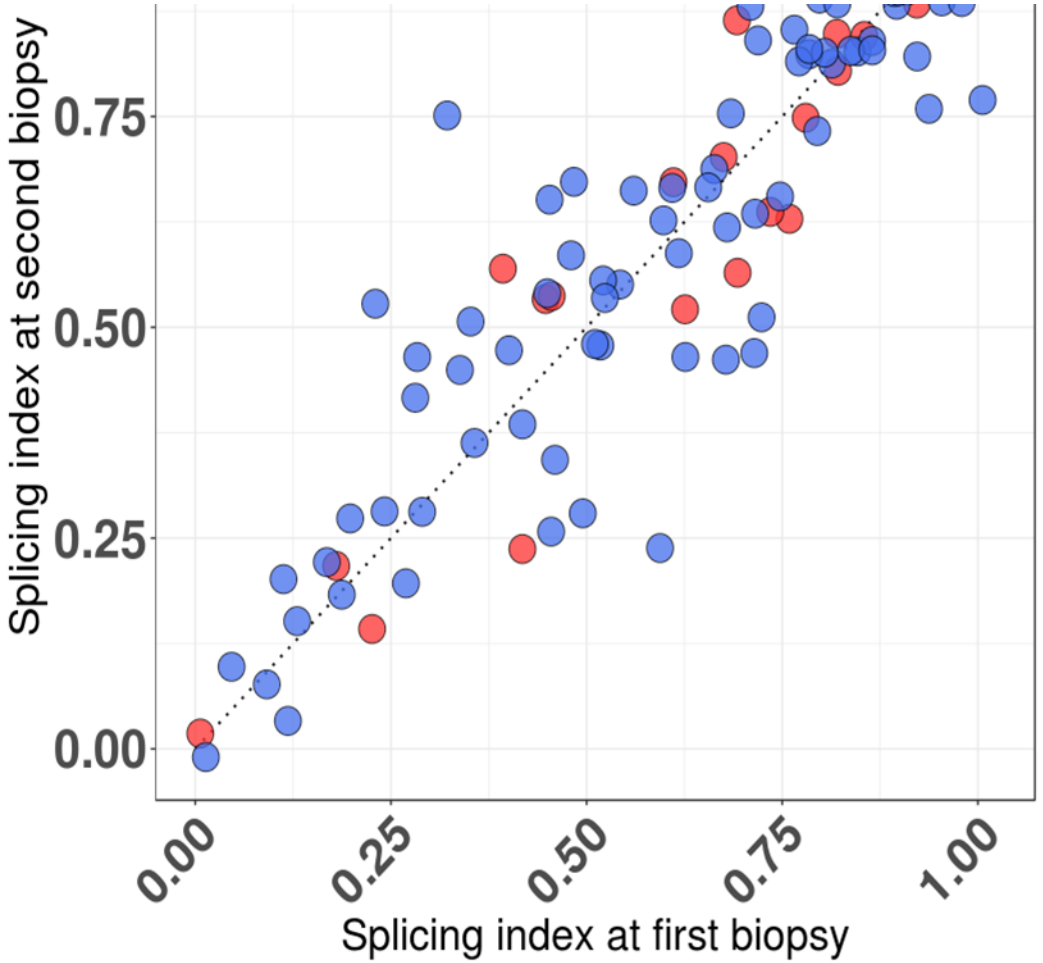
Change from pre-treatment to post-treatment



Graphs show changes toward the "normal" range in every individual splice events in two patients following treatment

Comparison to Non-Intervention Studies:

Variation of overall splicing index from 1st to 2nd biopsy, no treatment



n = 116 patients
DMCRN study sites

Time between biopsies
8 weeks
12 weeks

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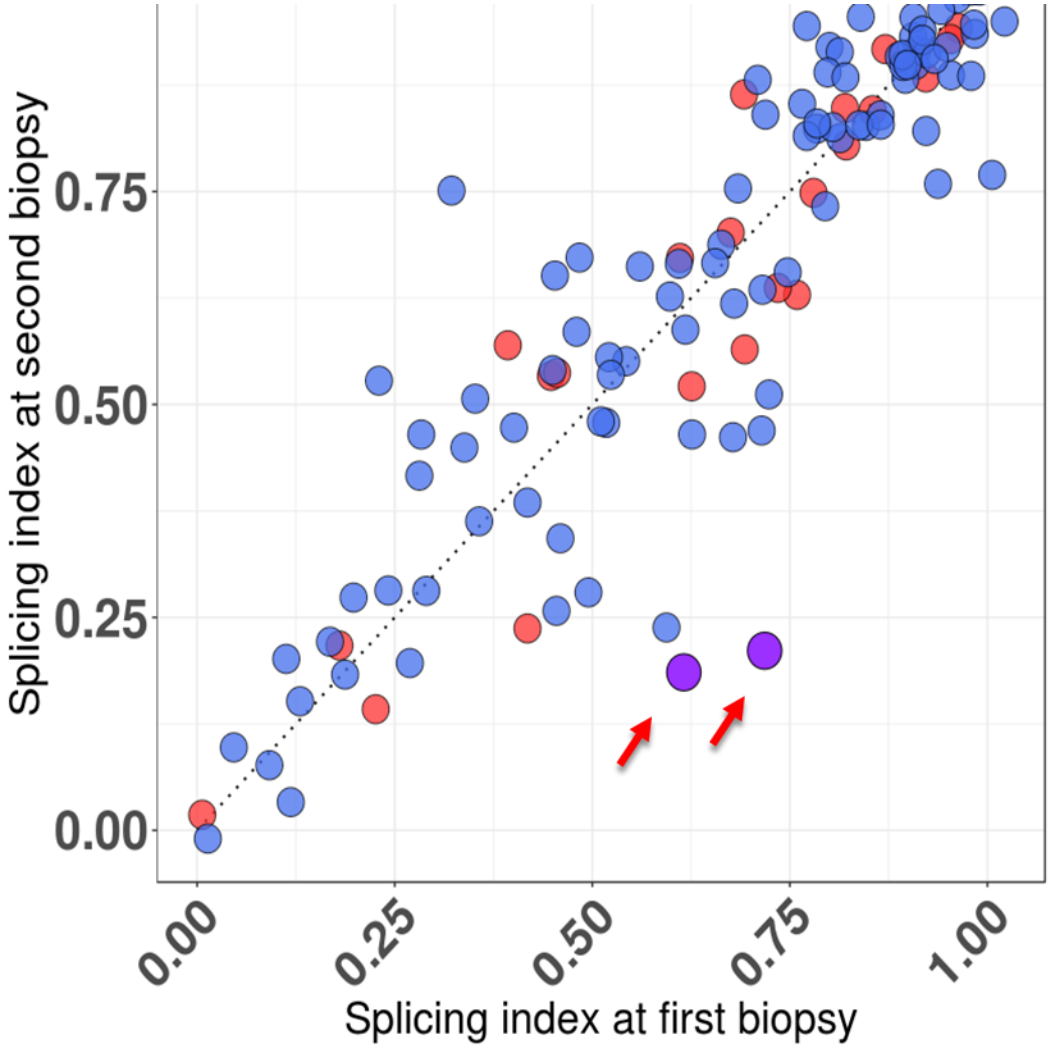
Comparison to Non-Intervention Studies:

Two Individuals Presented Earlier



n = 116 patients
DMCRN study sites

Time between biopsies
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12 weeks

These data support the importance of studying multiple splice events in patients as potential therapeutic biomarkers

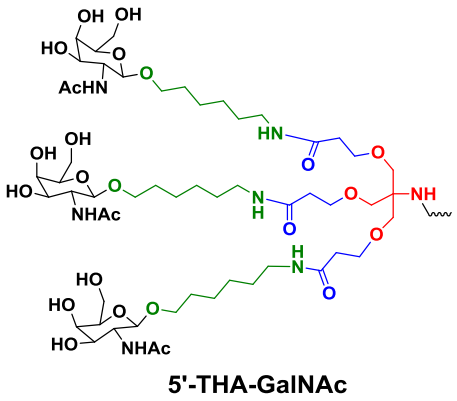
Matt Tanner

IONIS-DMPK-2.5$_{Rx}$: Phase 2 Clinical Trial – Conclusions

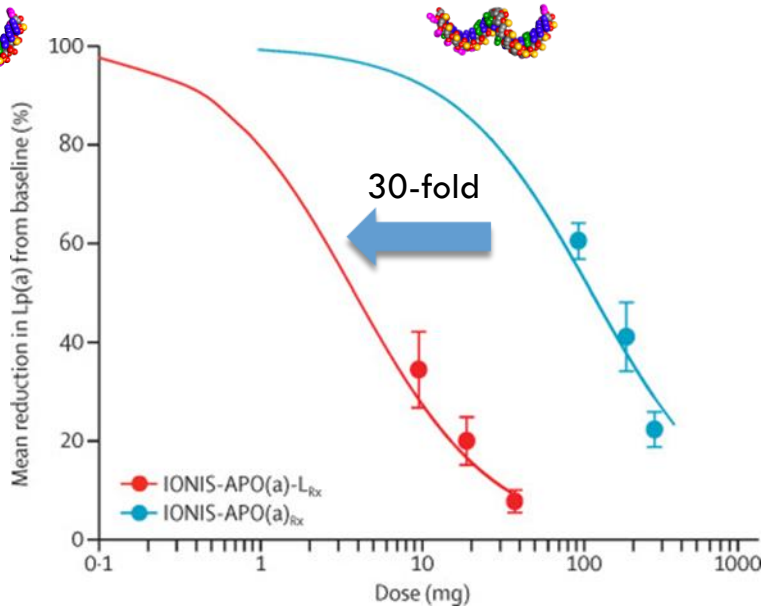
- Study drug was well-tolerated; no patient discontinued study
- Study was successful in many aspects:
  - Feasibility of multi-center trial
  - Ability to standardize all procedures including muscle biopsies and functional outcome measures
- But even at the highest dose (600 mg), drug concentration was not high enough to elicit expected splicing changes
  - 600 mg – 3 injections of 1mL every week – higher doses not feasible in the long-term
  - Lack of potency and need to go to higher dose led us to re-assess the molecule and try to obtain a better drug by changing the chemistry and/or adding a ligand that would take the drug to the target organ
- Two patients, "responders," may have shown improvements in various splicing biomarkers
  - Provides promise to future strategies targeting toxic RNA and provides support to use splicing events as potential therapeutic biomarkers

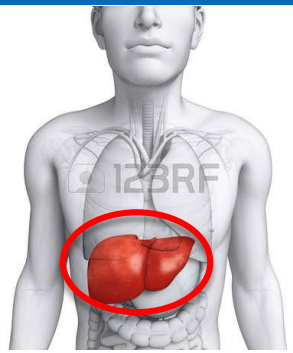
Focus on More Potent Molecule for Muscle:

ASGR mediated delivery to liver hepatocytes using GalNAc conjugation enhances ASO potency 30-fold in man



5'-THA-GalNAc



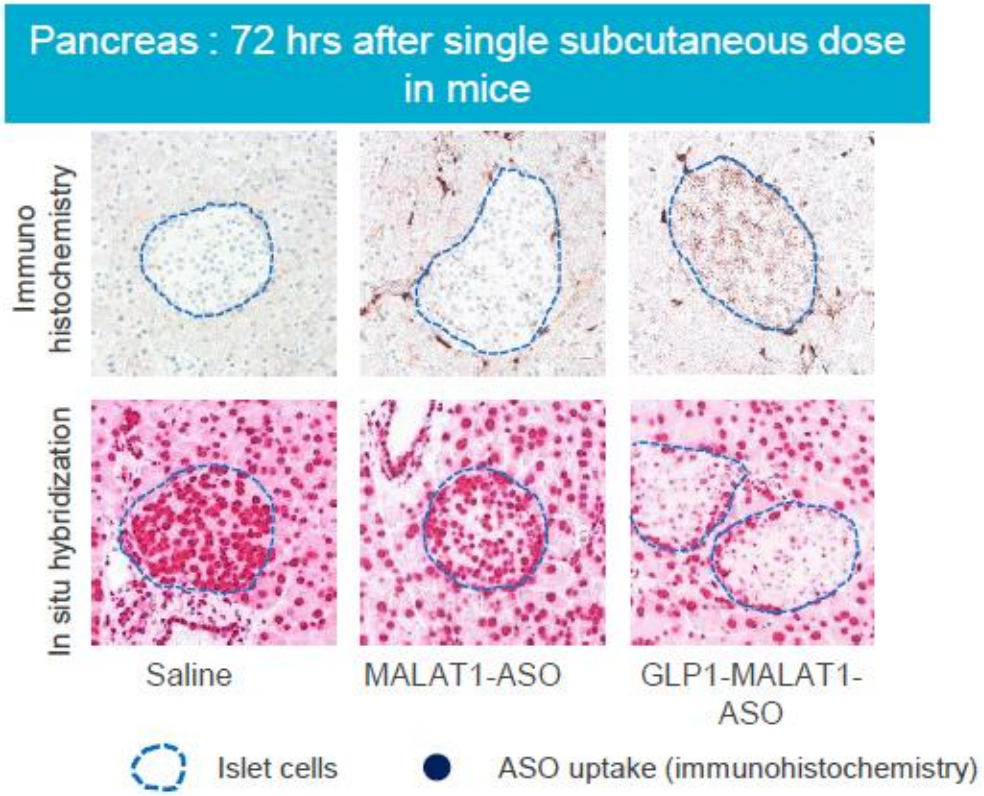


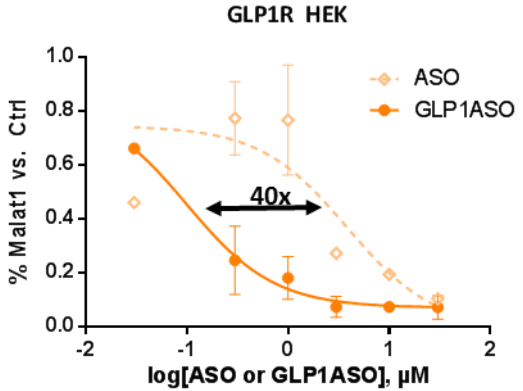
ASO (5'-3')	ED_{50} (mg/wk)
TGCTCCGTTGGTGCTTGTTC	122
THA-GalNAc-TGCTCCGTTGGTGCTTGTTC	4

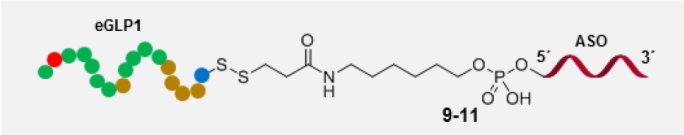
Prakash, (2016) *J. Med. Chem.*, **59**, 2718-2733.
Viney *et al.* (2016) *The Lancet*, **388**, 2239-2253

~12 GalNAc-ASOs currently in development at Ionis

GLP1-R targeting ASOs Reduce MALAT1 Only in Beta-Islets of Pancreas





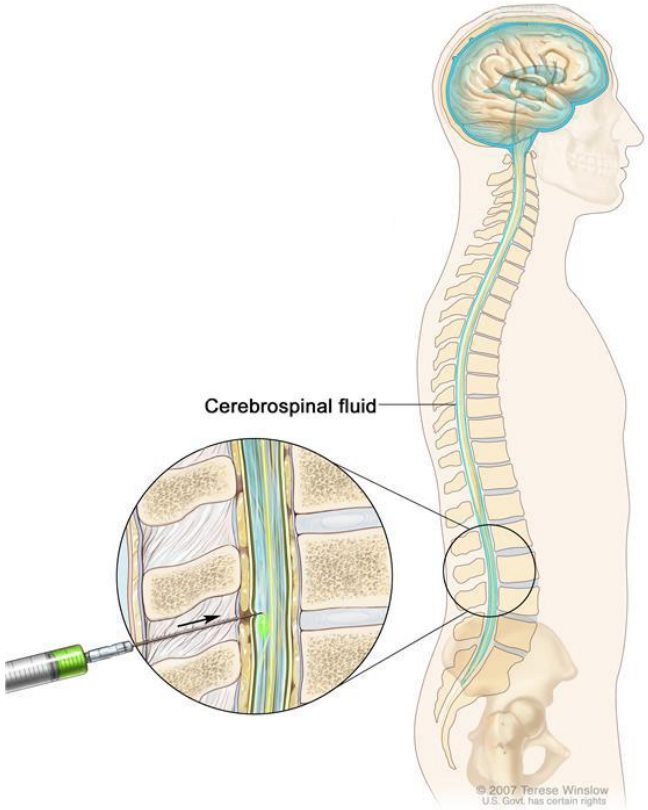


Ammala et al, accepted manuscript

Focus on Central Nervous System

Building on Recent Experiences

- While working on muscle conjugate, we are also looking into the CNS aspect of the disease
- Ionis' recent experience with CNS drugs
  - Spinraza in Spinal Muscular Atrophy
  - Ionis-HTT_{Rx} in Huntington's disease
  - Ionis-$SOD1_{Rx}$ in Amyotrophic Lateral Sclerosis
- ASO are delivered to the CNS via a lumbar puncture

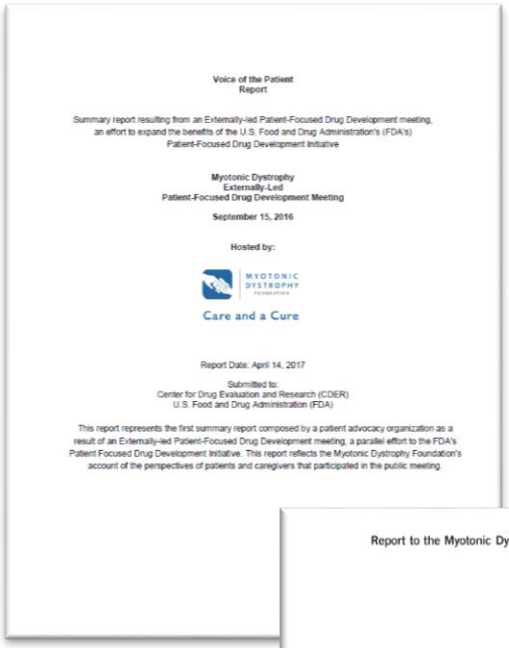


Path to Developing a Drug in CNS

- CNS Mouse model
  - Choosing the best model to test our strategy
- Biomarkers in the central spinal fluid
  - Need to find robust and reliable biomarker in the CSF
  - Data from muscles hint this should be feasible but the hurdle to find a CSF biomarker needs to be overcome
- Clinical endpoint
  - Dr. Janet Woodcock: "It turns out that what is really bothering the patient and what is really bothering the doctor can be radically different things… patients are true experts in their disease"
  - Need to cast a wide net and go beyond cognition and execution function; need to look at apathy, sleep, fatigue, structural measures (MRI)

Patient Input on CNS Symptoms

- September 2016: MDF set up the first externally-led Patient-Focused Drug Development meeting, resulting in the "Voice of the Patient Report"
- MDF Annual Meeting, September 2017: MDF lead "Bringing the Patient Voice to CNS-Targeting Drug Development in Myotonic Dystrophy" roundtable, resulting in an upcoming publication
- "Christopher Project Report" 2018, a survey mailed to participants, resulting in an expansive overview of DM1 and DM2



Muscle weakness and myotonia are considered prominent symptoms, but lives are affected to an even greater extent by other symptoms, such as excessive daytime sleepiness, fatigue, and cognitive dysfunction.

Reshaping the "Function and Feels" of a Patient into Clinical Endpoints

- Focus on merging the information from the patient reports with the sparse published longitudinal data available on CNS changes in myotonic dystrophy, and developing a survey to address:
  - What symptoms are important?
  - What improvements are expected?
  - What improvements are considered significant to the patient?
  - What level of benefit/risk would a patient accept in a medication?
- Draft survey developed by Lauren Gibbs, summer intern in Patient Advocacy at Ionis, and was tested on a few local patients
  - Feedback received to date will be used to refine and focus the survey
  - Next steps
    - Send the survey out through the MDF website, to hopefully hone in what symptoms are most bothersome -- Be on look-out for this and participate!
    - Develop a parallel caregiver survey to better assess the complexity of the CNS disease

Conclusion

- We are still mining the data obtained from the CS2 study and are working on a publication of the trial
- We are still focusing on a systemic therapy to treat muscle and other peripheral tissues
- We are investigating the potential to develop a CNS targeting therapy

Acknowledgments

THANKS TO ALL THE PATIENTS AND THEIR FAMILIES -- TO ALL OF YOU FOR YOUR CONTINUED SUPPORT AND FOR GETTING INVOLVED

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