IONIS-DMPK$_{Rx}$ Clinical Program in Myotonic Dystrophy

Laurence Mignon, PhD
Director, Clinical Development

Partnered with Biogen

IONIS® PHARMACEUTICALS

Development of a Treatment for Myotonic Dystrophy

How Ionis got involved in Myotonic Dystrophy

- Year 2008
- Within 1 week, Frank Bennett heard from:
  - Marigold Foundation
  - Association Française contre les myopathies (AFM)
  - Charles Thornton, University of Rochester

The Search for a Treatment for Myotonic Dystrophy

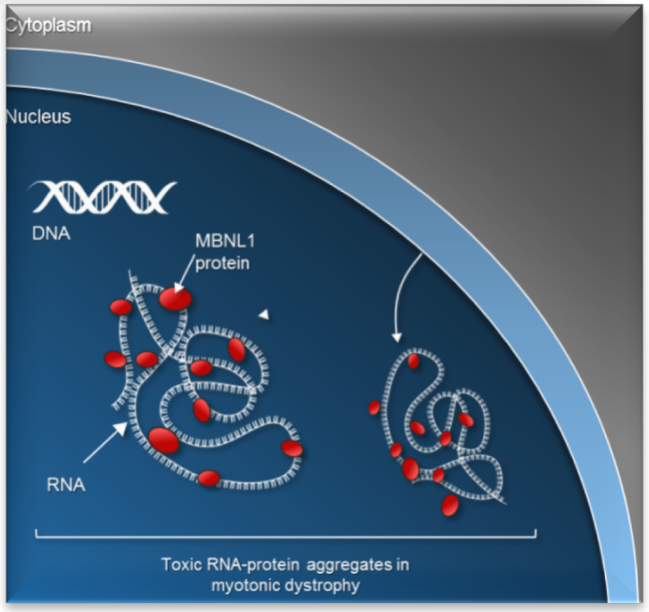
Why Ionis Became Interested in Myotonic Dystrophy

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 is correlated with number of repeats (higher # repeats = more sever disease)
- Broad spectrum of symptoms, including muscle dysfunction and GI tract issues
- Juvenile and adult forms of DM1

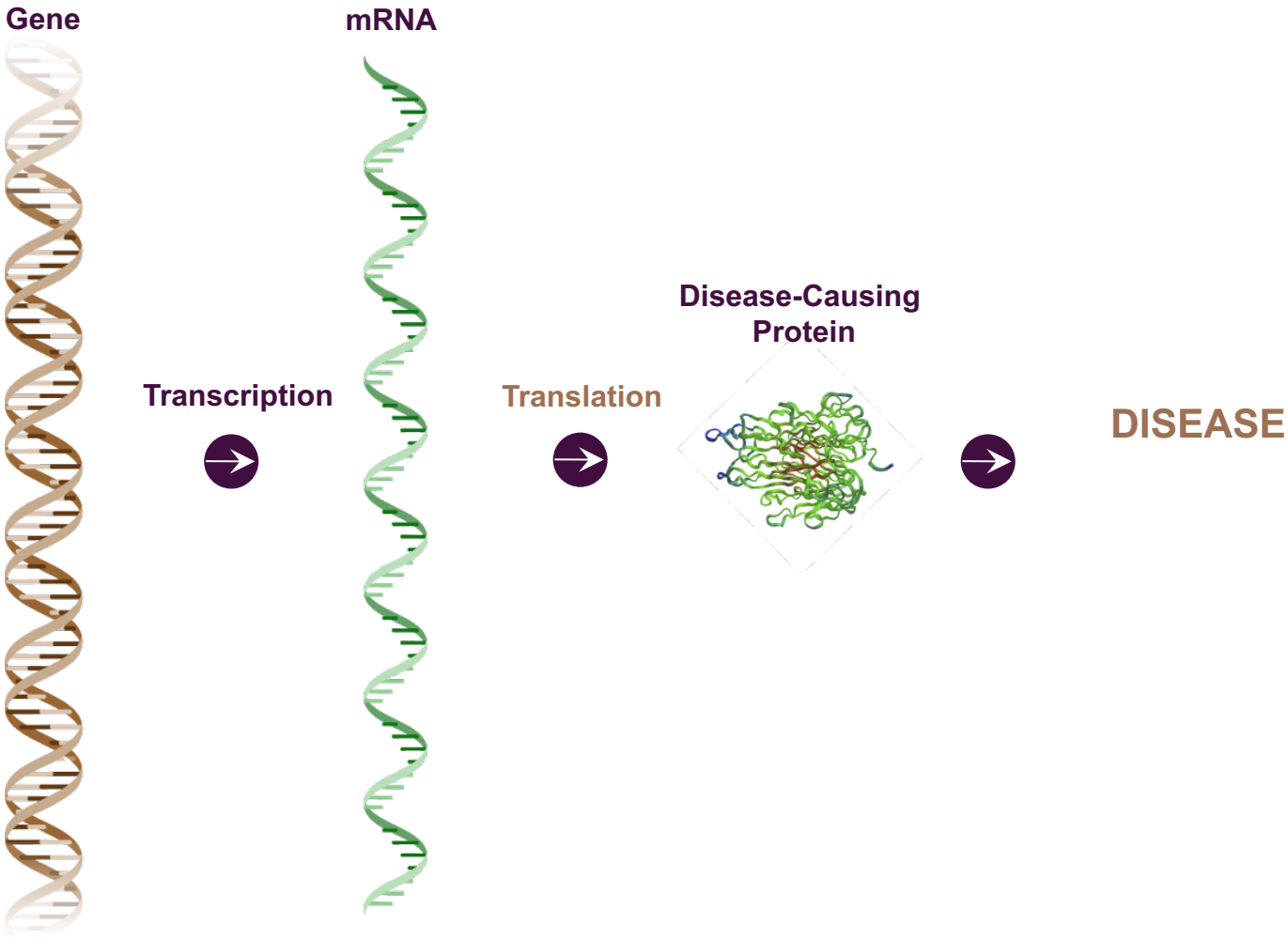
Why IONIS became interested in DM1

- 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

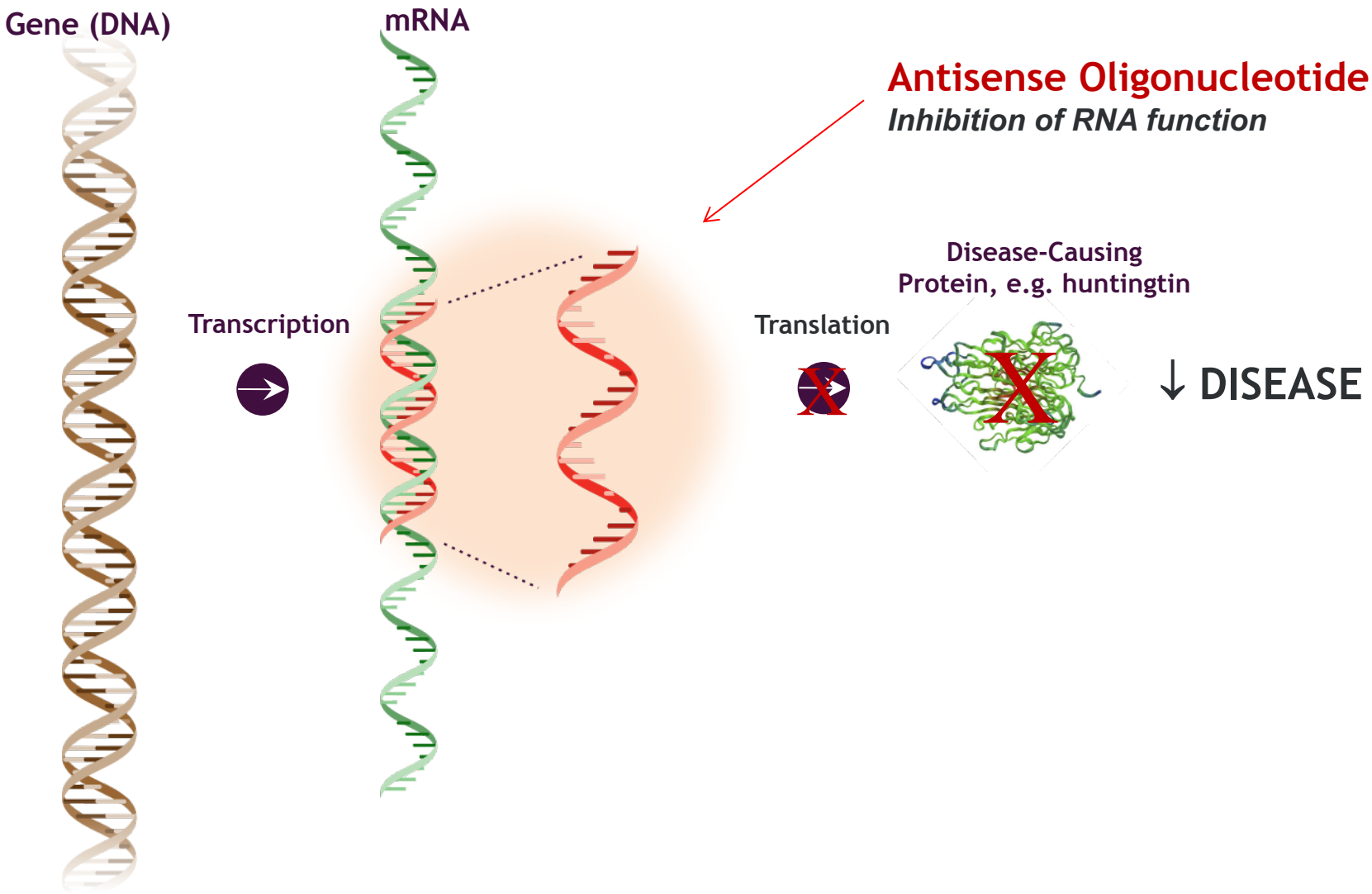


How Genetic Information Flows From in DNA → Protein

The “Central Dogma” of Molecular Biology

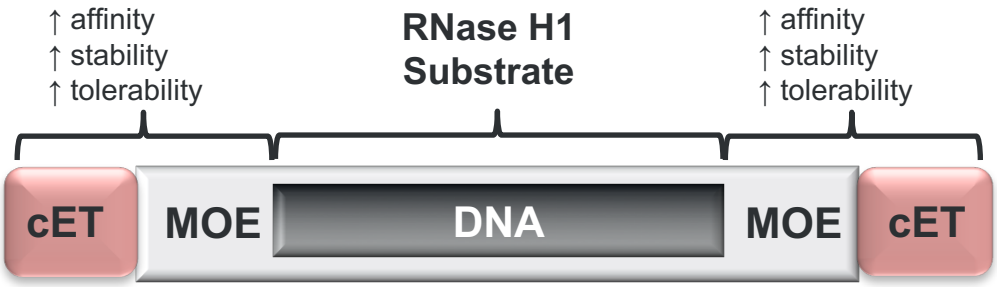


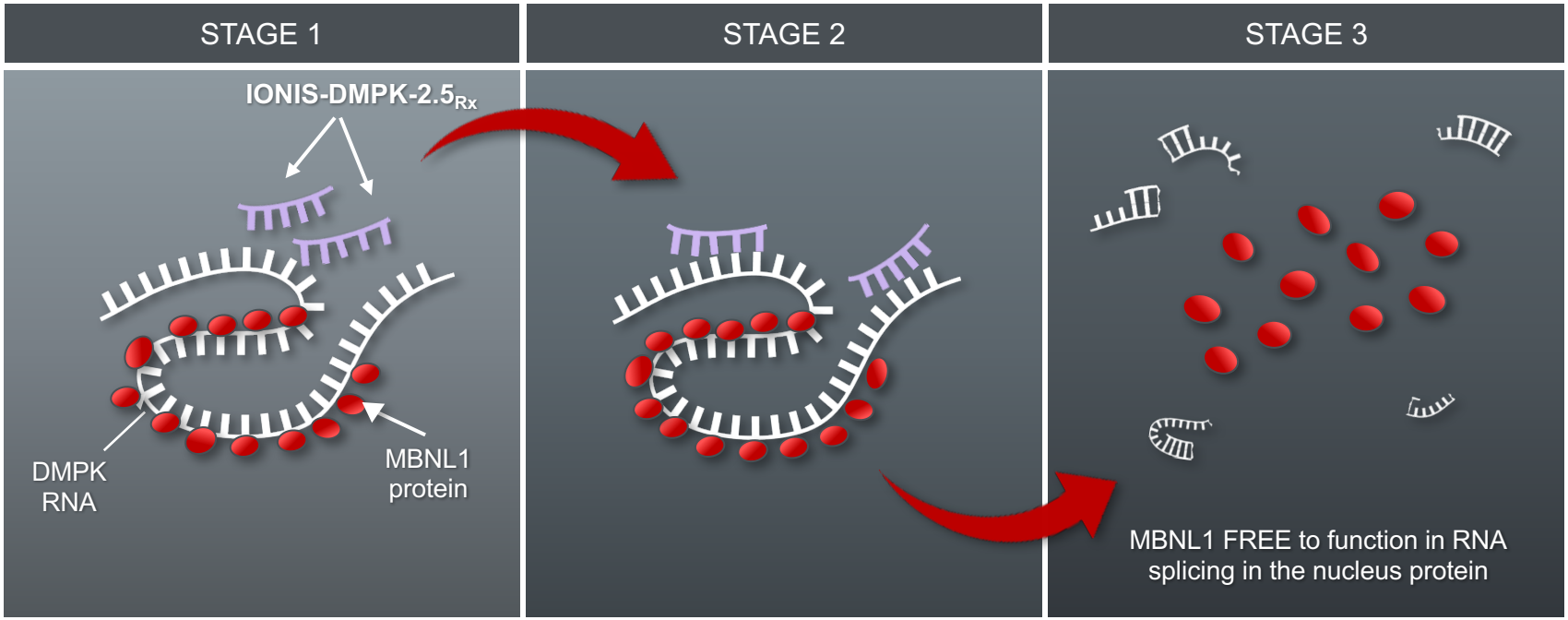
Antisense Drugs Target RNA, Not Proteins



IONIS-DMPK-2.5$_{Rx}$ is 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

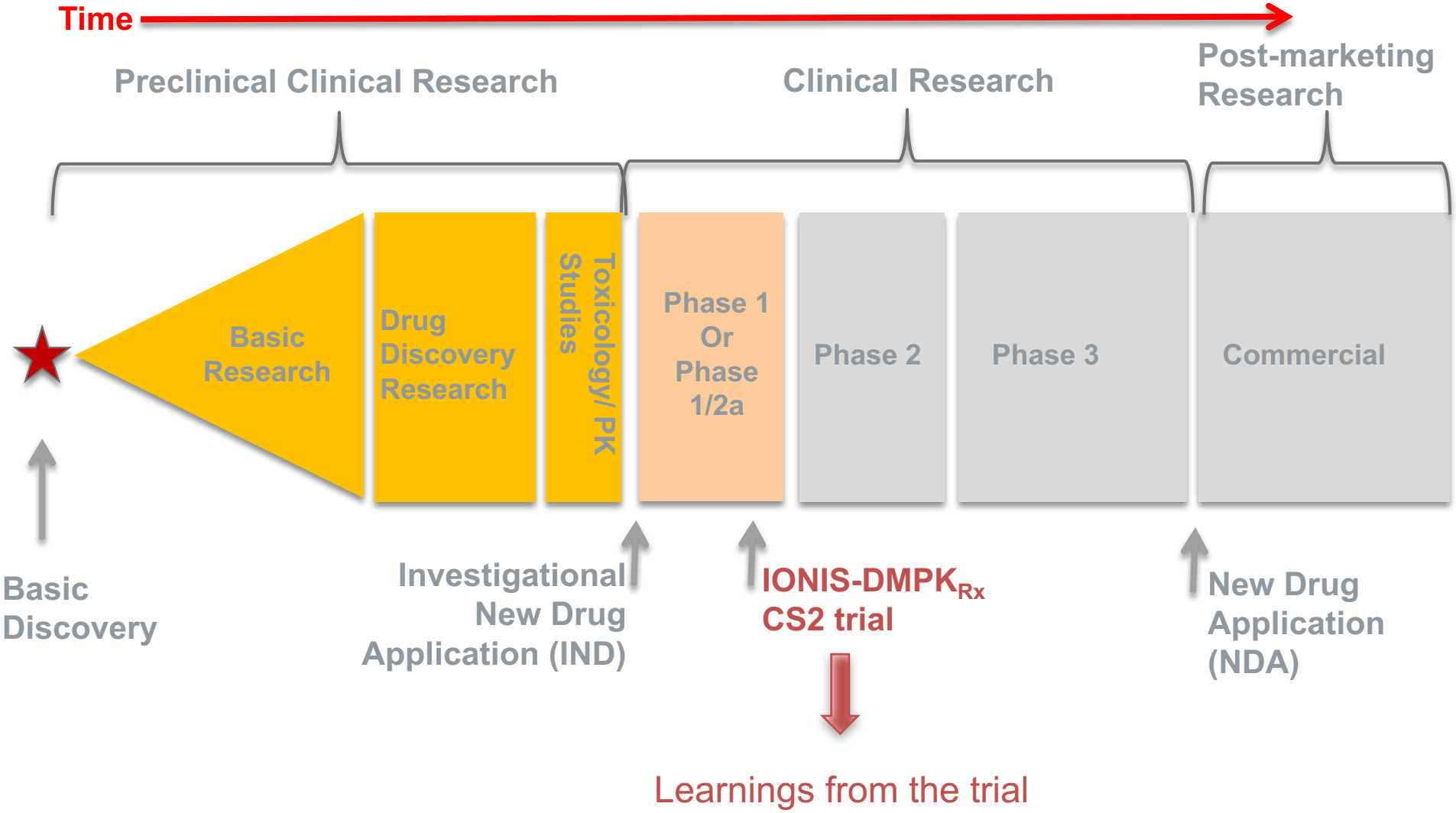




Cooper, T.. (2009) *Science*. 325:272-273

Drug Discovery

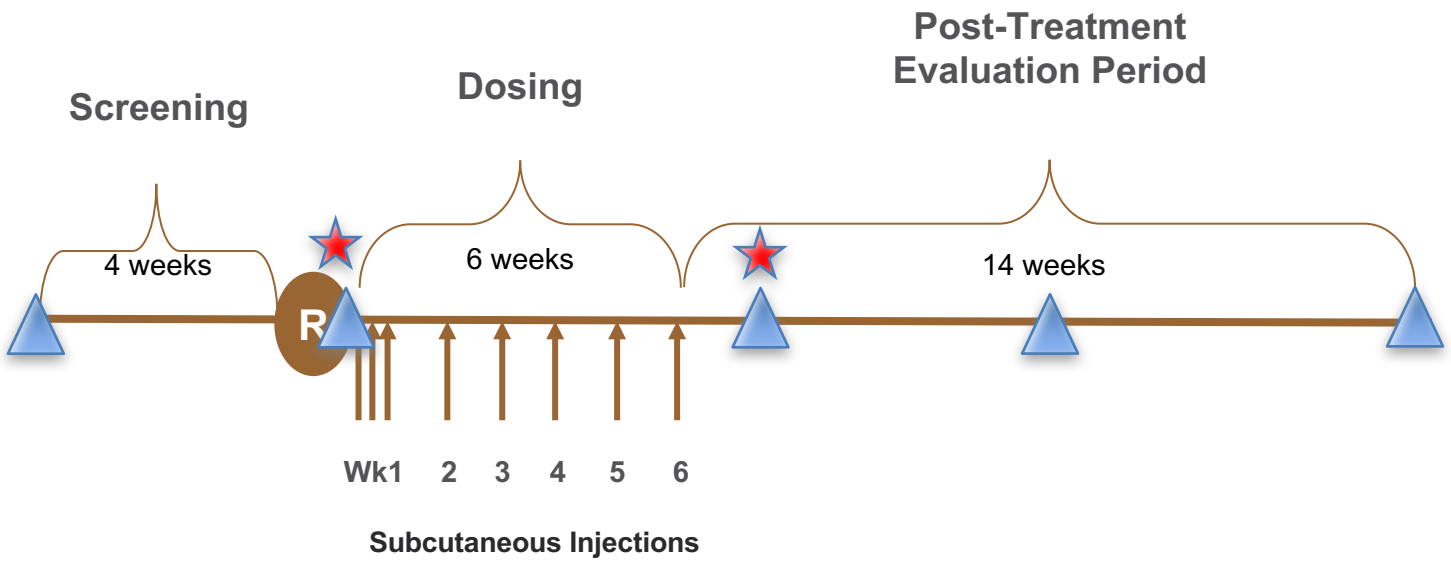
Steps in the Process



IONIS-DMPK$_{Rx}$-CS2: Phase 1/2a Multiple Ascending Dose Study in Adult Patients with Myotonic Dystrophy Type 1

Study Design

- Phase 1/2a Trial tests the safety of the drug in DM1 patients
  - Multiple-Ascending Dose Study
    - 8 centers in the US
    - 5 different dose levels are tested: 100mg, 200mg, 300mg, 400mg, 600mg
    - Short 6-week treatment duration



IONIS-DMPK$_{Rx}$-CS2: Phase 1/2a MAD Study in Adult Patients with Myotonic Dystrophy Type 1

Study Objectives

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

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

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

- Lab values
- ECGs
- How are injections tolerated

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

- Myotonia tests
- Strength tests
- Functional test
- Patient-reported outcomes

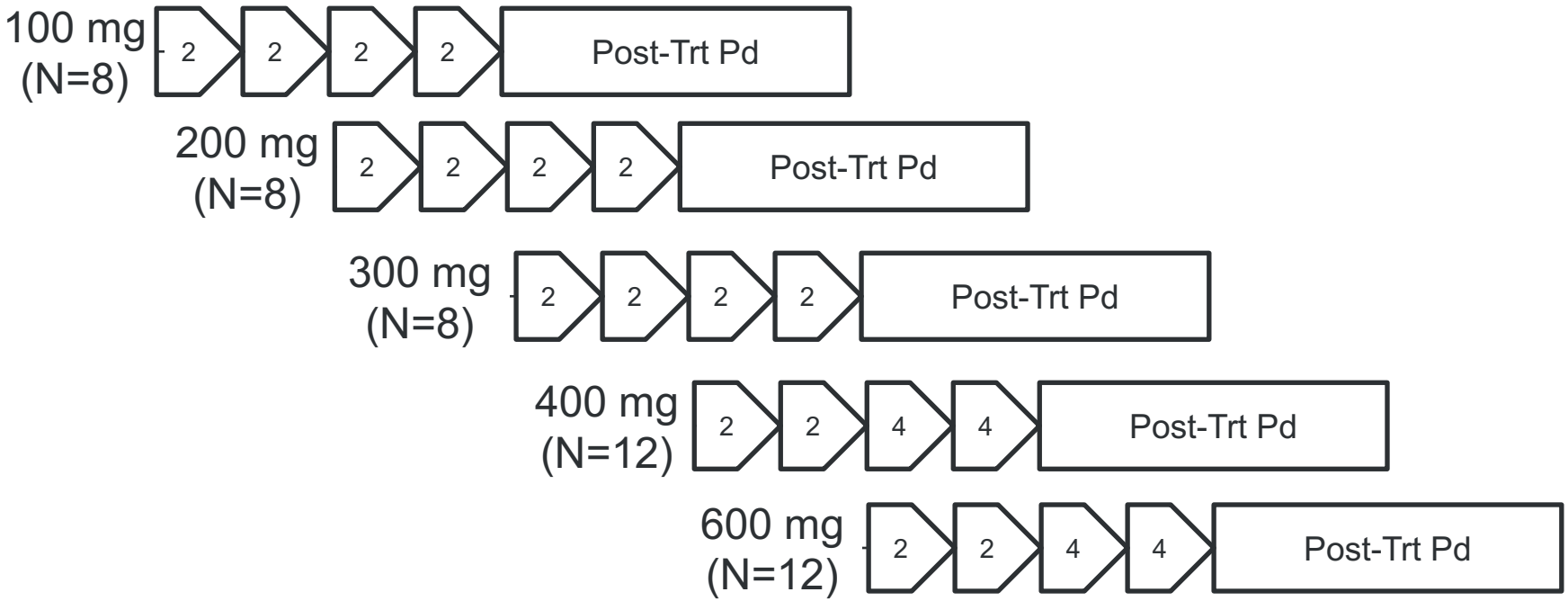
IONIS-DMPK$_{Rx}$-CS2: Phase 1/2a MAD Study in Adult Patients with Myotonic Dystrophy Type 1

Main Inclusion/Exclusion Criteria

- Inclusion Criteria
  - Males or females; 20-55 years old
  - BMI < 35 kg.m2
  - Genetic confirmation of DMPK CTG repeat length ≥100
  - Onset of disease after age 12
  - Clinically apparent myotonia equivalent to hand opening time of at least 2 seconds
  - Ambulatory
- Exclusion Criteria
  - Implanted device for the treatment of cardiac problems (pacemaker, defibrillator)
  - Clinically abnormal ECG or echocardiogram (central cardiac reader)

IONIS-DMPK$_{Rx}$-CS2: Phase 1/2a MAD Study in Adult Patients with Myotonic Dystrophy Type 1

Cohort Allocation



- Original protocol included 4 cohorts; added the 5th cohort at 600 mg based on satisfactory safety profile
- 2 patients treated with placebo in each cohort

Learnings from the IONIS-DMPK$_{Rx}$-CS2 Trial

Subject Baseline Demographics

	Placebo	100 mg	200 mg	300 mg	400 mg	600 mg
N	10	6	6	6	10	10
Age, Median (min, max)	38 (20, 48)	36 (26, 42)	33 (23, 47)	42 (33, 50)	39 (30, 46)	41 (25, 53)
Gender, Female, n (%)	5 (50%)	5 (83%)	3 (50%)	4 (67%)	8 (80%)	4 (40%)
Race, White, n (%)	8 (80%)	6 (100%)	6 (100%)	6 (100%)	10 (100%)	9 (90%)
Age at Sx onset Median (min, Max)	23 (12, 31)	22 (13, 33)	16 (13, 35)	23 (13, 45)	17 (12, 29)	30 (19, 44)
Age at Dx onset Median (min, Max)	31 (16, 40)	27 (24, 35)	28 (10, 43)	26 (23, 49)	28 (16, 37)	31 (19, 45)
CTG Repeats Median (min, Max)	432 (107, 1006)	271 (136, 546)	432 (256, 670)	616 (210, 1000)	645 (156, 1026)	368 (153, 763)
Isometric Handgrip Myotonia Relaxation Time in seconds, Median (Min, Max)	9.8 (1.4, 11.9)	7.6 (2.1, 11.3)	11.1 (2.3, 12.5)	5.4 (1.4, 7.6)	8.9 (2.8, 12.4)	1.3 (0.5, 10.4)
6 Minute Walk Test Median (Min, Max)	504 (285-661)	433 (357-545)	435 (260-645)	359 (223-640)	414 (283-508)	400 (250-637)
Myotonic Dystrophy Health Index, total score Median (Min, Max)	21 (5-52)	36 (34-41)	31 (30-47)	22 (5-48)	28 (20-47)	32 (17-44)

Learnings from the IONIS-DMPK$_{Rx}$-CS2 Trial

Heterogeneity of Patients

- Heterogeneity of patient population within and across dosing groups
  - Not unexpected, but exemplifying the mutli-systemic nature of the disease
  - Complicates interpretation of dose response relationship for clinical and molecular outcomes
    - Inclusion/exclusion criteria to focus on a more homogenous population
    - Need to use stratification for later stage trials
- Ongoing natural history studies aimed at helping better understand the heterogeneity and the progression of the disease throughout the spectrum of the disease

Learnings from the IONIS-DMPK$_{Rx}$-CS2 Trial

Outcomes Measures

- Myotonia tests:
  - Isometric handgrip myotonia
  - 6- minute walk test
  - 4 steps climb/descend
- Patient-reported outcomes
  - MDHI

1-2 day, in-person physical therapist training provided throughout the study:
- **Study start**
- **Yearly thereafter**

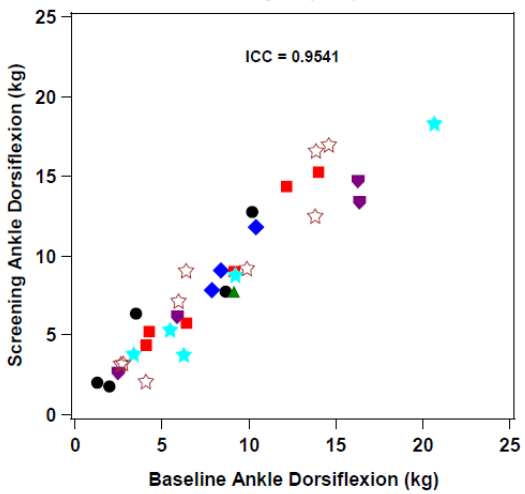
Lead trainer available for 1:1 sessions in person or by phone throughout the study

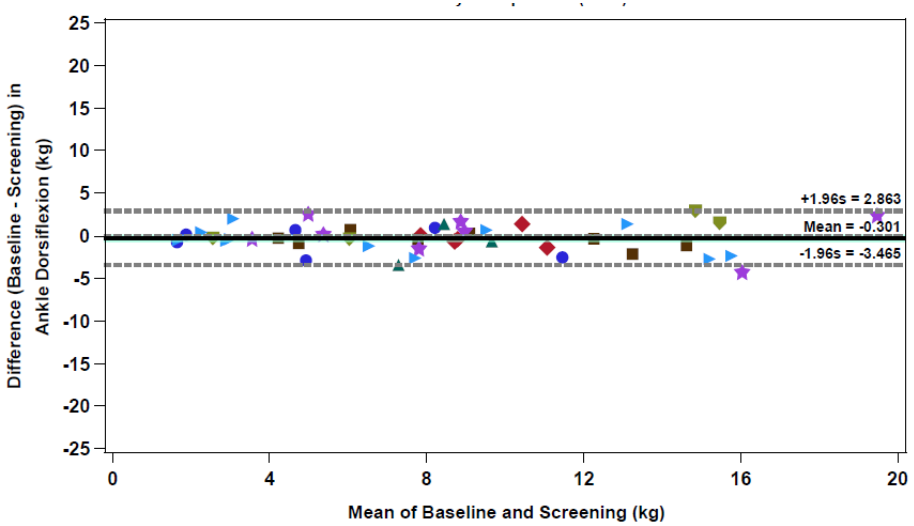
- Trial generated solid and reproducible data
  - Emphasized ability to do a multi-center trial
- Variabilities were seen between patients
- Natural history and network studies have laid the ground work with respect to clinical trial readiness

Learnings from the IONIS-DMPK$_{Rx}$-CS2 Trial

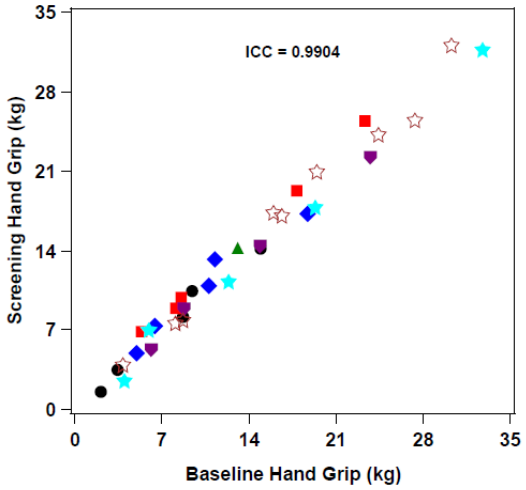
Reliability of Outcomes Measures Across Clinical Sites

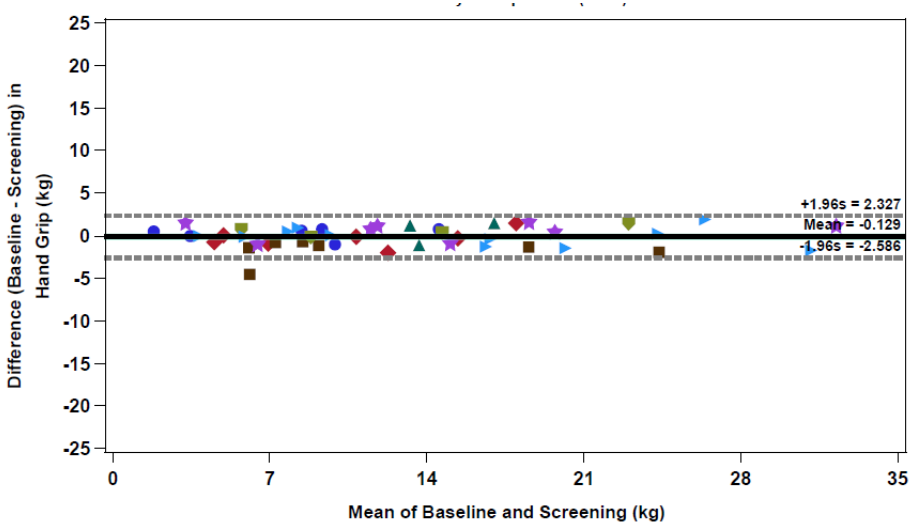
Ankle Dorsiflexion as measured by QMT





Hand Grip as measured by QMT





Learnings from the IONIS-DMPK$_{Rx}$-CS2 Trial

Biomarker Analysis

- Good quality of muscle biopsies across sites
- Good quality RNA extraction
- Initial biomarker analysis also showed variability—similar to outcomes measures
  - Changes were modest, with some trends
- More work required to better understand
  - How biomarkers are modulated
  - Impact of disease duration on biomarker changes
  - Impact of MBNL level on biomarker changes

Learnings from the IONIS-DMPK$_{Rx}$-CS2 Trial

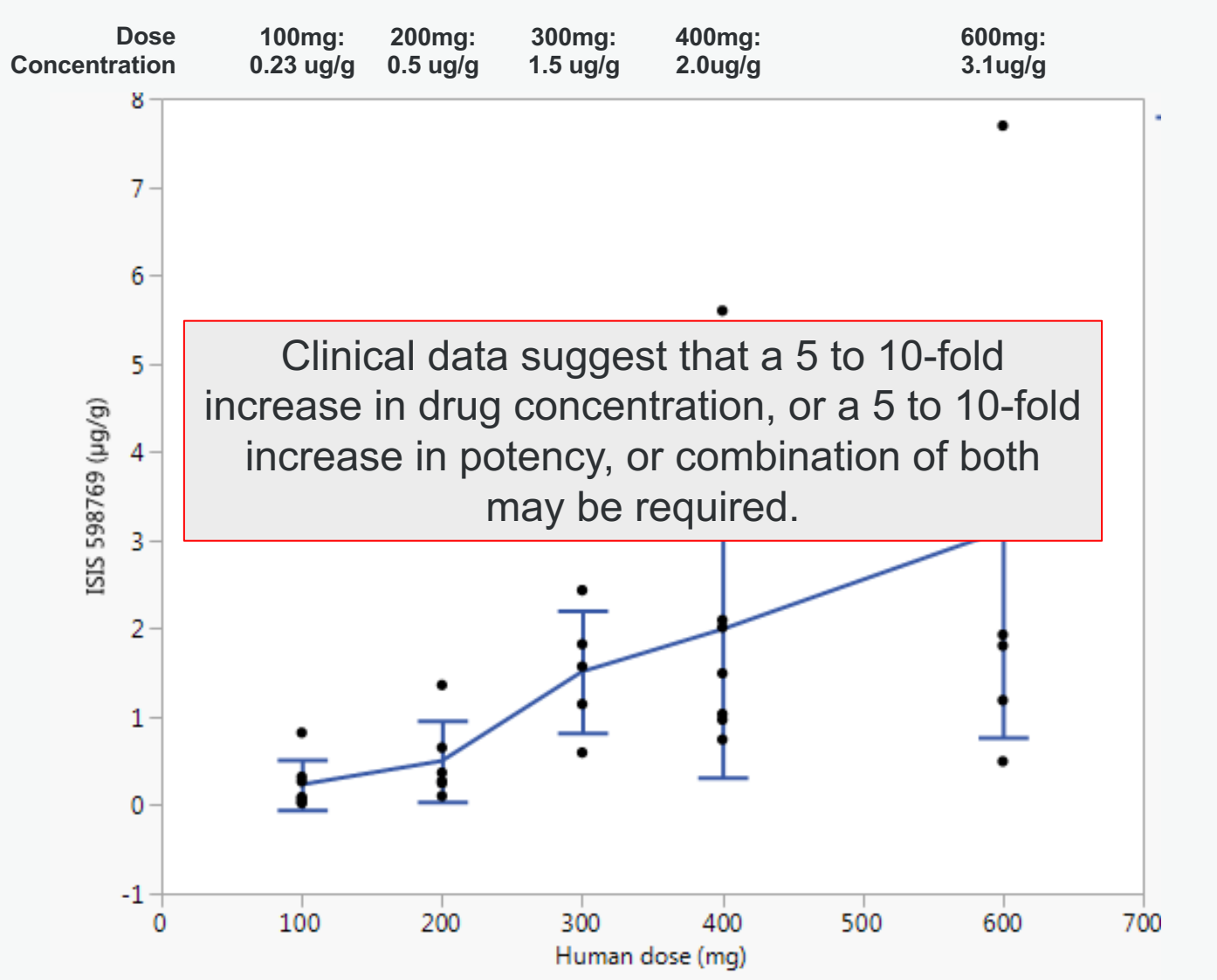
Muscle Pharmacokinetics – The Most Important Finding

- Muscle pharmacokinetics
  - Originally we did not anticipate to do this
    - small tissue size
    - need to prioritize biomarker analysis
  - Improvements in analysis methods, especially in the ability to use very small pieces of tissue, allowed us to measure drug concentration

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

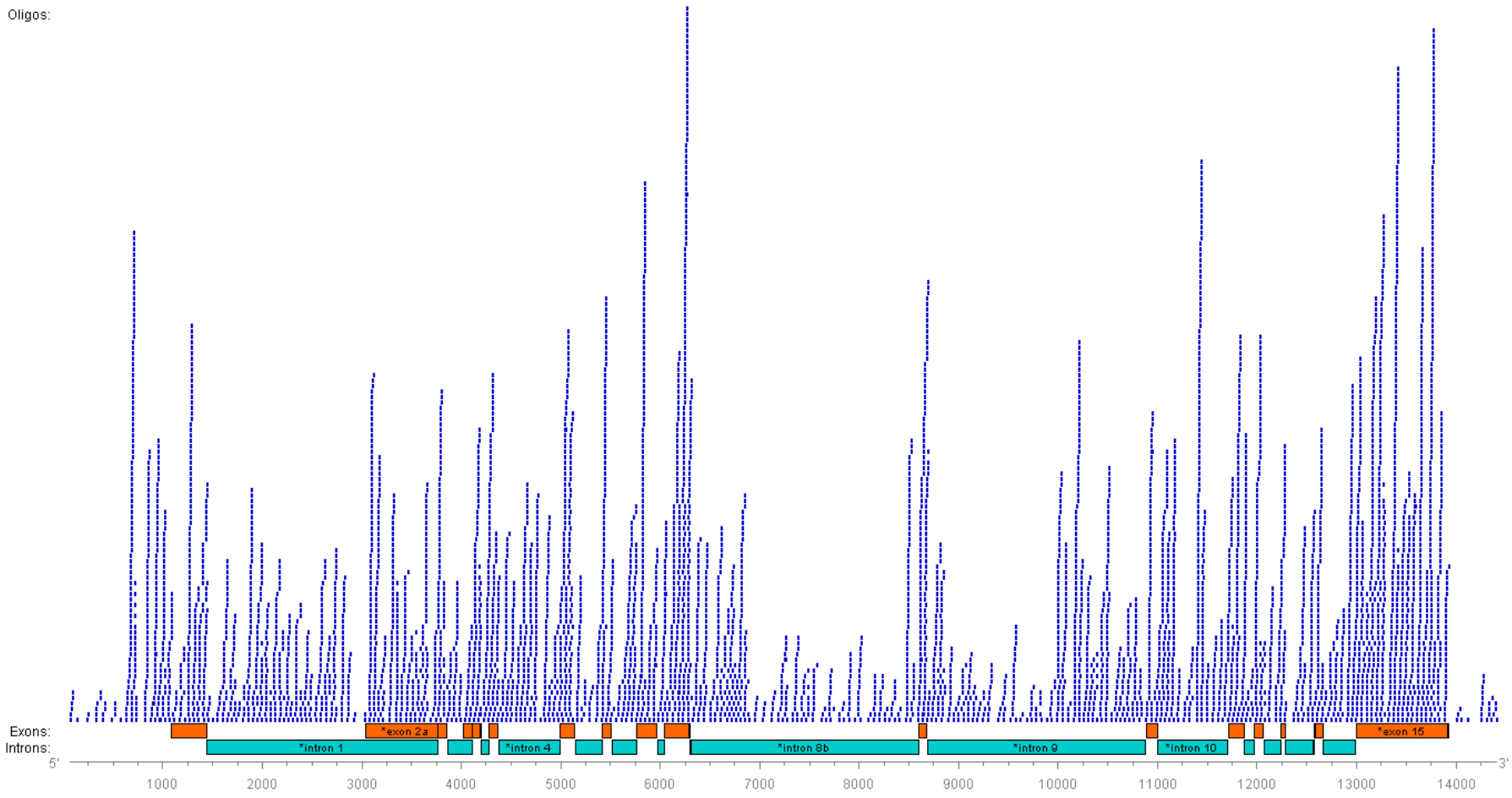
Target tissue concentration was determined to be 10-15 ug/gm to get ~50% KD in muscle

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



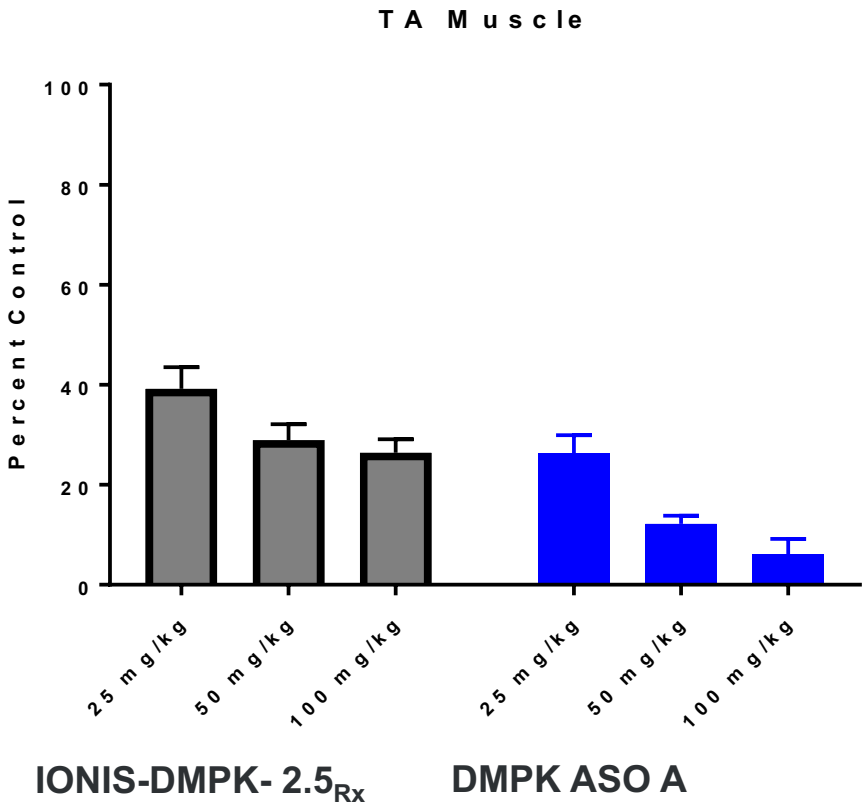
So What Now?

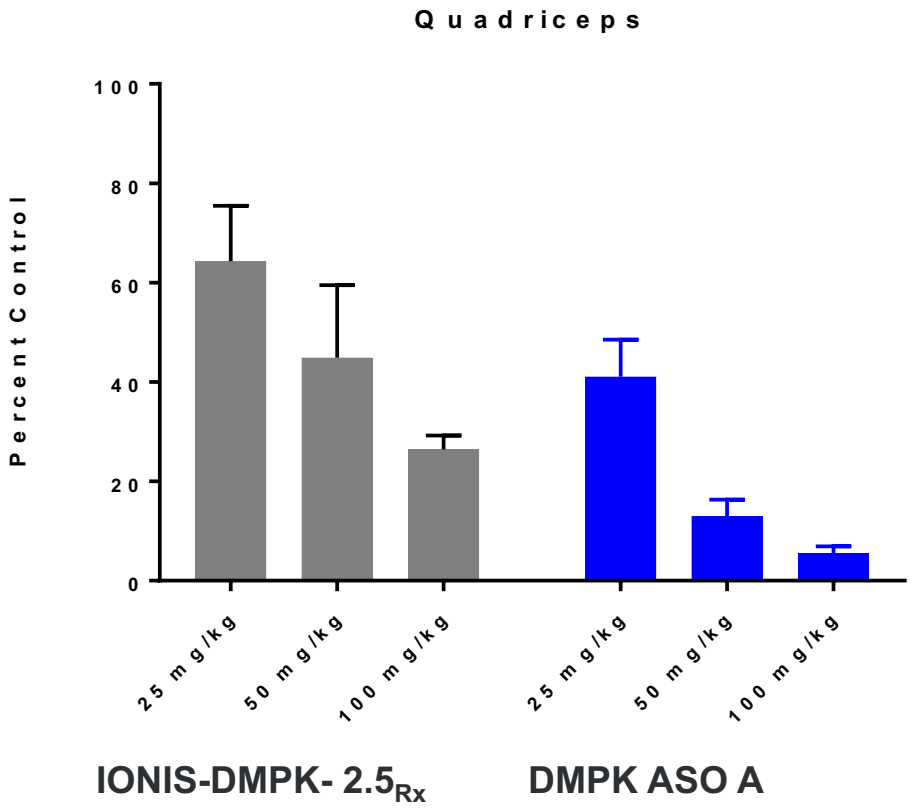
Antisense Oligonucleotides Designed to Human DMPK pre-mRNA



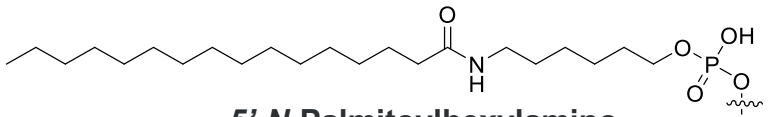
Example of a More Potent ASO Identified by Deeper Screening

Dose Dependent inhibition of human DMPK transgene in DMSXL Transgenic Mice



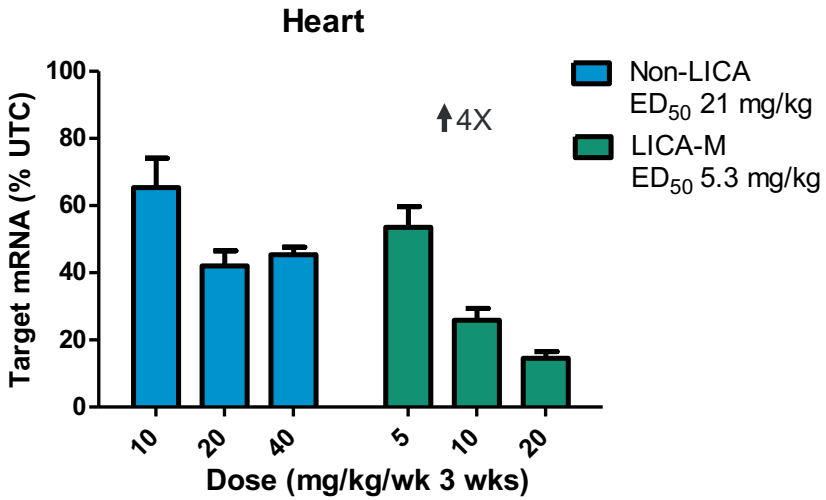


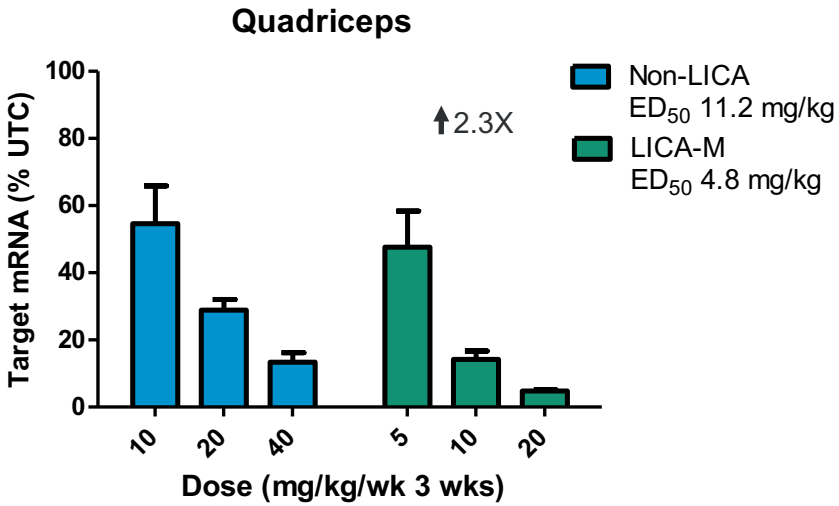
Working on Better Chemistries to Improve Activity of DMPK ASO



***5'-N*-Palmitoylhexylamino**

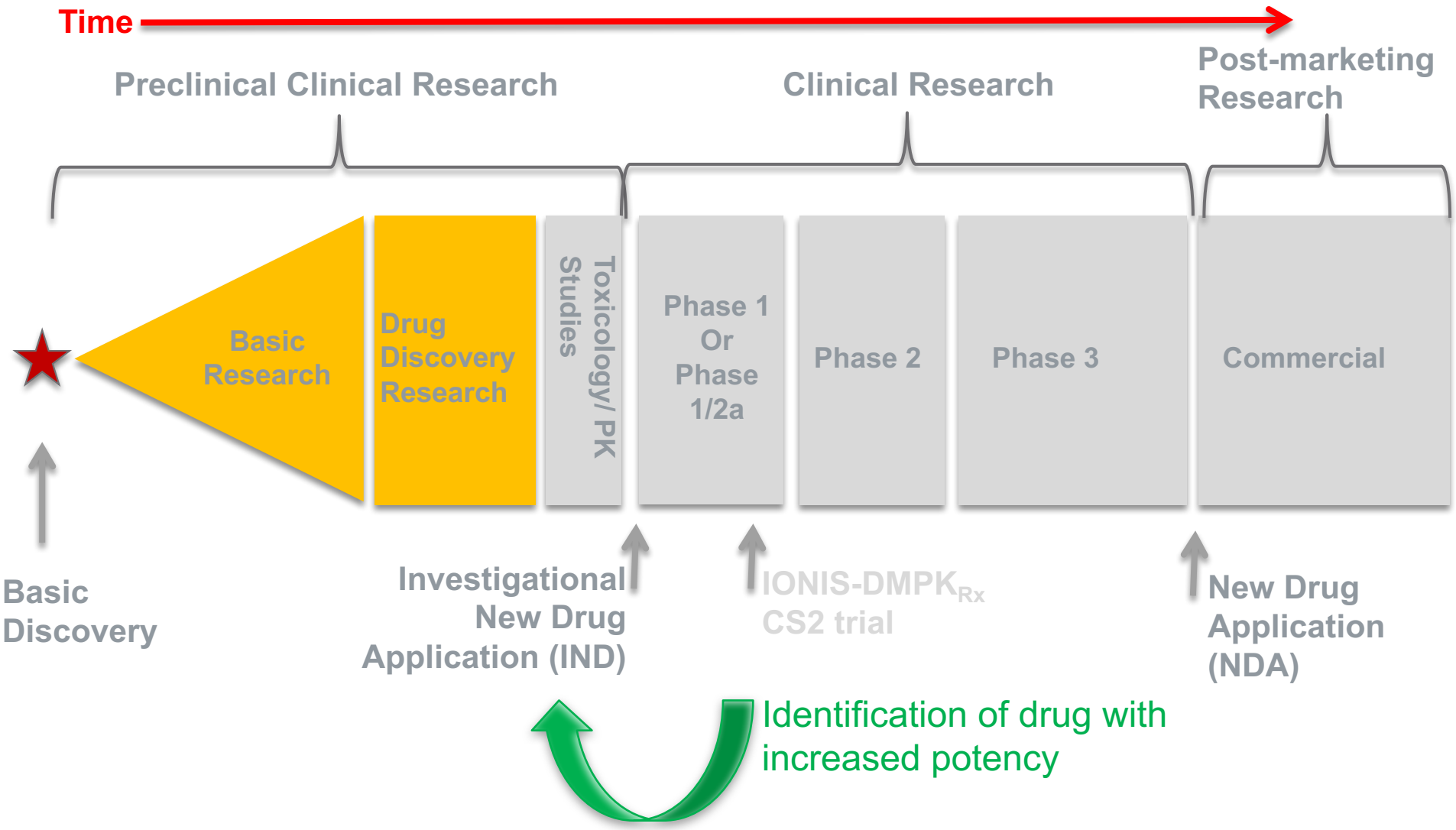
Isis #	Sequence (5' to 3')	Conjugate (X)	Heart ED_{50} (mg/kg/wk)	Quad ED_{50} (mg/kg/wk)
486178	ACAATAAATACCGAGG	none	21	11.2
877864	XoACAATAAATACCGAGG	5'-C16-hexyamino	5.3	4.8





Drug Discovery

Steps in the Process



Conclusion

- Collaborative effort (sites, patient advocacy groups, patient community) has laid the foundation for future trials
- Due to the heterogeneity of patients with myotonic dystrophy it is important to have robust longitudinal data across the entire population for the measures used in a trial
- Our current research efforts focus on optimization of a drug with better potency
- Extracting all the data we can from the CS2 trial
- Ionis is committed to the development of a therapy for myotonic dystrophy

Acknowledgments

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TO ALL OF YOU FOR YOUR SUPPORT AND HARD WORK

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Care and a Cure

Partnered with:
Biogen