Introduction to Entrada and the Endosomal Escape Vehicle (EEV™) Platform to Enhance Oligonucleotide Delivery in Myotonic Dystrophy Type I

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MEET ENTRADA

Our Commitment

- Developing treatments for people living with devastating diseases for which no or insufficient options currently exist
- Partnering with patient communities to ensure the perspectives of patients and their loved ones inform our research programs

Our Culture

- We are building a company culture where everyone can belong, contribute and grow
- Fostering a workplace environment that embraces diversity, equity and inclusion
- Prioritizing the experiences and perspectives of patients and their loved ones

Our Team

- ~130 employees with an experienced leadership team
- Recognized as a Top Place to Work 2021 by *The Boston Globe*
- Entrada plans to move our science from the lab to the clinic over the next year for two neuromuscular conditions

OUR COMMITMENT TO THE DM1 COMMUNITY

Our partnerships with community leaders and patient advocacy organizations are at the heart of our work to bring innovative therapies to people living with devastating diseases

As we progress our research program from the lab to the clinic, we look forward to learning from the experiences of individuals living with myotonic dystrophy type 1 (DM1) and their families, and to keeping you informed of our progress.

We are proud to partner with the **Myotonic Dystrophy Clinical Research Network (DMCRN)** to study the natural history of myotonic dystrophy Type 1 through END-DM1. Thank you to those who have contributed to this important resource!

PURSUING A TREATMENT OPTION FOR PEOPLE LIVING WITH DM1

- ENTR-701 is a potential approach to treating individuals with DM1
- Our preclinical studies in animal models of DM1 support moving this work into human studies
- We are planning an **Investigational New Drug (IND) application in 2023** for ENTR-701

THE CHALLENGE WITH DRUG DELIVERY

Oligonucleotides offer a therapeutic approach to treat genetic disorders such as DM1. However, they often cannot effectively reach the disease-causing targets inside cells

of all disease-causing targets are located **inside cells.**[1]

Yet, most are still considered **INACCESSIBLE.**

There are two major challenges to delivering a therapy to a target within the cell:

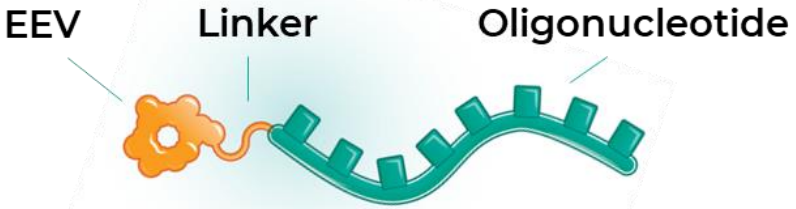
1. Getting the therapy inside the cell.
2. Most importantly, avoiding the cell's natural clearing system.

At Entrada Therapeutics, we believe we have discovered the solution.

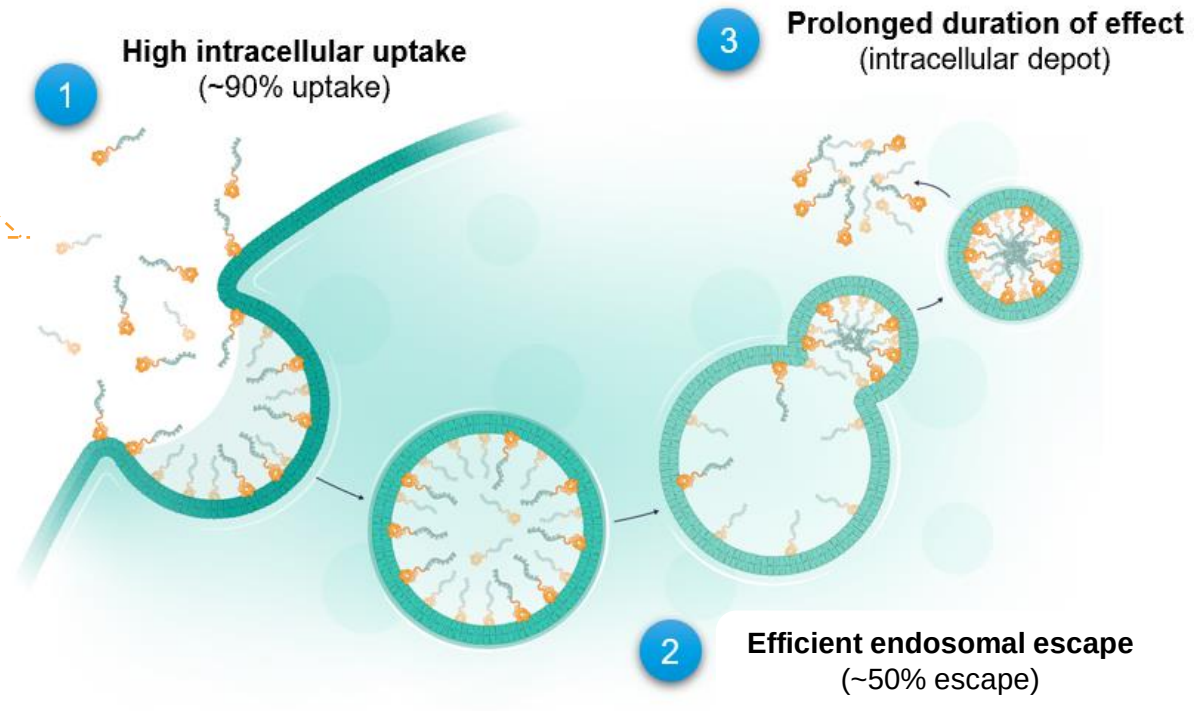
[1]Verdine GL, Walensky LD. *Clin Cancer Res*. 2007;13(24):7264-70.

ENDOSOMAL ESCAPE VEHICLE (EEV™) PLATFORM

We are developing EEV-oligonucleotide conjugates for the treatment of individuals with DM1



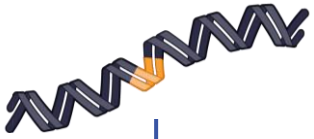
- **Entrada's EEV™ platform** consists of a library of proprietary cyclic peptides with unique chemistry that **enable improved uptake into the cell and escape from the endosome**
- In animal studies, we have observed that our EEV-Oligonucleotide approach has **corrected disease relevant biomarkers in various muscle groups**



Qian, Z. et al. *ACS Chem. Biol.* 2013; Qian, Z. et al. *Biochemistry* 2014; Qian, Z. et al. *Biochemistry* 2016; Sahni, A. et al. *ACS Chem. Biol.* 2020; Pei, D. *Acc. Chem. Res.* 2022.

DNA AND RNA PLAY IMPORTANT ROLES IN THE CREATION OF PROTEINS

Deoxyribonucleic acid (DNA)



TRANSCRIPTION

Messenger ribonucleic acid (mRNA)

TRANSLATION

Protein

Genes or short sections of **DNA** carry genetic instructions

Genes are transcribed to **mRNA,** a single-stranded copy of the genetic instructions

mRNA is then translated into the associated **protein** molecule

Disruptions at **any stage** of this process can interfere with important cellular processes and **cause disease**

DM1 OVERVIEW AND OUR THERAPEUTIC APPROACH

Myotonic Dystrophy Type 1 (DM1) is a multisystemic disease caused by CUG trinucleotide repeats in *DMPK* mRNA that sequester MBNL proteins

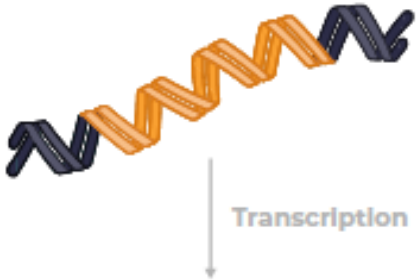
Healthy Individual

***DMPK* gene with few CTG repeats**

Normal transcription and proper downstream MBNL protein activity

Individual with DM1

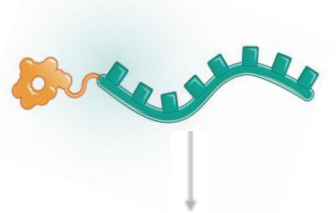
***DMPK* gene with 1000s of CTG repeats**



Mutant mRNA sequesters MBNL proteins and inhibit downstream splicing function

ENTR-701 Approach in DM1

ENTR-701 is a CUG repeat blocking oligonucleotide conjugated to our EEV

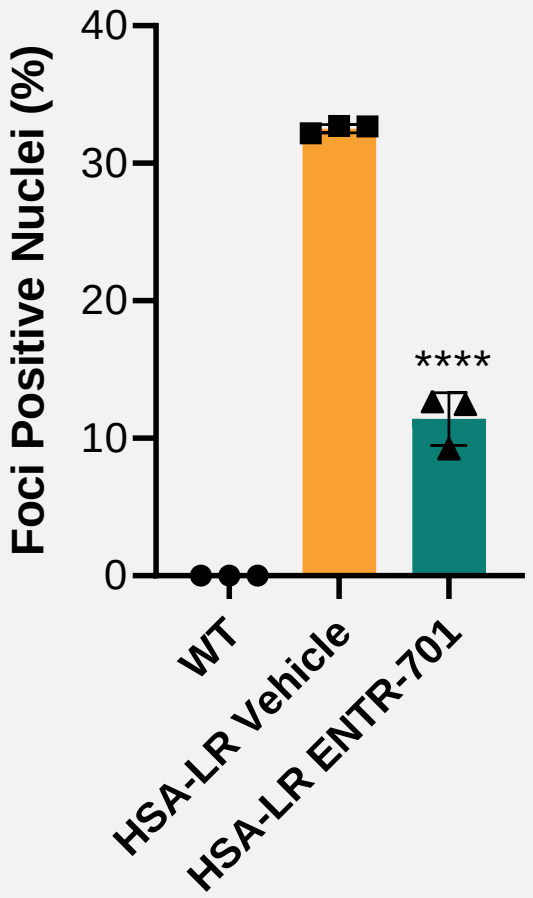


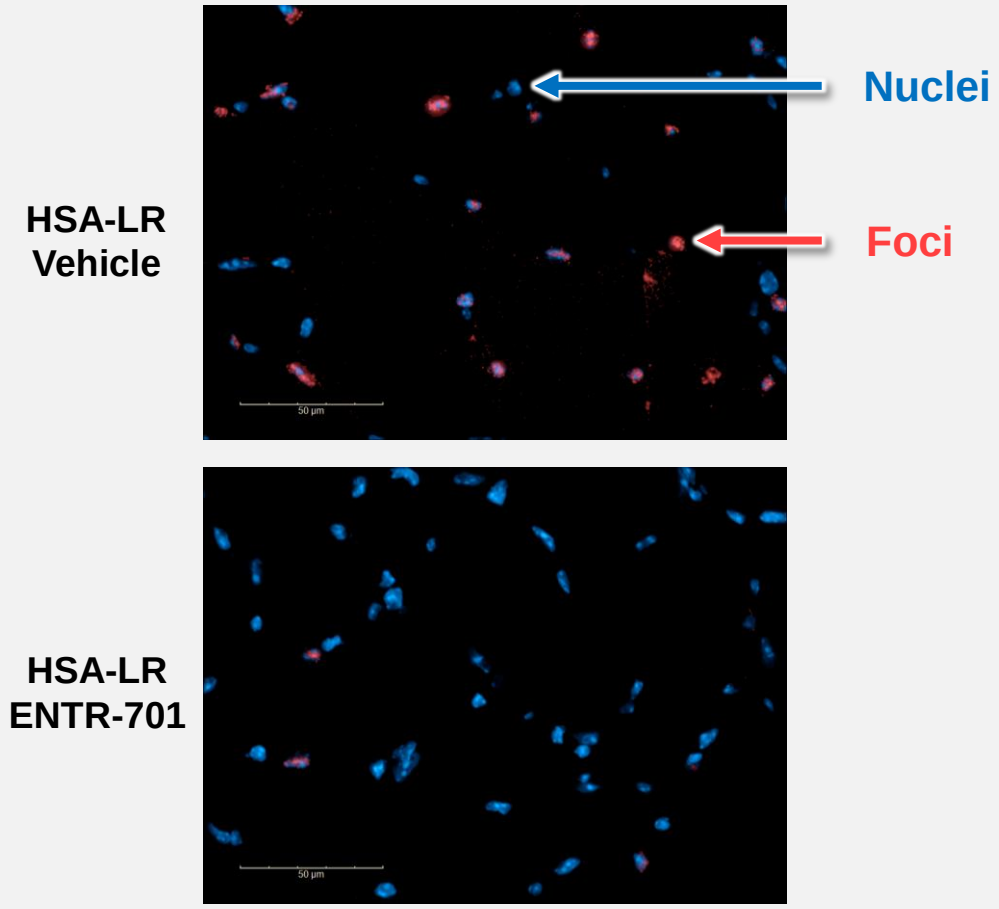
ENTR-701 blocks mutant DMPK mRNA and reduces nuclear foci, restores MBNL function and splicing defects

DMPK, DM1 protein kinase; **MBNL**, muscleblind like splicing regulator; **ENTR-701** is the clinical candidate selected for DM1.

PROMISING EFFICACY DATA OF ENTR-701 IN A DM1 MOUSE MODEL

Nuclear Foci Reduction





Tibialis anterior section

Our data in DM1 mouse model showed:

- Dose-dependent reduction of nuclear foci *(left)*
- **Reduced CUG-repeat containing DMPK mRNA**
- **Correction of aberrant splicing**

Visit us at the poster session to learn more!

ENTR-701 is the clinical candidate selected for DM1, composed of CUG-repeat blocking PMO conjugated to EEV; ***p<0.001, ****p<0.0001, shown as mean ± standard deviation.

MYOTONIA CORRECTION IN A DM1 MOUSE MODEL

A single dose of ENTR-701 ameliorated pinch-induced myotonia for at least 8 weeks

HSA-LR Mouse: **Non-treated**

HSA-LR Mouse: **ENTR-701 Treated**

ENTR-701 is the clinical candidate selected for DM1, composed of CUG-repeat blocking PMO conjugated to EEV.

OUR PRECLINICAL DATA SUPPORT ADVANCEMENT OF ENTR-701

Single Dose of ENTR-701 Demonstrates Prolonged Effect for >8 Weeks

Substantial reduction of nuclear foci, CUG-repeat-specific mRNA reductions and robust splice correction, which **may indicate restoration of MBNL protein function**

Myotonia correction in a DM1 mouse model following a single dose of ENTR-701

We plan to submit an Investigational New Drug (IND) application in 2023

Phase 1/2 ascending dose studies of ENTR-701 will assess safety, tolerability and pharmacokinetics, mRNA knockdown and spliceopathy in adults living with DM1*

*Following regulatory feedback and potential IND clearance.

THANK YOU FROM THE WHOLE ENTRADA TEAM!

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For questions, contact:
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