2016 MDF
ANNUAL CONFERENCE

September 15-17 2016, Washington DC

MYOTONIC DYSTROPHY FOUNDATION

Care and a Cure

UPDATE ON IONIS-DMPK-2.5$_{RX}$

Laurence Mignon, PhD, Ionis Pharmaceuticals, Inc

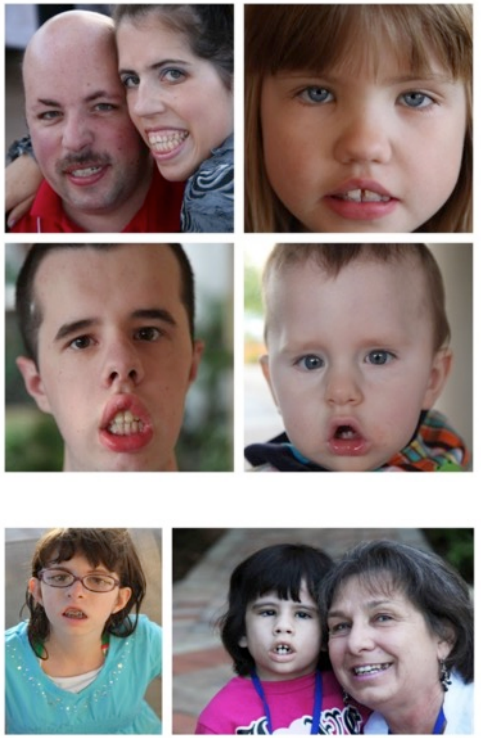
Myotonic Dystrophy Foundation Annual Meeting, Sept 2016

Overview

- Background on Ionis and platform
- Preclinical Work
- Clinical Update

Improving Patient Lives by Treating Diseases…through targeting RNA

- Ionis Pharmaceuticals was founded in 1989
- Located in California; ~450 employees
- Drug discovery, early development, manufacturing
- A different approach to treating Disease—targeting the RNA

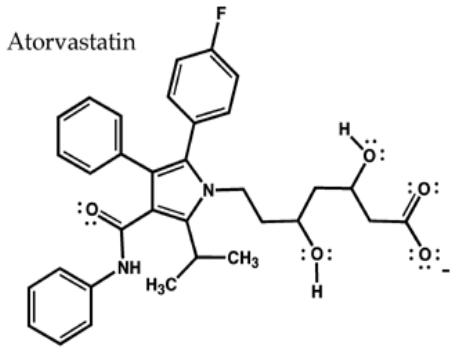


IONIS™ PHARMACEUTICALS

Three Current Drug Discovery Platforms

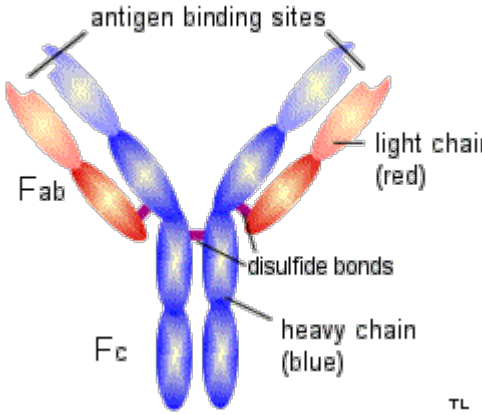
Small Molecules

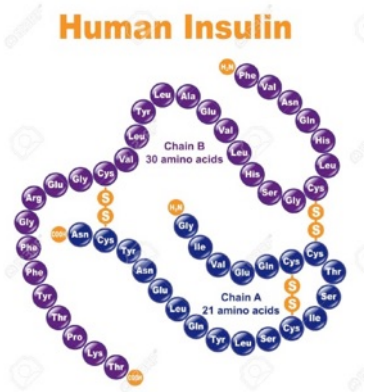
Lipitor



Proteins

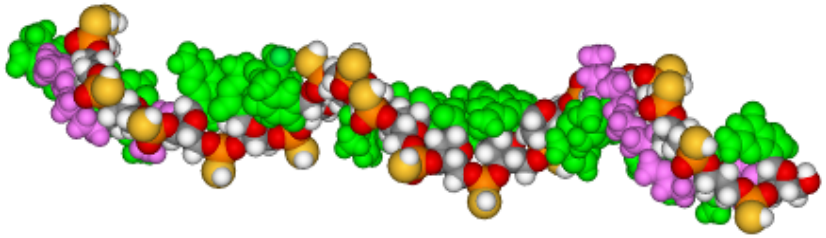
Antibodies, e.g. Humira





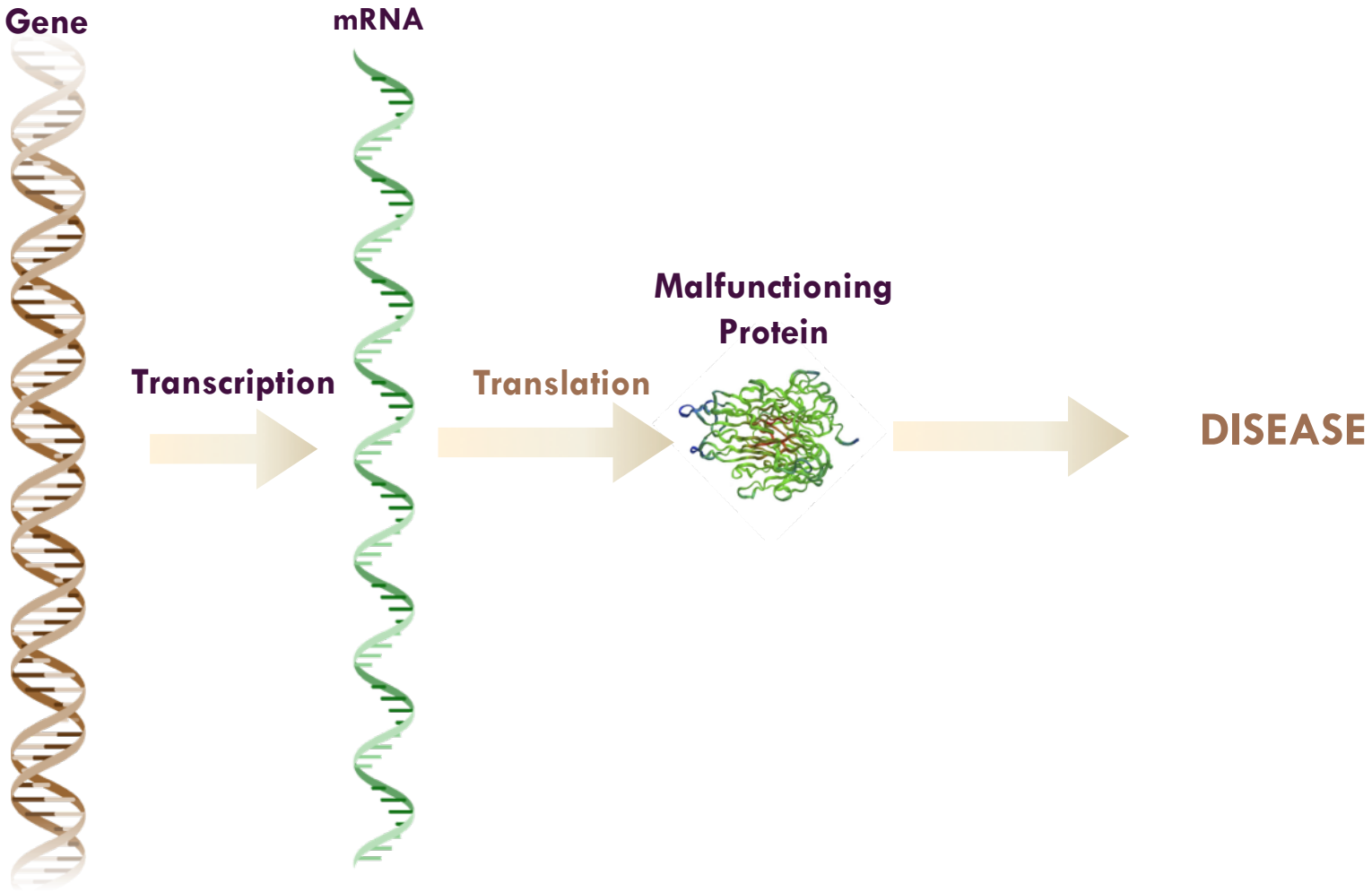
Nucleic Acids

Antisense drugs, e.g. Kynamro



How Genetic Information Flows From DNA → Protein:

The "Central Dogma" of Molecular Biology



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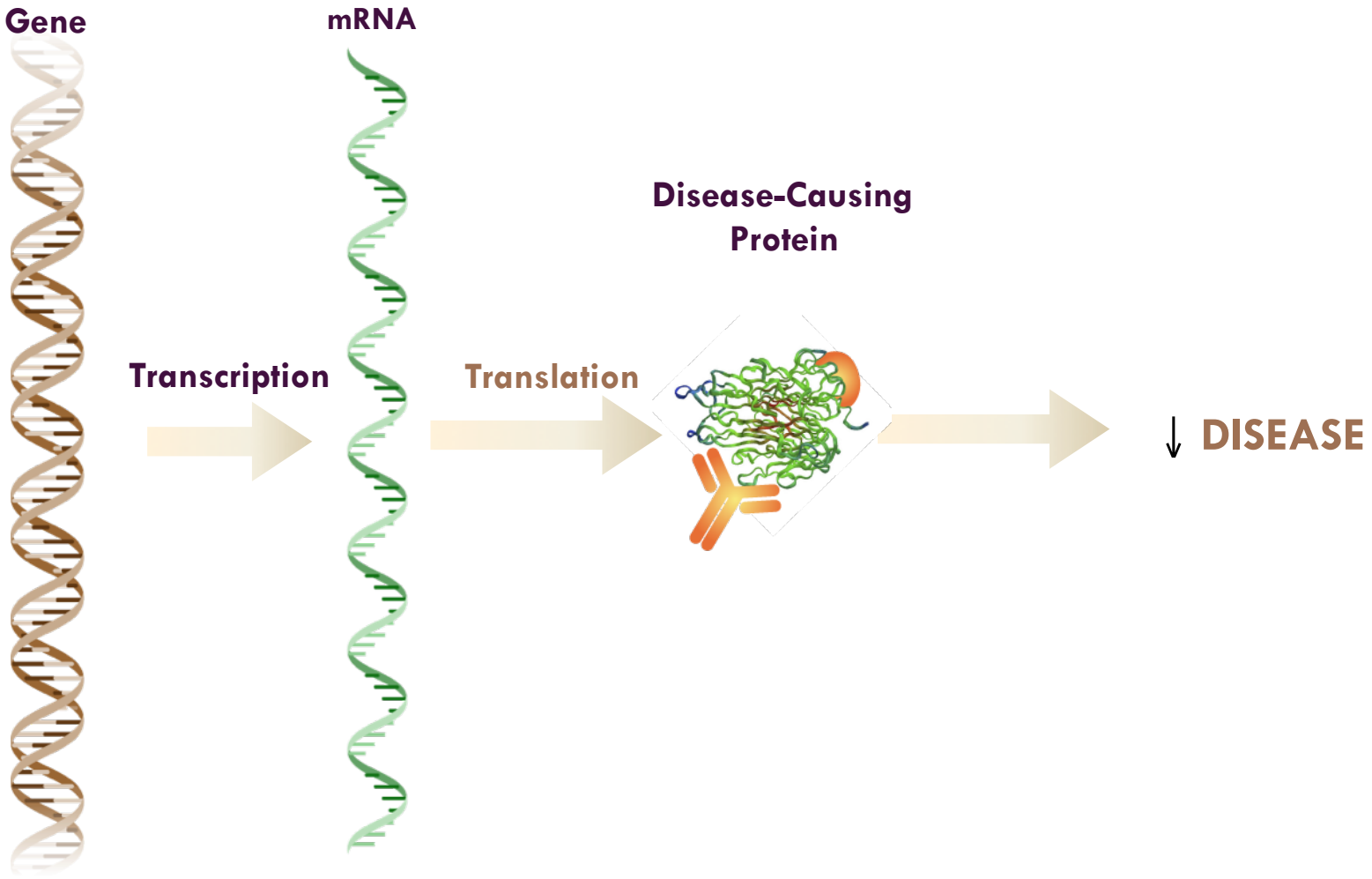
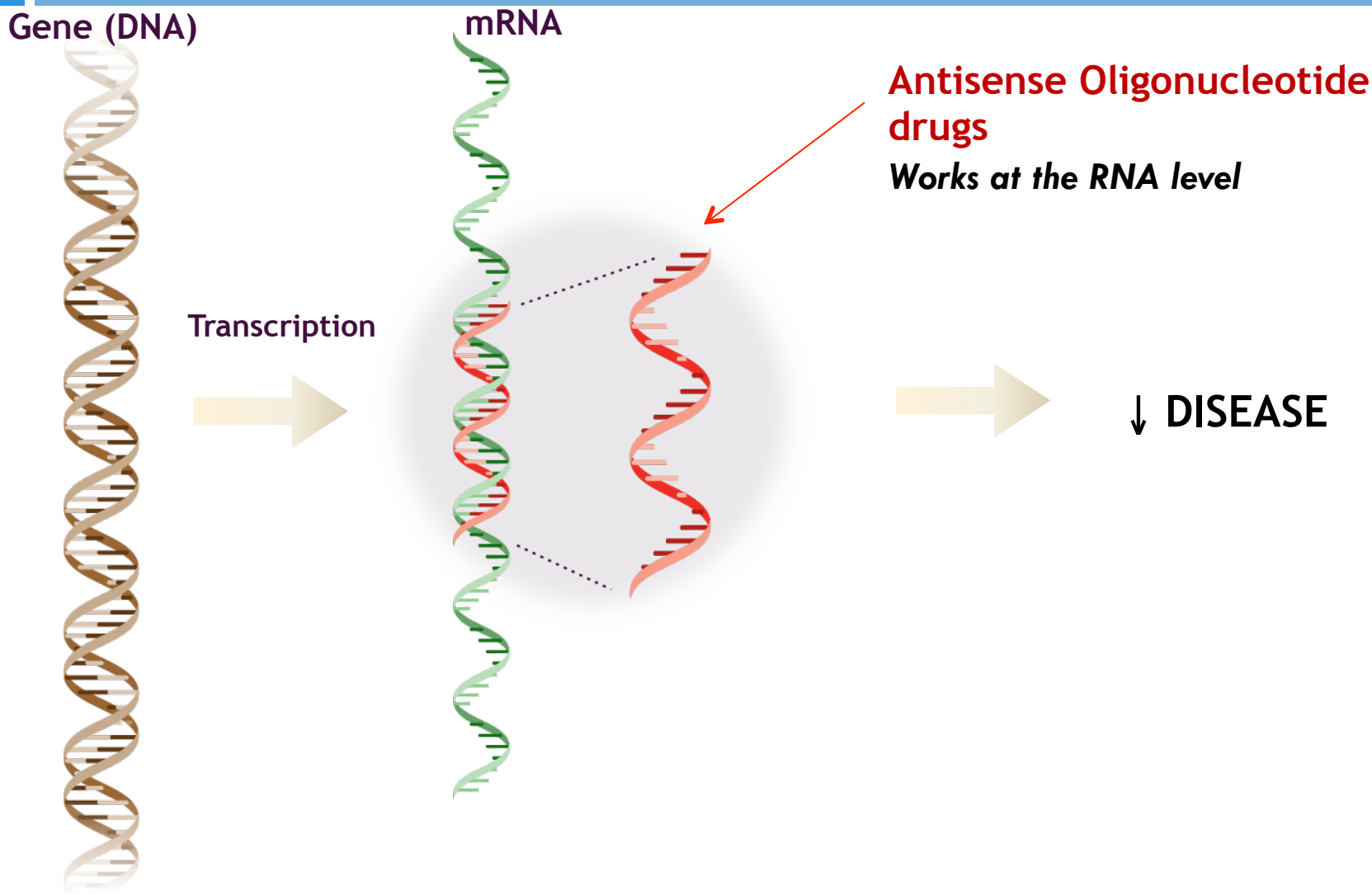


Antisense Drugs Target RNA, Not Proteins



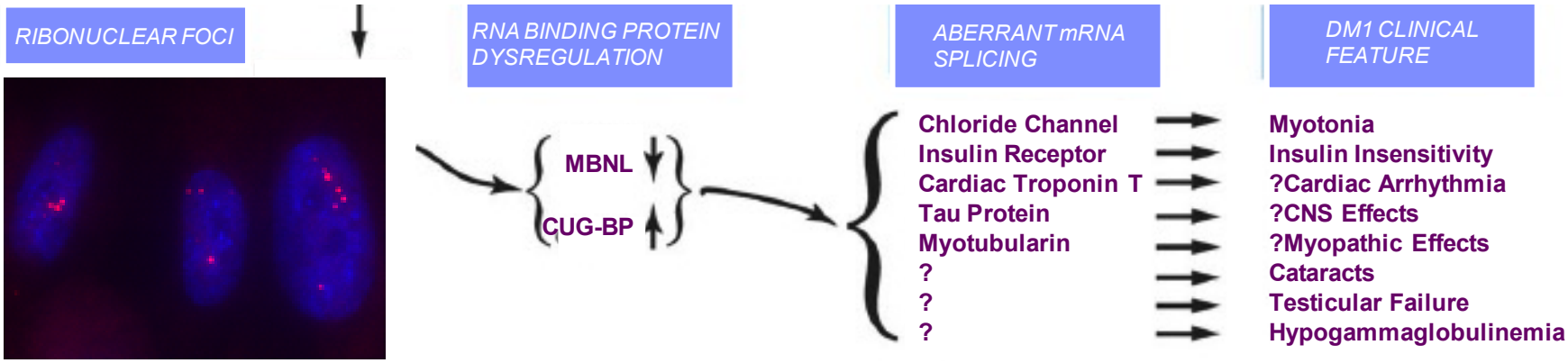
The Distinctive Genetic Mechanism of DM1:

A target suited for antisense oligonucleotide drugs

- The gene responsible for DM1 is DMPK (Dystrophia Myotonica-Protein Kinase) & found on chromosome 19.
- The disease is characterized by long stretches of repeated base pairs (CTG's) in the DNA of the DMPK gene; located at one end of the gene (3'-UTR) .
  - Called a triplet repeat disease because of the repetition of these three DNA base pairs.
  - Toxic RNA clumps in the nucleus and binds to RNA splicing proteins, resulting in altered splicing events
- People with DM1 have expanded repeats which can contain anywhere from 50 to more than 4,000 repeats of the CTG.
  - Healthy people have between 5 and 37 repeats
- Expansion of the section of CTG repeats over each generation results in an earlier-appearing, more severe form of the disease. - This is called "anticipation

Myotonic Dystrophy at the Molecular Level

Toxic RNA, sequestration of MBNL proteins

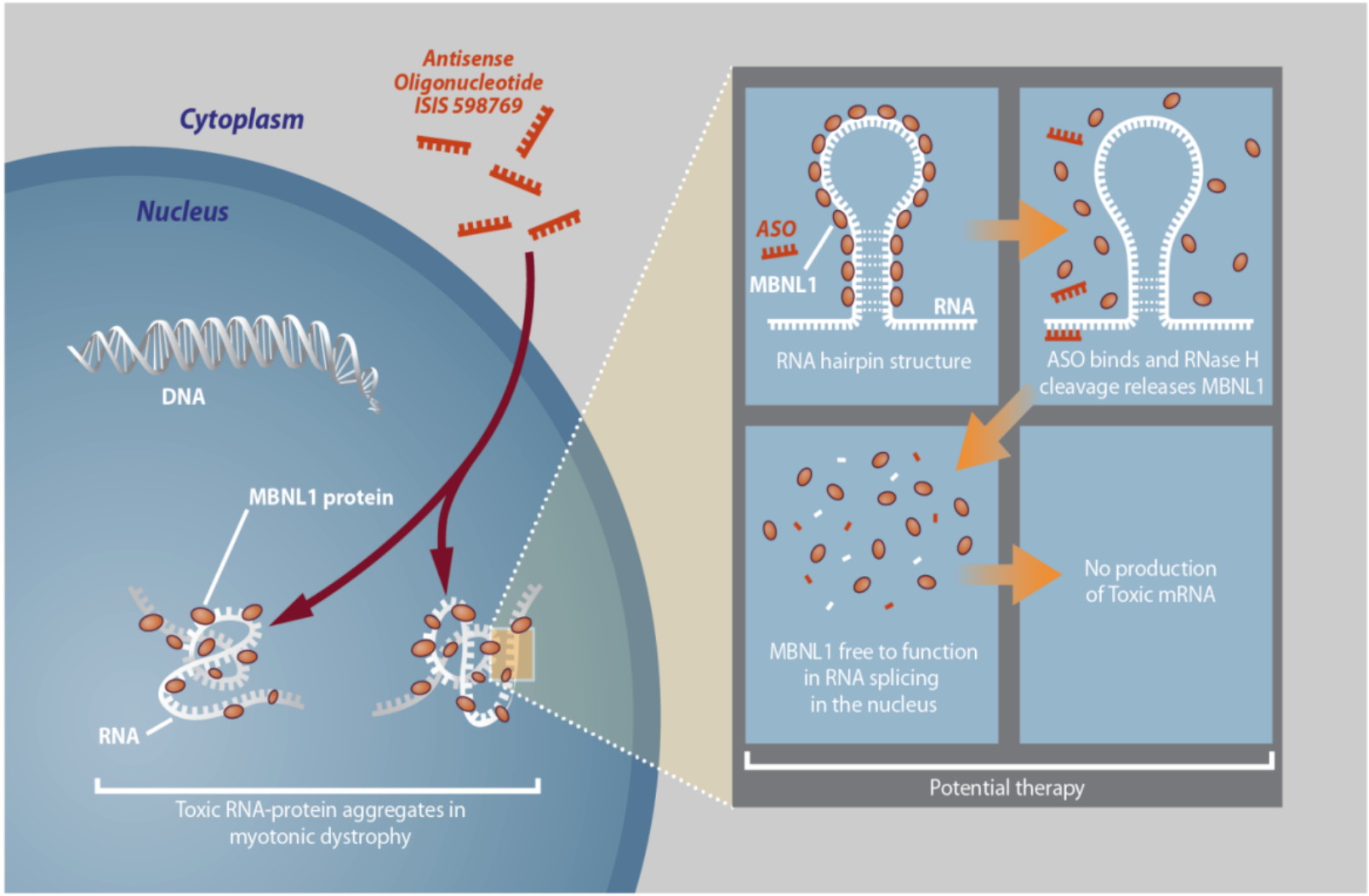


Muscleblind (MBNL), a family of RNA binding proteins, is sequestered by toxic RNA forming clumps in the nucleus

- leads to mis-regulation of splicing events in other genes
- results in disease symptoms

Mechanism of Action of IONIS-DMPK-2.5$_{Rx}$

Degradation of toxic RNA, release of MBNL proteins



Preclinical Work with IONIS-DMPK-2.5$_{Rx}$

- In different mouse models of DM1, we showed
  - Good knock-down of DMPK in different tissues
  - Improvements in various splicing events
  - Improvements in myotonia
  - Long-lasting effects

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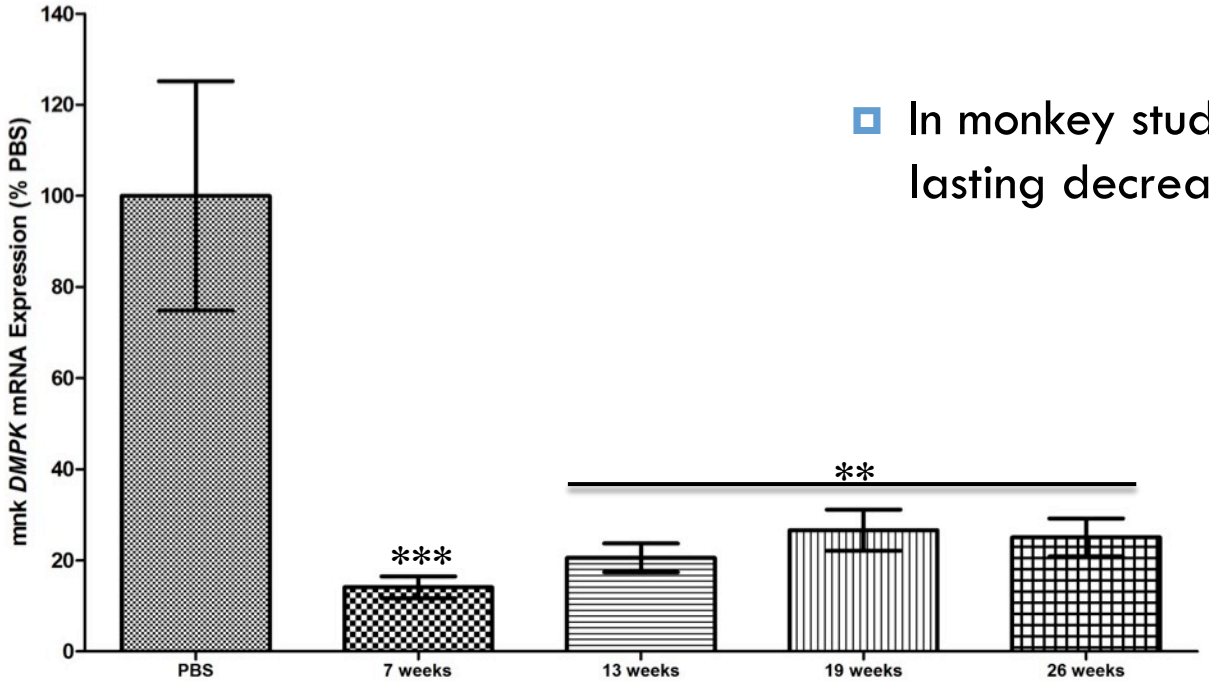


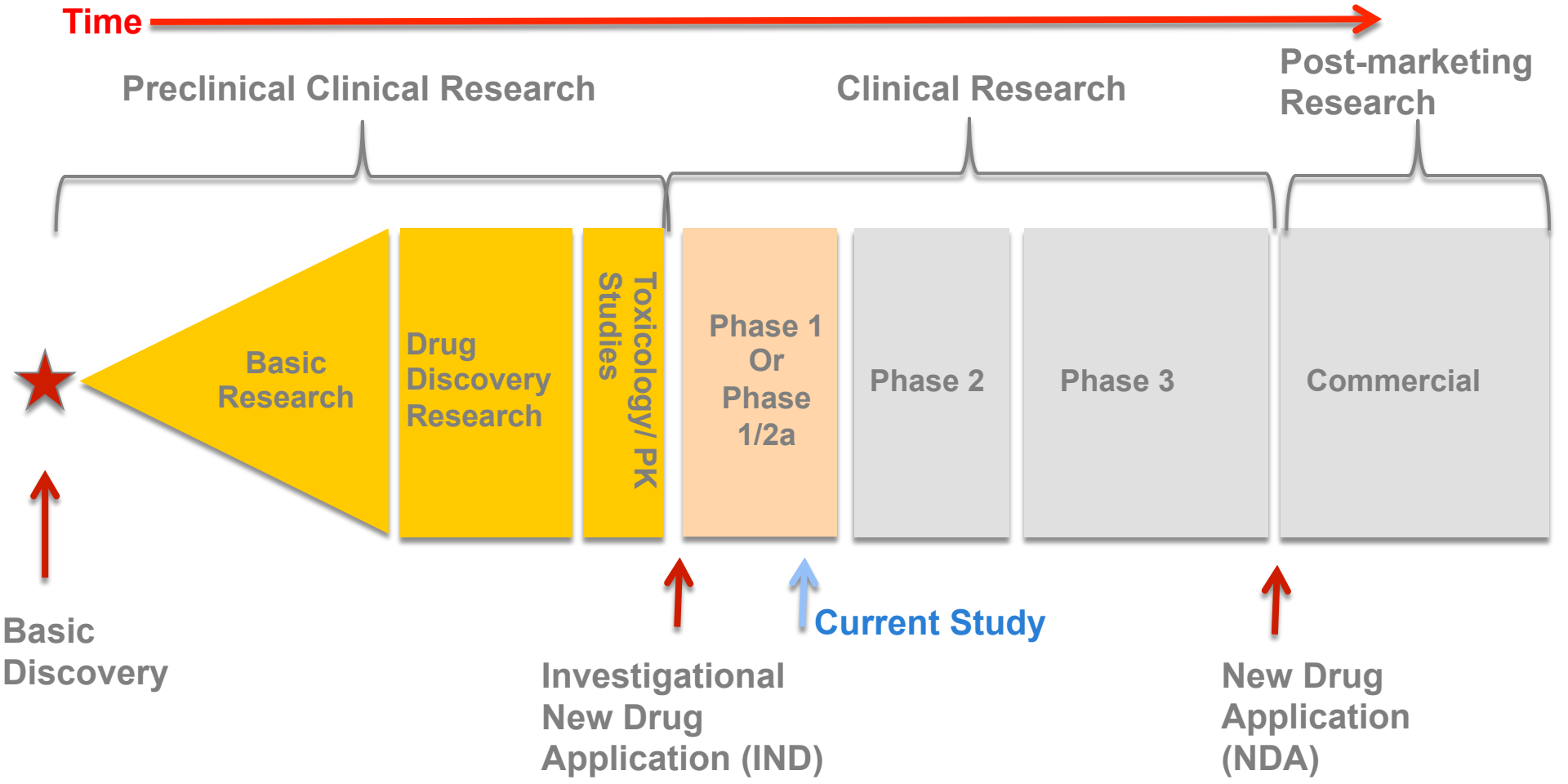
Pandey et al., JPET 2015, Fast Forward Online

- In monkey studies we also showed long-lasting decreases in DMPK mRNA

DMPK mRNA in Tibialis Anterior of monkeys; 13 weeks of dosing at 40 mg/kg

Drug Discovery

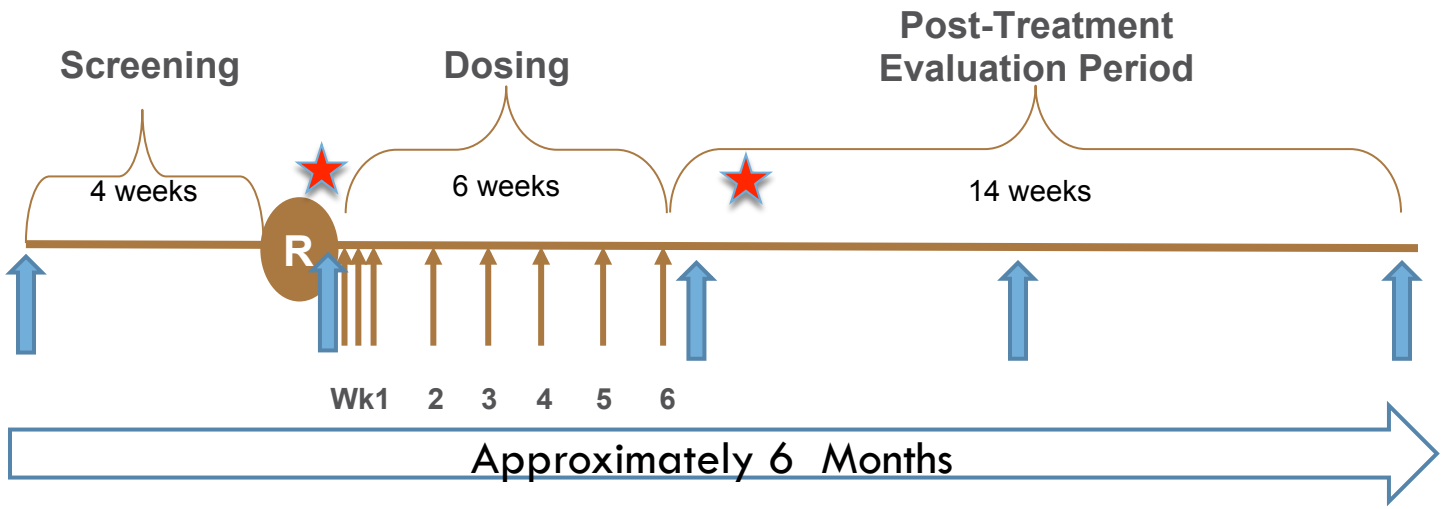
Steps in the Process



IONIS-DMPK-2.5$_{Rx}$ Phase 1/2a Clinical Trial

Study Design

- Phase 1/2a Trial tests the safety of the drug in DM1 patients
  - Multiple-Ascending Dose Study
    - 8 centers in the US
      - University of Rochester, Ohio State, University of Kansas, University of Florida, Kennedy Krieger Institute, University of Utah, Stanford University, Houston Methodist



IONIS-DMPK-2.5$_{Rx}$ Phase 1/2a Clinical Trial

Inclusion/Exclusion Criteria

- Main 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
- Main Exclusion Criteria
  - Implanted device for the treatment of cardiac problems (pacemaker, defibrillator)
  - Clinically abnormal ECG or echocardiogram (central cardiac reader)

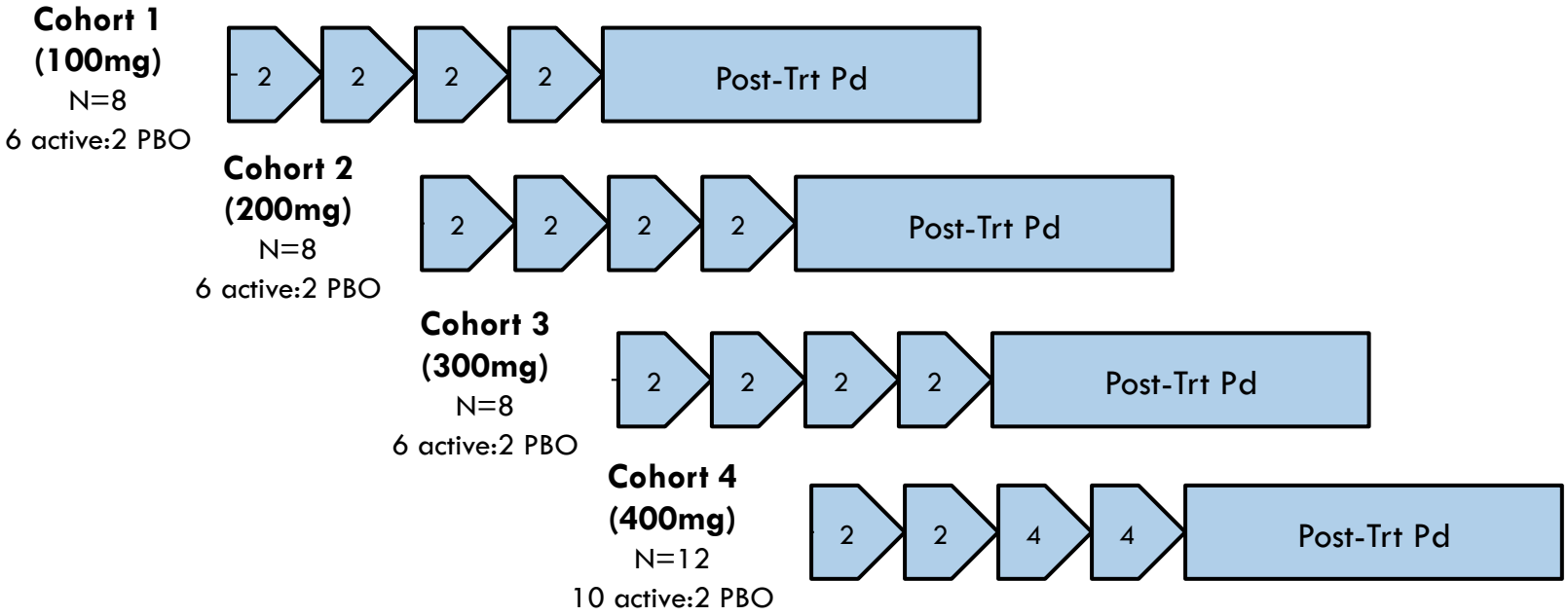
IONIS-DMPK-2.5_{Rx} Phase 1/2a Clinical Trial

Study Objectives of this Safety Trial

- Primary Objective
  - Safety and tolerability
- Secondary Objectives
  - Blood and urine pharmacokinetics
  - Muscle tissue effects
- Exploratory Objectives
  - Biomarkers and clinical outcomes

IONIS-DMPK-2.5$_{Rx}$ Phase 1/2a Clinical Trial

Multiple-Ascending Dose Studies Take Time to Complete



- 4 original cohorts have been enrolled and patients have completed the study

IONIS-DMPK-2.5$_{Rx}$ Phase 1/2a Clinical Trial

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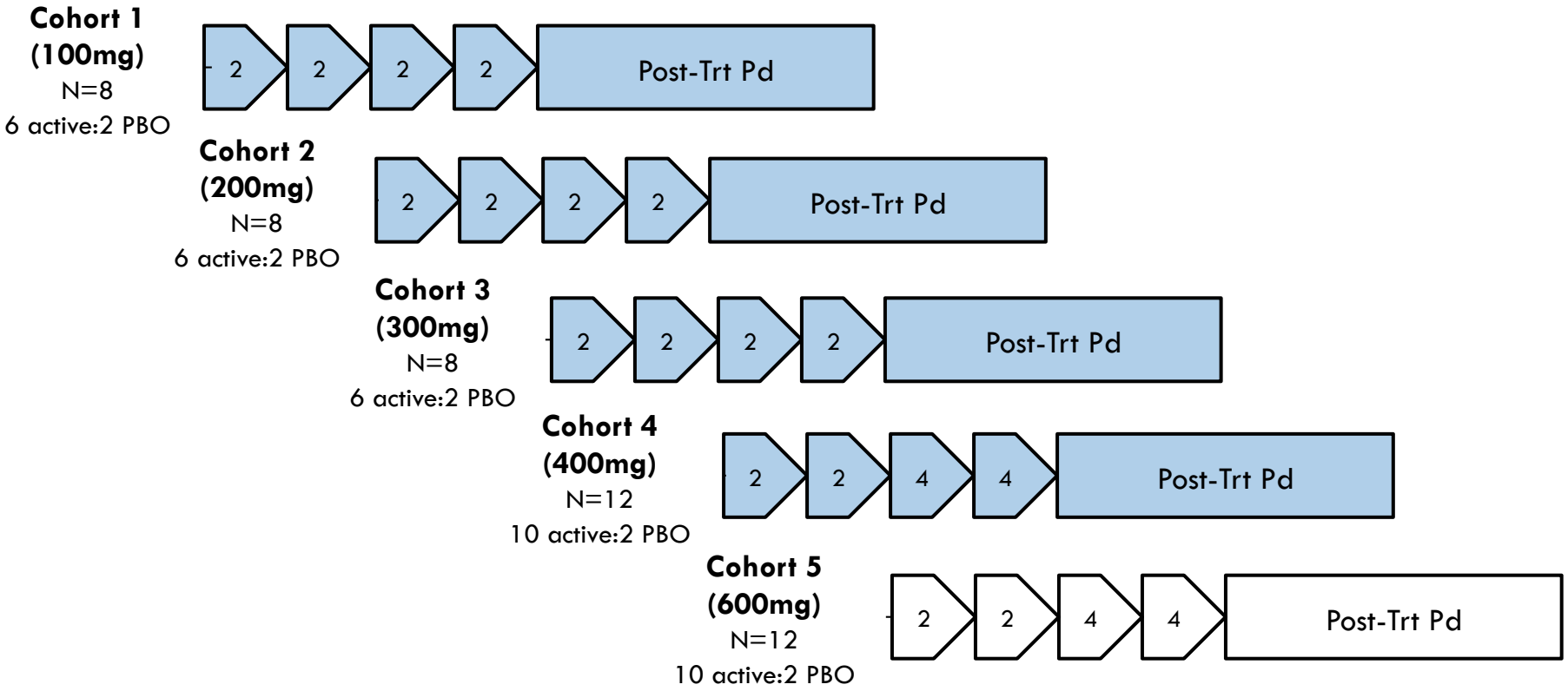


- Based on safety data we added a higher dose cohort at 600 mg
- Currently analyzing the data to determine steps forward – data anticipated end of the year

IONIS-DMPK-2.5$_{Rx}$ Phase 1/2a Clinical Trial

Subject 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 Symptom onset Median (min, Max)	23 (12, 31)	22 (13, 33)	16 (13, 35)	23 (13, 45)	17 (12, 29)	30 (19, 44)
Age at Diagnosis 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)

IONIS-DMPK-2.5_{Rx} Phase 1/2a Clinical Trial

Study Visits

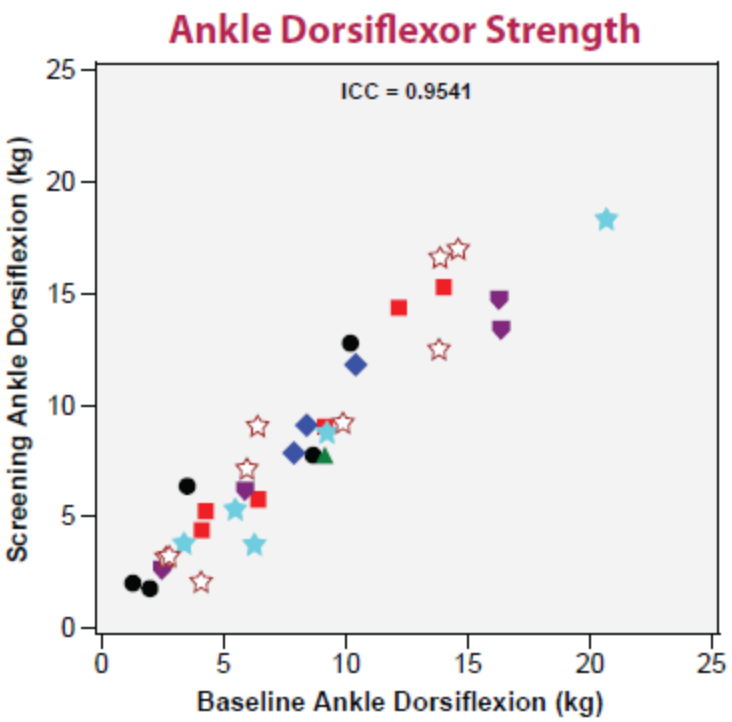
- Study visits are busy for everyone
  - Muscle testing (Manual Muscle Test, Quantitative Muscle Testing)
  - Myotonia testing (electromyography, video hand opening test, isometric handgrip myotonia)
  - Functional tests (6 minute walk test, 30 foot walk/run, climb/ descend 4 steps)
  - Patient-reported outcomes (Myotonic Dystrophy Health Index, SF-36, CGI-I)

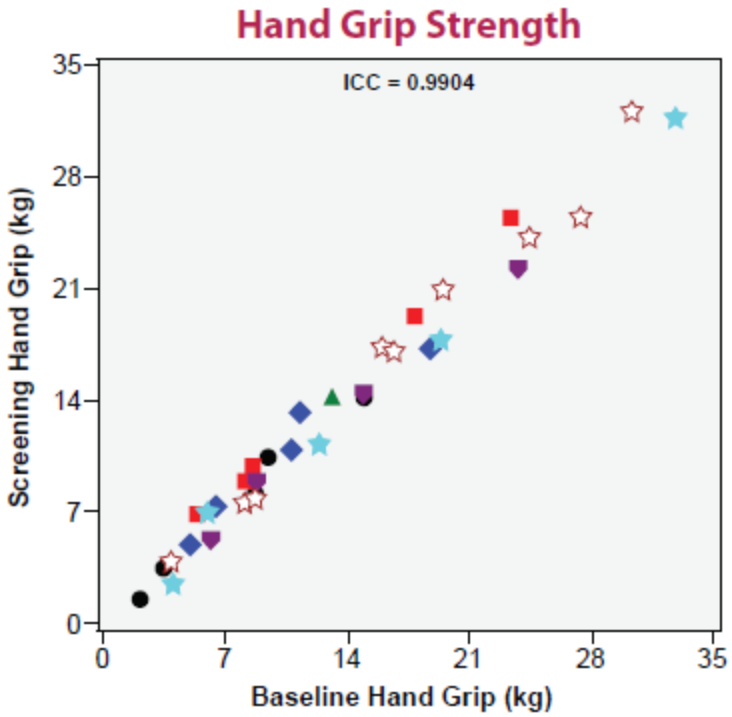
Goal is to standardize the tests across multiple sites, familiarize the patients with the procedures, and determine how reproducible the results are.

IONIS-DMPK-2.5$_{Rx}$ Phase 1/2a Clinical Trial

Standardization of Functional Outcomes

Quantitative Muscle Testing



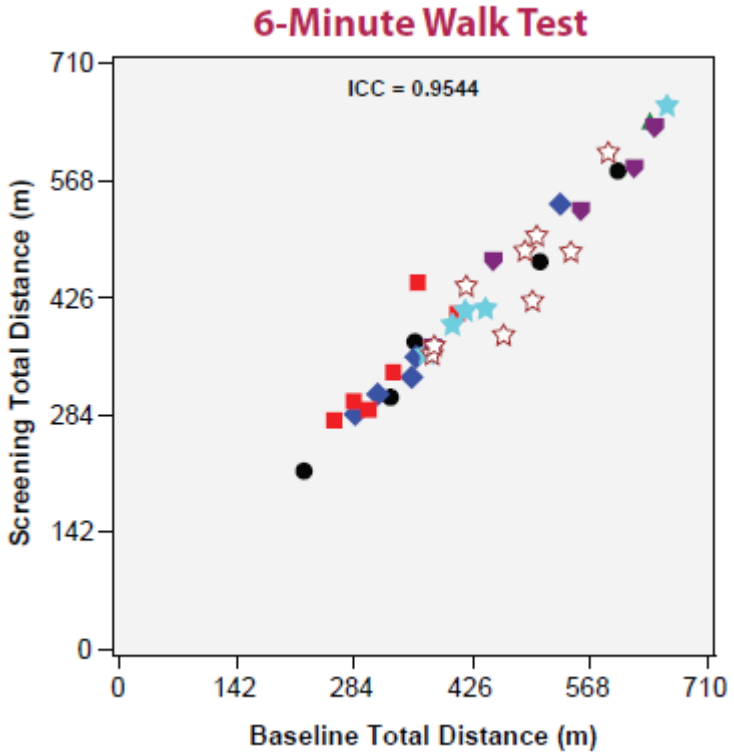


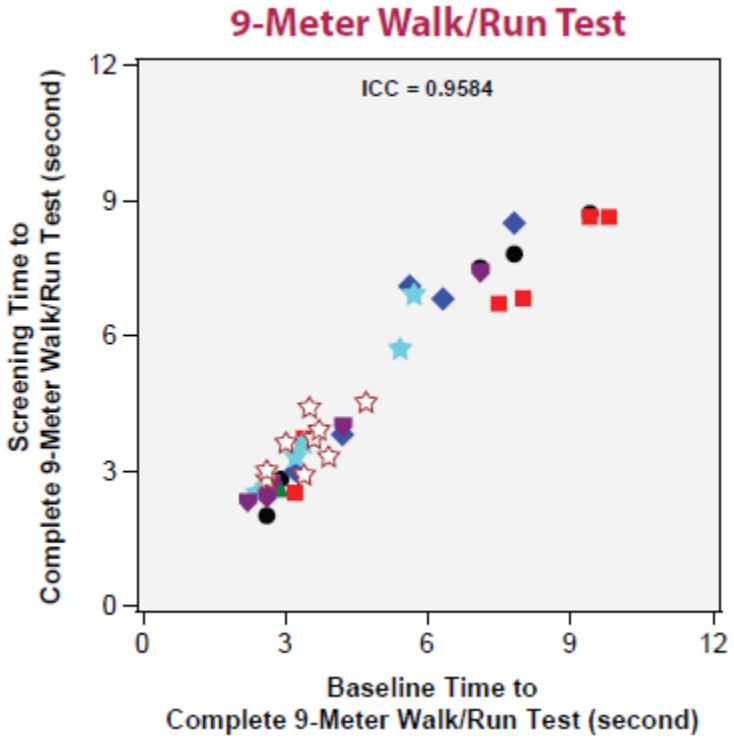
There was good reliability among the sites, and among the raters—there was no evidence for higher variance at different sites.

IONIS-DMPK-2.5$_{Rx}$ Phase 1/2a Clinical Trial

Standardization of Functional Outcomes

Functional Tests





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Summary

- Safety and exploratory data are currently being analyzed—data anticipated end of the year
- Due to the heterogeneity of DM1, individual-based analysis will be needed to better understand the relationship between the effects of the drug, splicing changes, and functional outcomes changes
- This analysis will provide important data for designing future studies in DM1

Clinical Sites and Partners

University of Rochester
Liz Leubbe
Jeanne Deckdebrun
Kathryn Eastwood
Lindsay Baker

University of Utah
Russell Butterfield
Winter Redd
Melissa Dixon
Susan Bonner
Caren Trujillo
Evan Pusillo
Deanna DiBella

Kansas University
Jeffrey Statland
Mamatha Pasnoor
Mazen Dimachkie
Maureen Walsh
Yunxia Wang
April McVey
Kelly Emmons
Gabrielle Rico
Nicole Jenci
Laura Herbelin

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Stanley Iyadurai
William Arnold
Julie Agriesti
Filiz Muharrem
Sharon Chelnick
Colleen Pineda
Wendy Koesters
Matthew Yankie

Stanford
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Neelam Goyal
Ana Carolina Tesi Rocha
Bona Purse
Jennifer Perez
Tina Duong
Richard Gee

Kennedy Krieger
Kathryn Wagner
William Reid Thompson III
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Genila Bibat
Carly Stock

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Phuong Deleyrolle
Desmond Zeng
Aika Konn
Alison Barnard

Houston Methodist
Tetsuo Ashizawa
Erika Simpson
Luis Lay
Della Brown
Wendy Schell
Kayla Butler

MYOTONIC DYSTROPHY FOUNDATION

Partnered with: Biogen

IONIS-DMPK-2.5$_{Rx}$ & Myotonic Dystrophy

Working with the Community

Working to develop a treatment for myotonic dystrophy

Committed to helping create a healthier future