DESIGN THERAPEUTICS

Designing a novel class of genomic medicines

FOR GENETIC DISORDERS

Q1 2023

Disclaimers

Forward-Looking Statements

This presentation contains forward-looking statements. All statements other than statements of historical facts contained in this presentation are "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995. These statements include, but are not limited to projections from early-stage programs, preclinical data and early-stage clinical data; the therapeutic potential of DT-216; expectations for reporting data and the timing thereof; the potential benefits of restoring FXN in FA patients; expected initial data report for the MAD Phase 1 clinical trial for DT-216 in patients with FA and the timing thereof; the expected initiation of Design's Phase 2 clinical trial for DT-216 in patients with FA and the timing thereof; DT-216's potential to be a promising candidate for future treatment of FA patients; Design's anticipated timeline to submit an IND and begin clinical development of DT-168 for the treatment of FECD; Design's FECD GeneTAC™ program and its potential therapeutic benefits and advantages; Design's anticipated timeline to begin clinical development of its GeneTAC™ program for the treatment of DM1 and its potential therapeutic benefits and advantages; Design's ability to deliver on our short- and long-term goals; Design's ability to design and tailor GeneTAC™ molecules from our novel platform to address diverse monogenic diseases; anticipated steady cadence of new GeneTAC™ candidates and clinical trials; and the capabilities and potential advantages of Design's pipeline of GeneTAC™ molecules. Because such statements are subject to risks and uncertainties, actual results may differ materially from those expressed or implied by such forward-looking statements. Words such as "believes," "designed to," "anticipates," "planned," "expects," "estimate," "intends," "will," "potential" and similar expressions are intended to identify forward-looking statements. These forward-looking statements are based upon Design's current expectations and involve assumptions that may never materialize or may prove to be incorrect. Actual results and the timing of events could differ materially from those anticipated in such forward-looking statements as a result of various risks and uncertainties, which include, without limitation, risks associated with conducting a clinical trial and patient enrollment, which is affected by many factors, and any difficulties or delays encountered with such clinical trial or patient enrollment may delay or otherwise adversely affect such clinical trial; the process of discovering and developing therapies that are safe and effective for use as human therapeutics and operating as a development stage company; Design's ability to develop, initiate or complete preclinical studies and clinical trials for its product candidates; the risk that promising early research or clinical trials do not demonstrate safety and/or efficacy in later preclinical studies or clinical trials; changes in Design's plans to develop its product candidates; uncertainties associated with performing clinical trials, regulatory filings and applications; risks associated with reliance on third parties to successfully conduct clinical trials and preclinical studies; Design's ability to raise any additional funding it will need to continue to pursue its business and product development plans; regulatory developments in the United States and foreign countries; Design's reliance on key third parties, including contract manufacturers and contract research organizations; Design's ability to obtain and maintain intellectual property protection for its product candidates; Design's ability to recruit and retain key scientific or management personnel; competition in the industry in which Design operates, which may result in others discovering, developing or commercializing competitive products before or more successfully than Design; and market conditions. For a more detailed discussion of these and other factors, please refer to Design's filings with the Securities and Exchange Commission ("SEC"), including under the "Risk Factors" heading of Design's Quarterly Report on Form 10-Q for the quarter ended September 30, 2022, as filed with the SEC on November 3, 2022. You are cautioned not to place undue reliance on these forward-looking statements, which speak only as of the date hereof. All forward-looking statements are qualified in their entirety by this cautionary statement and Design undertakes no obligation to revise or update this presentation to reflect events or circumstances after the date hereof, except as required by law.

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INTRODUCTION

GeneTAC™ Molecules:

We are designing and developing small-molecule gene targeted chimera therapeutic candidates capable of dialing up or dialing down expression of individual genes to enable treatment of the underlying cause of inherited nucleotide repeat expansion diseases

Led by expert team with proven track records of success

- Leadership with demonstrated success in drug discovery, development and product launches
- Proprietary GeneTAC™ platform represents opportunity for a new class of treatments
- Robust pipeline of novel assets with first-in-class and/or best-in-class potential
- Efficient operational structure with extensive capabilities across discovery, development, clinical translation, regulatory, manufacturing and business operations
- Well-capitalized, with ~$344M in cash and equivalents at the end of the third quarter 2022 to fund operations and initial clinical trials

João Siffert, M.D.
President and CEO

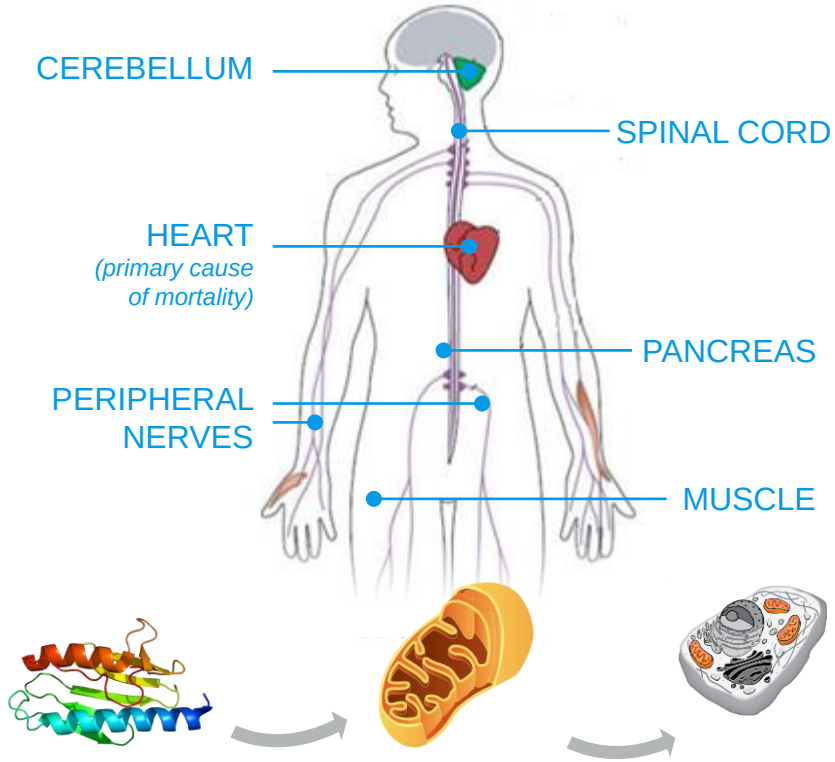
Sean Jeffries, Ph.D.
Chief Operating Officer

Pratik Shah, Ph.D.
Executive Chair

Three clinical GeneTAC™ programs expected in the next three years

DEVELOPMENT PROGRAMS	NEXT ANTICIPATED MILESTONE	EXPECTED TIMING
Friedreich ataxia (FA; GAA) – DT-216	Data from MAD trial	Mid-2023
	Initiate phase 2	2H 2023
Fuchs endothelial corneal dystrophy (FECD; CTG) – DT-168	IND	2H 2023
Myotonic dystrophy type 1 (DM1; CTG)	IND	2024
RESEARCH PROGRAMS	**ESTIMATED US PREVALENCE**	
Fragile X syndrome (FXS; CGG)	~80,000	
Huntington disease (HD; CAG)	~40,000	
C9orf72-amyotrophic lateral sclerosis/ frontotemporal dementia (ALS/FTD; GGGGCC)	~7,000	
Other CTG-expansion diseases	~25,000	

Friedreich ataxia: Debilitating disease with no treatment options today



Frataxin localizes to mitochondria
FXN deficiency leads to mitochondrial dysfunction, including ROS production, ferroptosis, depletion of endogenous antioxidant, deficient mitochondrial biogenesis, deficient mitochondrial respiration

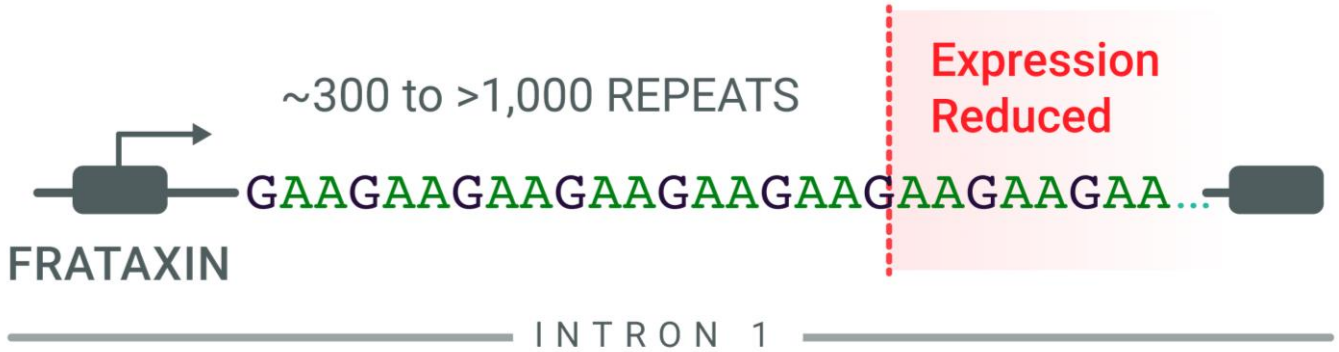
- Multi-system, inherited disease caused by GAA-repeat expansion in the frataxin (FXN) gene
- FXN gene mutation leads to low FXN protein levels
- FXN deficiency causes all disease manifestations reflecting mitochondrial and cellular dysfunction downstream of FXN loss
- FXN levels correlate with FA onset, rate of progression, and neurological function
- FXN restoration reverses FA phenotype in mice and in FA patient cells
- >5,000 patients with FA in US

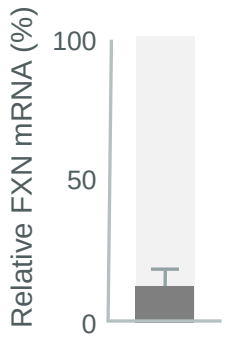
Our treatment goal: FXN restoration in affected organs

Distribute to all affected cells; avoid over/under expression

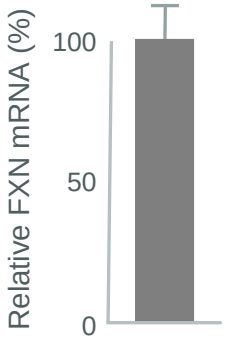
Reduction of Frataxin (FXN) can be measured in FA patient cells

FA PATIENT (two expanded copies)



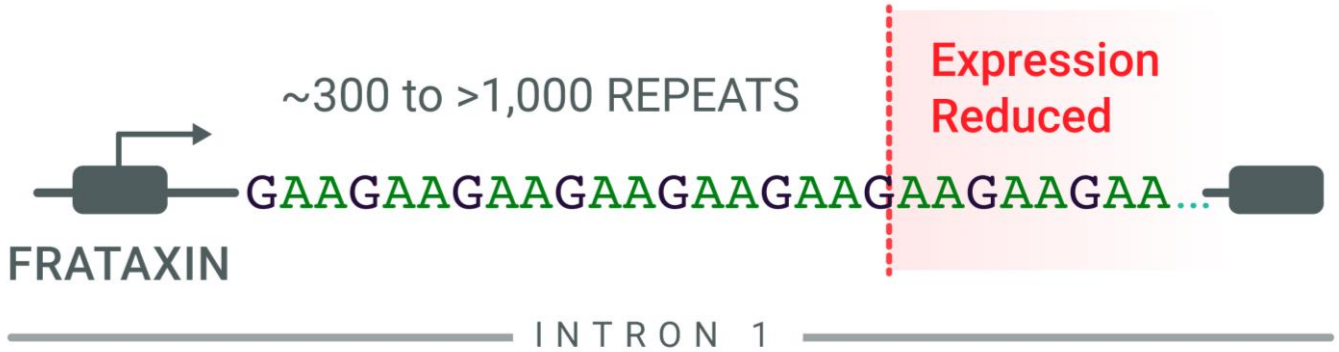


HEALTHY INDIVIDUAL (two normal copies)

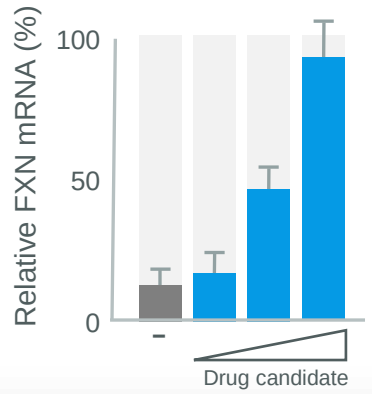


FA GeneTAC™ molecules normalized FXN levels in FA patient cells but did not alter FXN levels in cells from a healthy individual

FA PATIENT (two expanded copies)

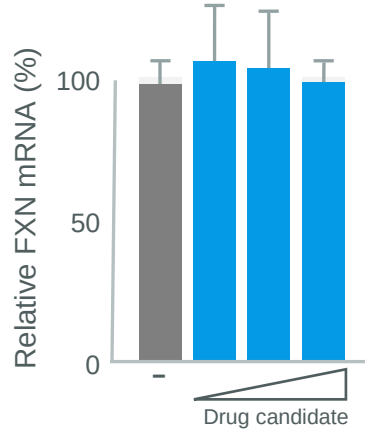


GeneTAC™ molecules normalized levels[1]



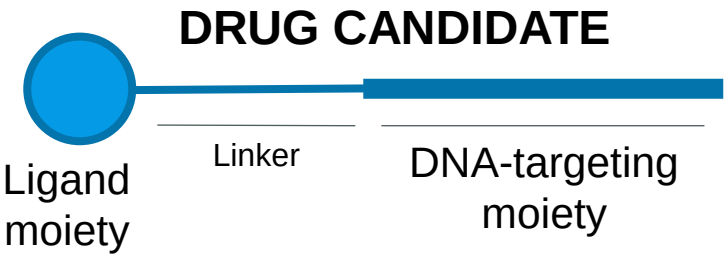
HEALTHY INDIVIDUAL (two normal copies)

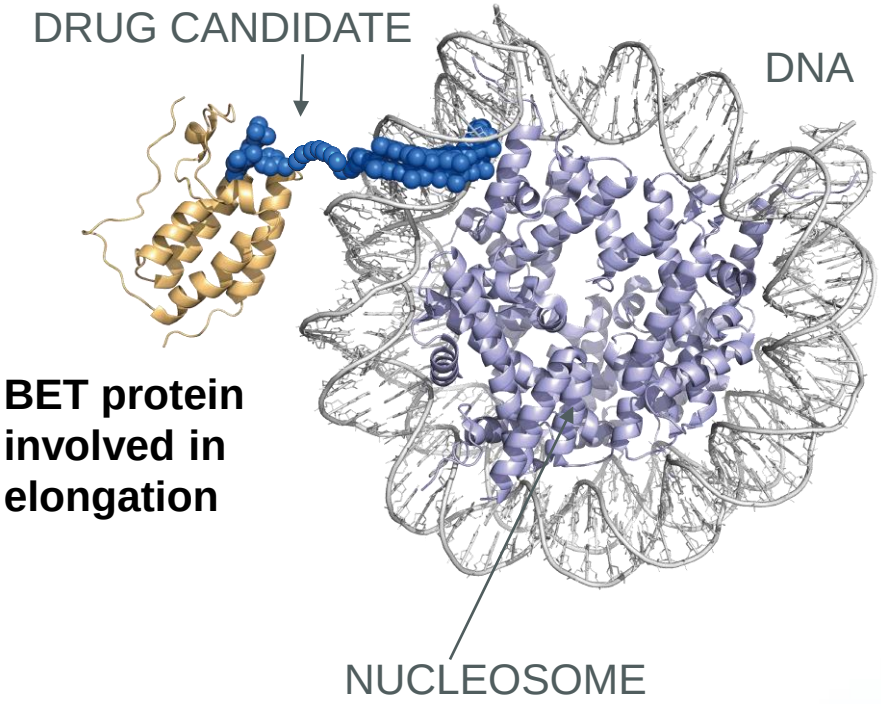
FXN levels unaltered in healthy cells[1]



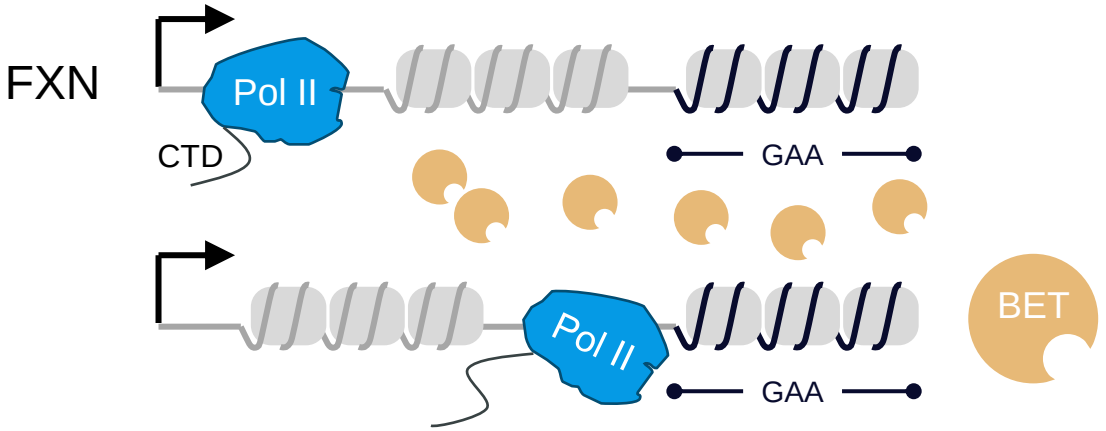
1. Graph x-axis represents increasing levels of cellular exposure to FA GeneTAC™ molecules

Mode of action of FA GeneTAC™ molecules

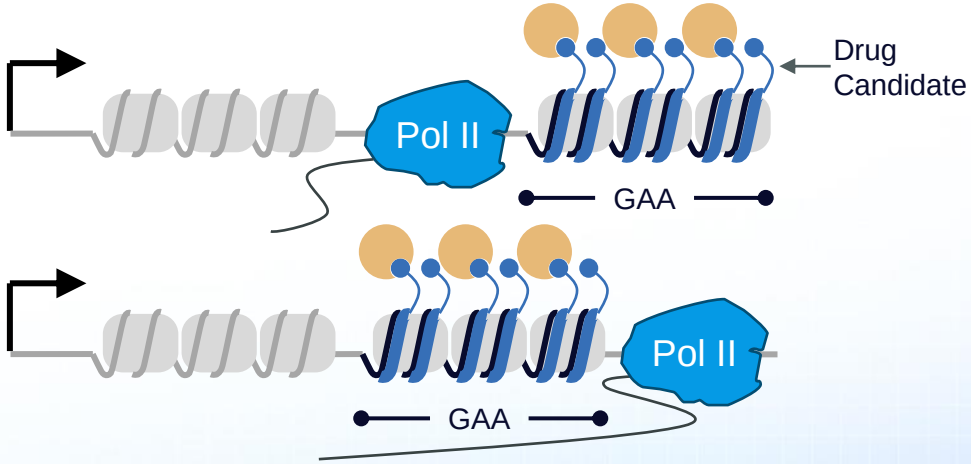




BET protein involved in elongation



Long stretches of GAA repeats cause RNA polymerase to fall off

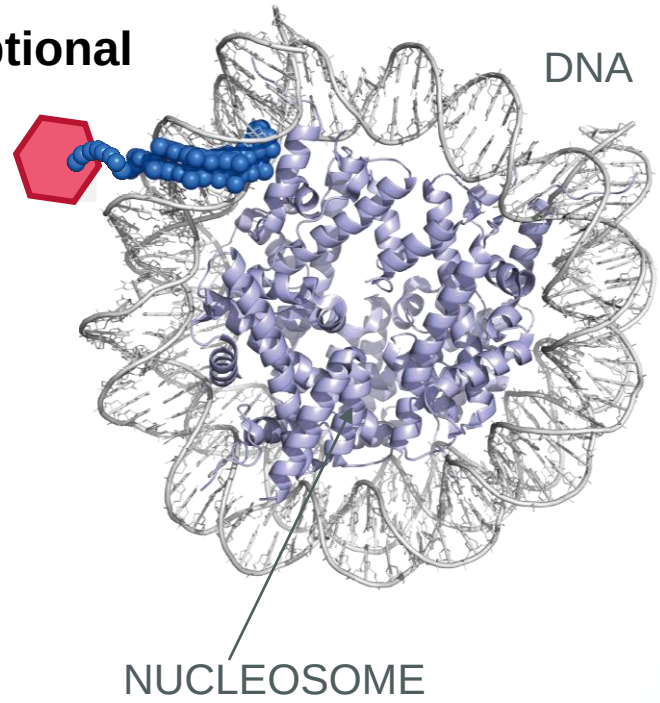


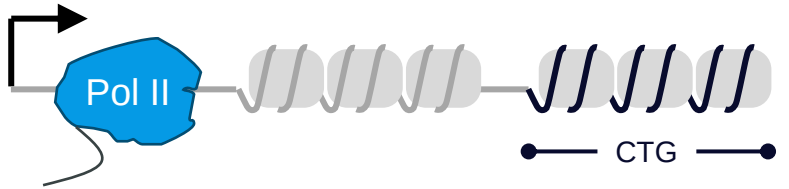
Our molecules are designed to facilitate transcription through the locus

Mode of action of GeneTAC™ molecules for dialing down expression (e.g. DM1 or FECD)

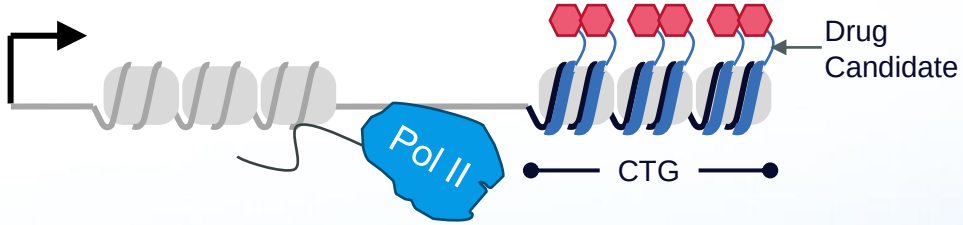
DRUG CANDIDATE

Transcriptional blocker



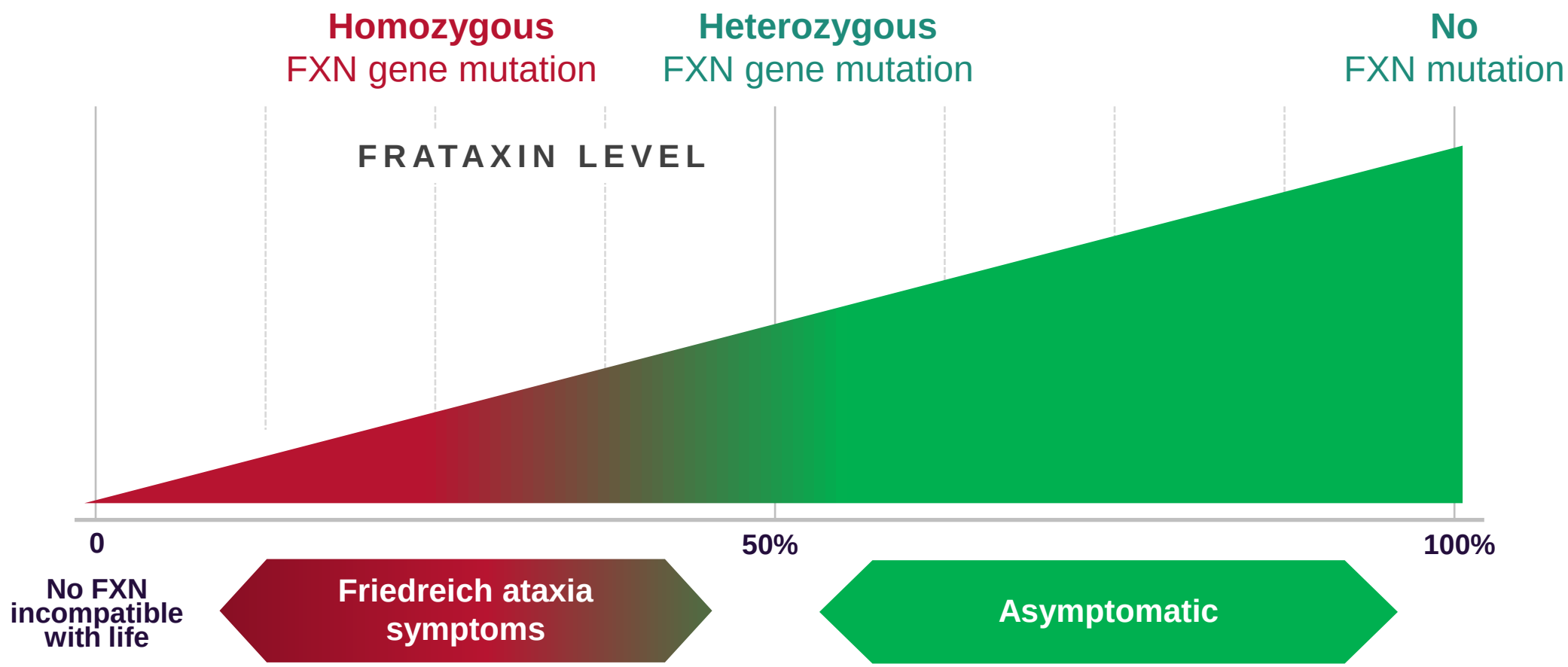


RNA polymerase is able to fully transcribe the toxic mRNA



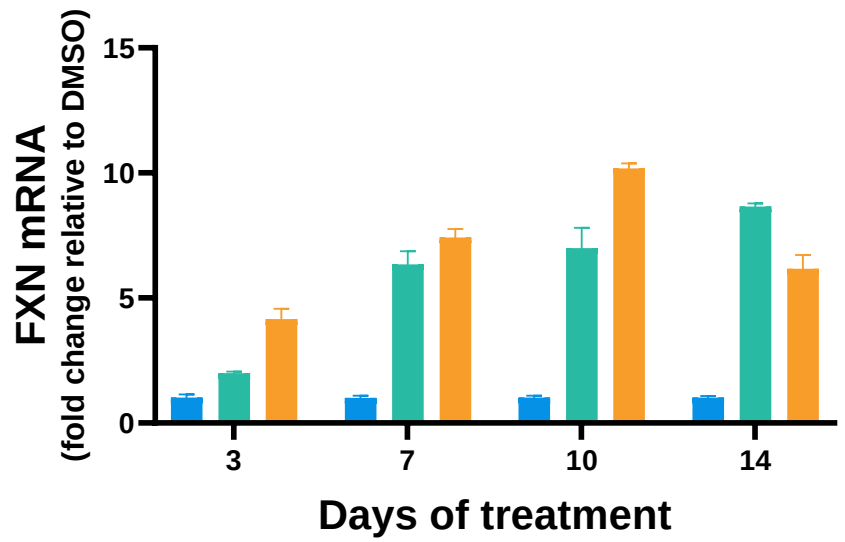
Our molecules are designed to block transcription specifically through the mutant locus

Frataxin Levels and Friedreich Ataxia Phenotype

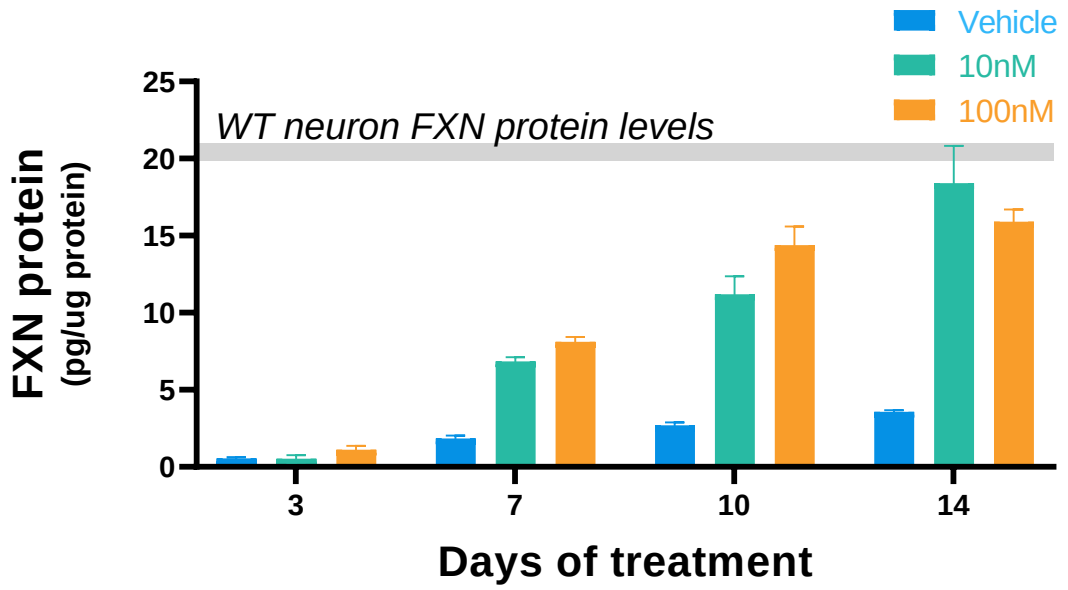


Low concentrations of DT-216 molecule restored endogenous FXN levels in FA patient iPS-neurons

FXN mRNA



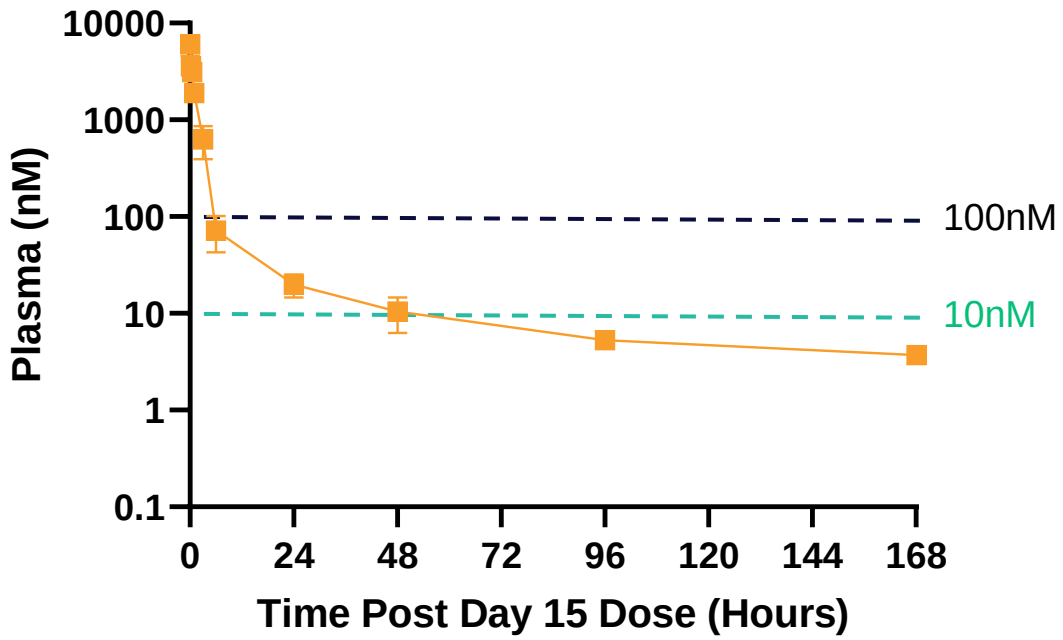
FXN Protein

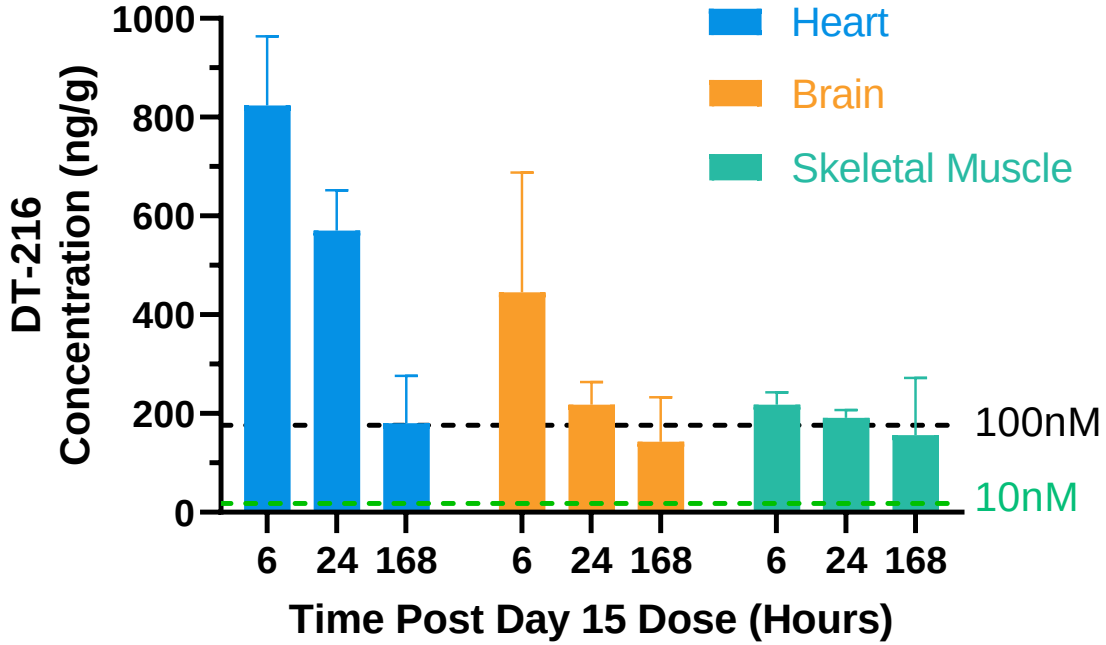


Note: Bars represent standard error of the mean. Cells treated with DT-216 FA GeneTAC™ molecule.

DT-216 levels in tissues remain higher than levels in plasma for multiple days in non-human primates

NHP





Note: Bars represent standard error of the mean. Animals dosed with DT-216 FA GeneTAC™ molecule at a dose that allometrically scales to within the range of doses tested in the Phase 1 human clinical study. Samples for both PK and distribution taken after 3 weekly doses on days 1, 8 and 15 from the same study. Brain is average of multiple areas of the brain: cerebrum, cerebellum and brainstem. EC90 for DT-216 is ~10nM.

DT-216 shown to be generally well-tolerated in Phase 1 Single Ascending Dose (SAD) study in FA patients

Study design

Primary and Secondary study objectives:
Evaluate safety and tolerability, and pharmacokinetics (PK) of DT-216 in FA patients

Design

- 6 Dose Cohorts (N=39)
  - 5-10 patients per cohort (adaptive sample management)
  - Randomized DT-216:Placebo (at least 2 PBO per cohort)
- DT-216 dosed IV as single bolus or split administration
- Safety data available by treatment assignment for cohorts 1-5[1]

Patient Population

- FA patients with homozygous GAA repeat expansions
- Age, mean (SD): 32y (9.8)
- Functional Staging of Ataxia, mean (SD): 4.0 (1.0)
- Without clinically significant concomitant medical conditions

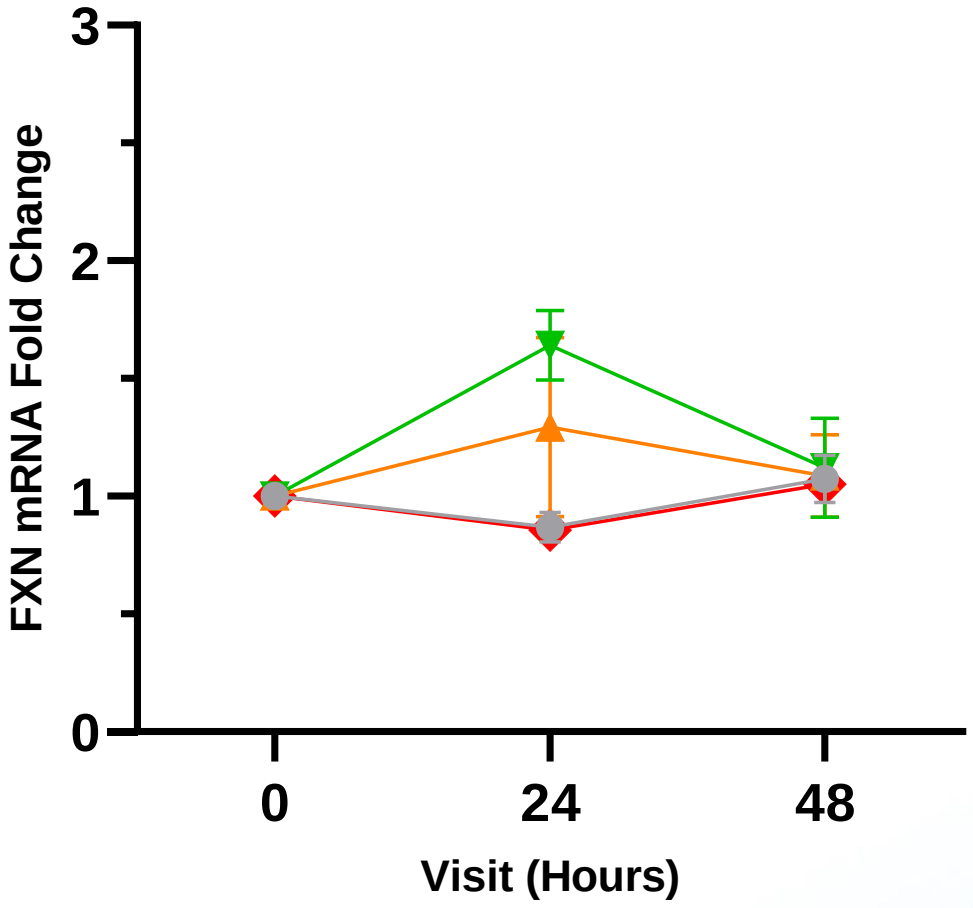
Safety outcome

	DT-216	Placebo
Treatment-emergent adverse event (AE)	16 (73%)	8 (73%)
Serious AEs	0	1[2]
AE leading to study discontinuation	0	0

- Most AEs were mild and transient, including 3 injection-site reactions that were local and self-limited
- No clinically significant changes in vital signs, physical exams, electrocardiogram, clinical safety laboratories (including liver function tests and serum creatinine)

1. The 600 mg cohort (N=6) remains blinded to treatment assignment until the last patient completes the 30-day treatment follow-up period, per study protocol
2. Venous thromboembolism (deep venous thrombosis with pulmonary embolism) in wheelchair-bound patient after air travel

Lower doses of DT-216 start to show FXN mRNA response in peripheral blood mononuclear cells (PBMCs)



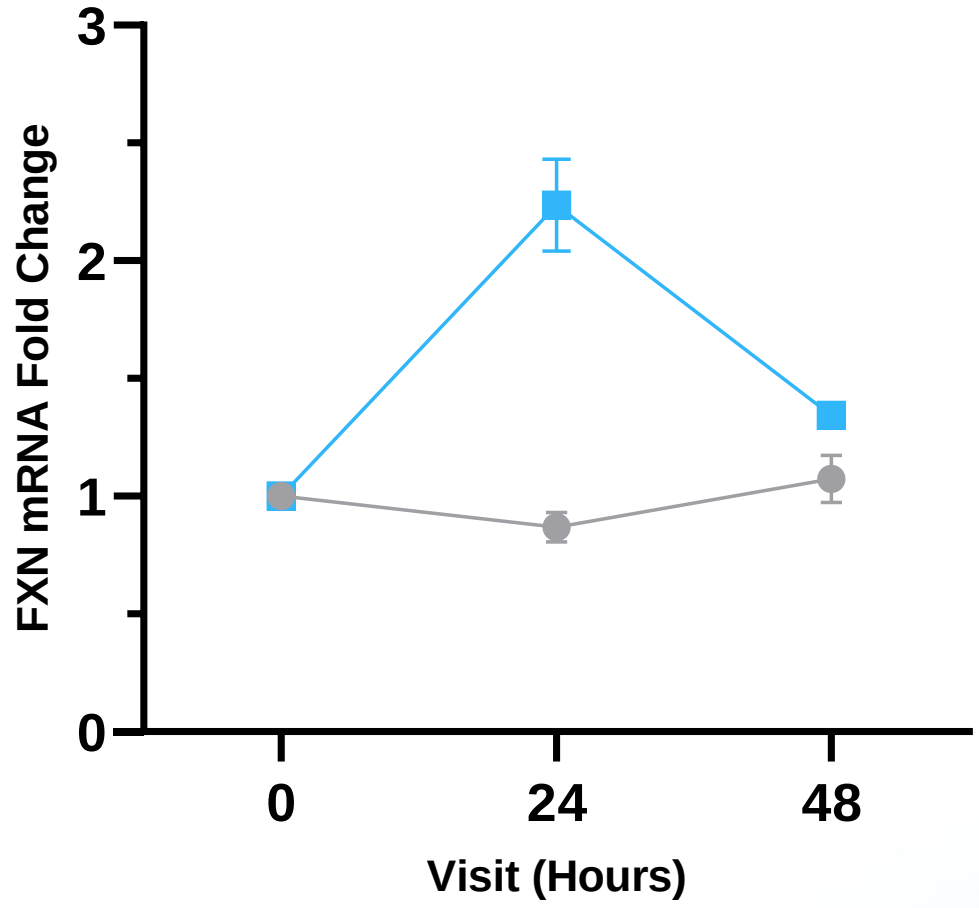
Pooled Placebo (N=11)
DT-216 25 mg (N=3)
DT-216 50 mg (N=4)
DT-216 100 mg (N=4)

NS
NS
*

* $p < 0.01$
NS = not significant

Note: Post-splice FXN mRNA measured using intron spanning RT-qPCR to detect post-spliced mature mRNA. Exploratory statistical analyses were conducted using an ANCOVA model which includes a main effect for the treatment group and the baseline delta Ct as a covariate and compares each active treatment group against the pooled placebo group. The reported p values are based on parametric statistical analysis methods. Non-parametric analyses gave similar results. Bars represent standard error of the mean.

Sustained exposure from 400 mg single split administration dose shows a doubling of FXN mRNA in PBMCs



Pooled Placebo (N=11)

DT-216 400 mg Split Administration (N=3)

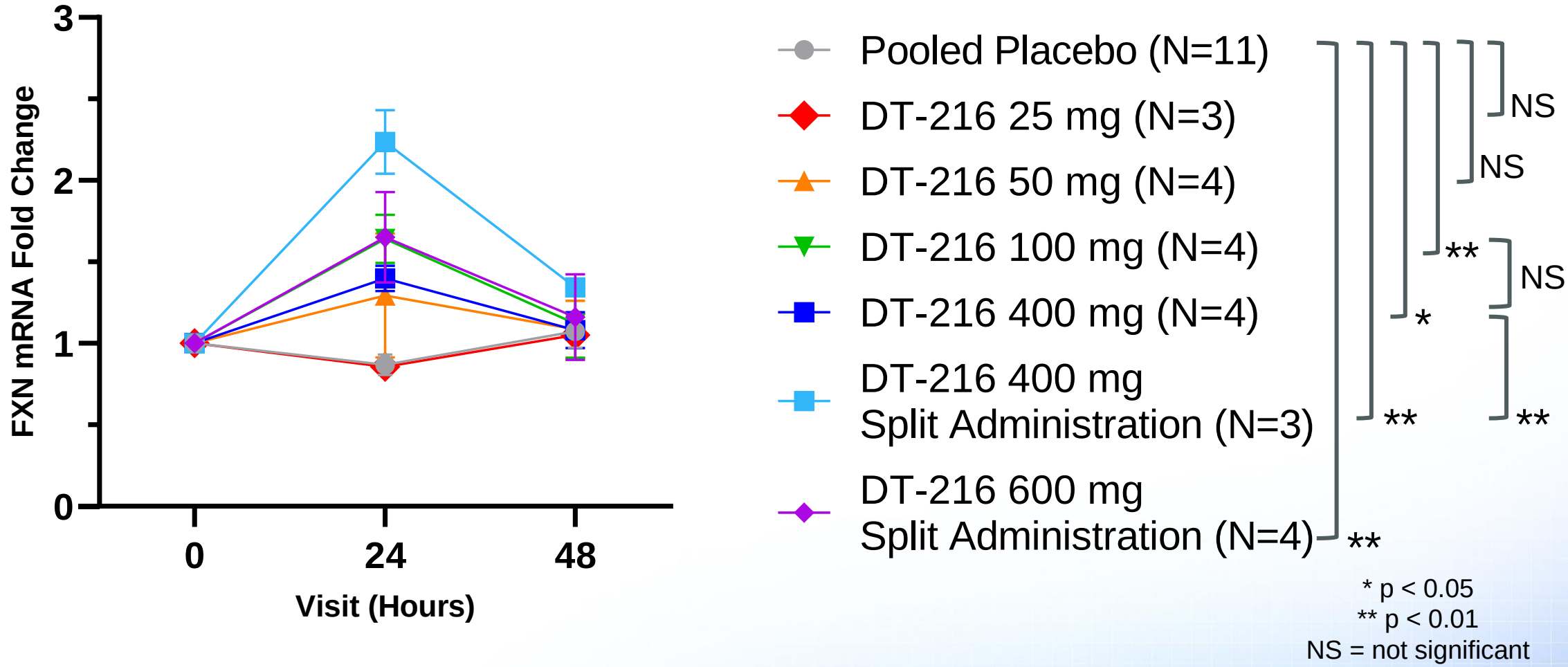
*

* $p < 0.01$

NS = not significant

Note: Post-splice FXN mRNA measured using intron spanning RT-qPCR to detect post-spliced mature mRNA. Exploratory statistical analyses were conducted using an ANCOVA model which includes a main effect for the treatment group and the baseline delta Ct as a covariate and compares each active treatment group against the pooled placebo group. The reported p values are based on parametric statistical analysis methods. Non-parametric analyses gave similar results. Bars represent standard error of the mean.

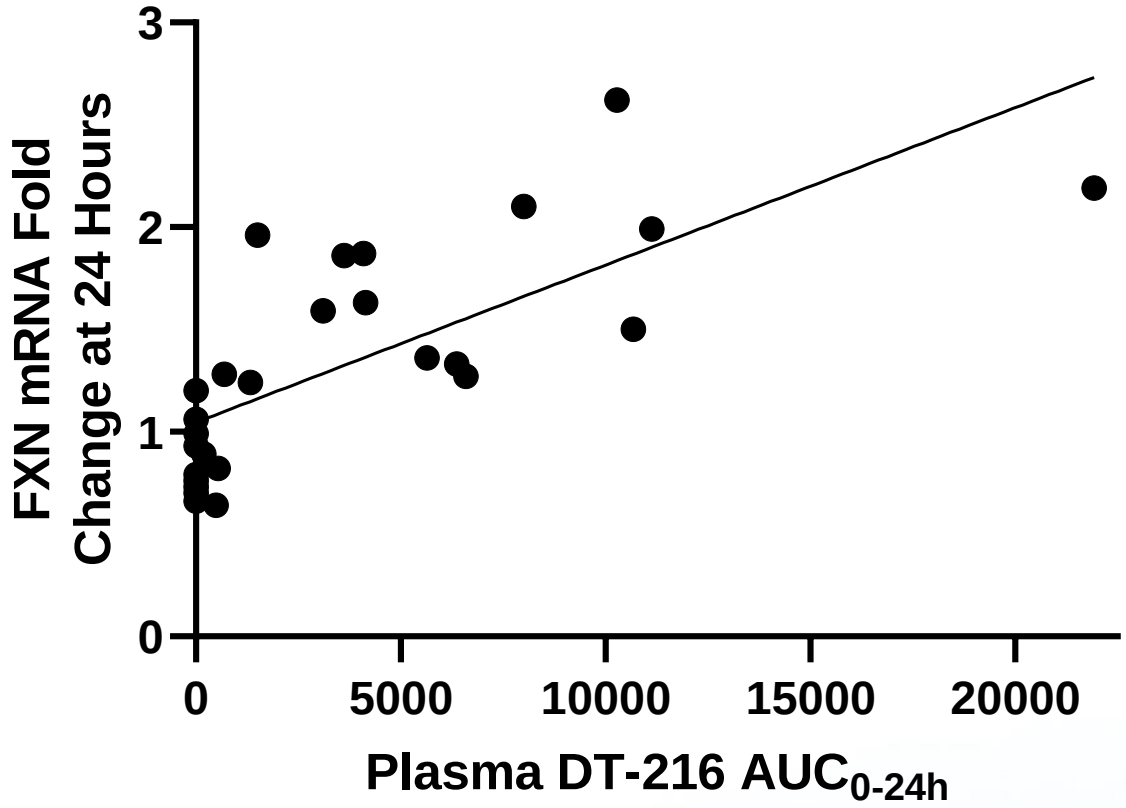
Increases in FXN mRNA in PBMCs were observed in all patients dosed with 100 mg or more of DT-216



Note: Post-splice FXN mRNA measured using intron spanning RT-qPCR to detect post-spliced mature mRNA. Pharmacodynamic data from Cohort 4 (200 mg) excluded from analysis due to third-party issues with sample handling. Exploratory statistical analyses were conducted using an ANCOVA model which includes a main effect for the treatment group and the baseline delta Ct as a covariate and compares each active treatment group against the pooled placebo group. The reported p values are based on parametric statistical analysis methods. Non-parametric analyses gave similar results. Bars represent standard error of the mean.

Relationship observed between DT-216 exposure and FXN mRNA response in PBMCs

FXN mRNA fold change at 24 hours vs DT-216 plasma PK ($AUC_{0\text{-}24h}$)

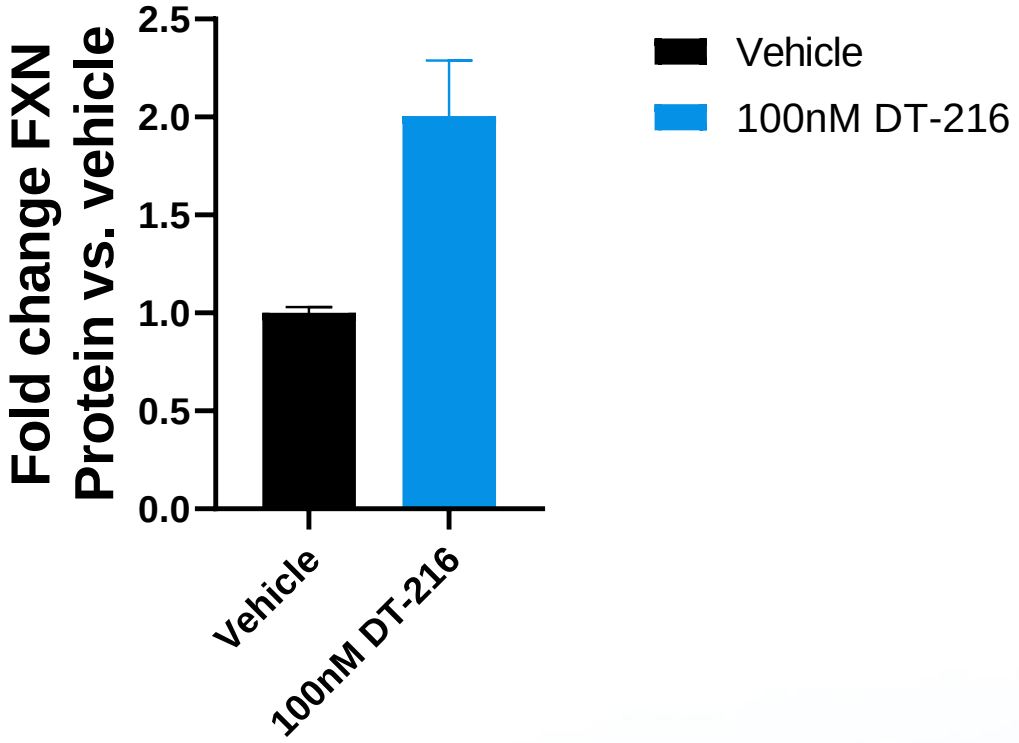


FXN mRNA fold change at 24 hr vs DT-216 plasma PK slope is significantly positive, nominal $p < 0.0001$; Linear regression with best-fit line

Note: Post-splice FXN mRNA measured using intron spanning RT-qPCR to detect post-spliced mRNA. Pharmacodynamic data from Cohort 4 (200 mg) excluded from analysis due to third-party issues with sample handling.

Extended *ex vivo* exposure with DT-216 doubled FXN protein in PBMCs collected pre-dose from SAD trial patients

60 hour *ex vivo* treatment of PBMCs from trial FA patients (N=10)



To verify the fundamental tenet that mRNA transcription results in protein production, we isolated pre-treatment PBMCs from ten trial patients, treated with 100nM DT-216 for 60 hours and found that increased mRNA resulted in a doubling of FXN protein with sufficient duration of exposure in their PBMCs

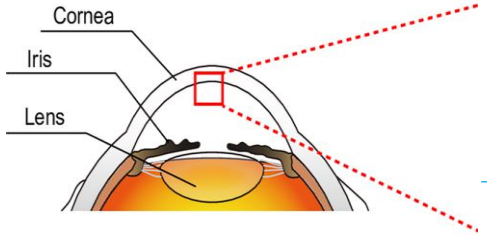
Note: Bars represent standard errors.

Stepwise development of DT-216

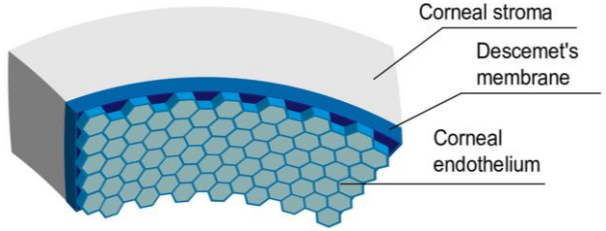
Complete	*Ongoing – data mid 2023*	*Planned 2H 2023 start*
RIGHT DRUG: Demonstrate proof of mechanism	**RIGHT DOSE: Determine dose levels for longer-term studies**	**RIGHT DURATION: Evaluate clinical impact of steady state exposure**
Phase 1 single ascending dose study in FA patients (proof of mechanism)	**Phase 1 multiple ascending dose study in FA patients (dose determination - 3 weekly doses)**	**Longer-term study in FA patients**
• Safety across a wide dose range • Pharmacokinetics • Frataxin expression in PBMCs	• Safety of multiple doses of DT-216 • Pharmacokinetics • Tissue biodistribution of DT-216 in skeletal muscle • Frataxin expression in PBMCs	• Safety of DT-216 over longer term • Frataxin expression and mitochondrial activity • Clinical measures of cardiovascular function, energy metabolism, and neurological function

FECD is a common cause of progressive visual loss in older adults

- **Loss of corneal endothelial cells (CECs) leads to corneal edema and visual impairment**
- **~4% of Americans over 40 currently have signs of FECD (> 6 million people in the US)**
- **Only approved option for treating advanced FECD is corneal transplantation**



Heathy individuals



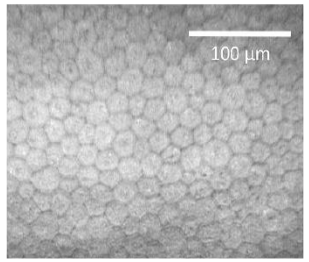
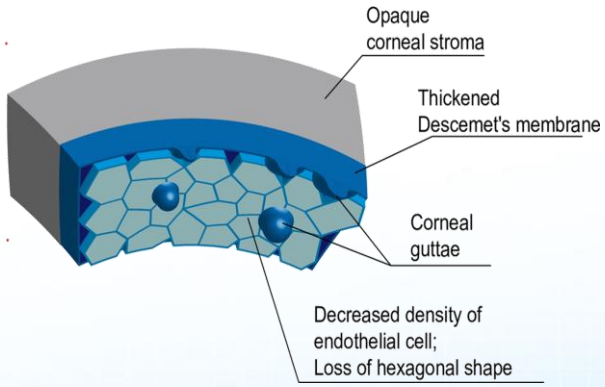


Image of CEC layer

FECD patients



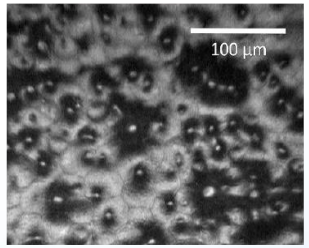


Image of CEC layer

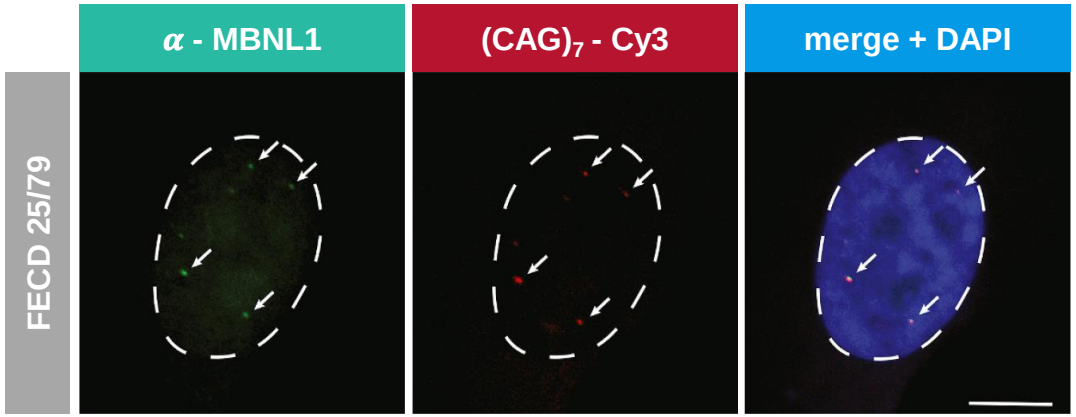
FECD is usually caused by mutant CTG repeat expansions in the TCF4 gene, leading to accumulation of pathogenic mRNA in corneal cells

CTG repeat expansions in *TCF4* intron 3 are enriched in patients with FECD

- *Patients with FECD commonly have >50 repeats in leukocytes and >1000 repeats in CECs*

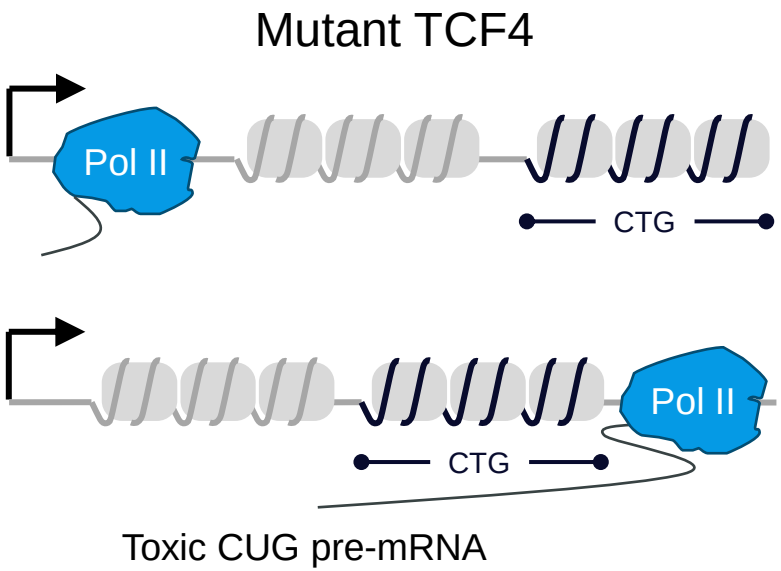
Expansion creates pathogenic TCF4 RNAs that form toxic nuclear foci

- *Foci sequester RNA splicing factors including MBNL1 leading to perturbed global splicing and loss of CECs*

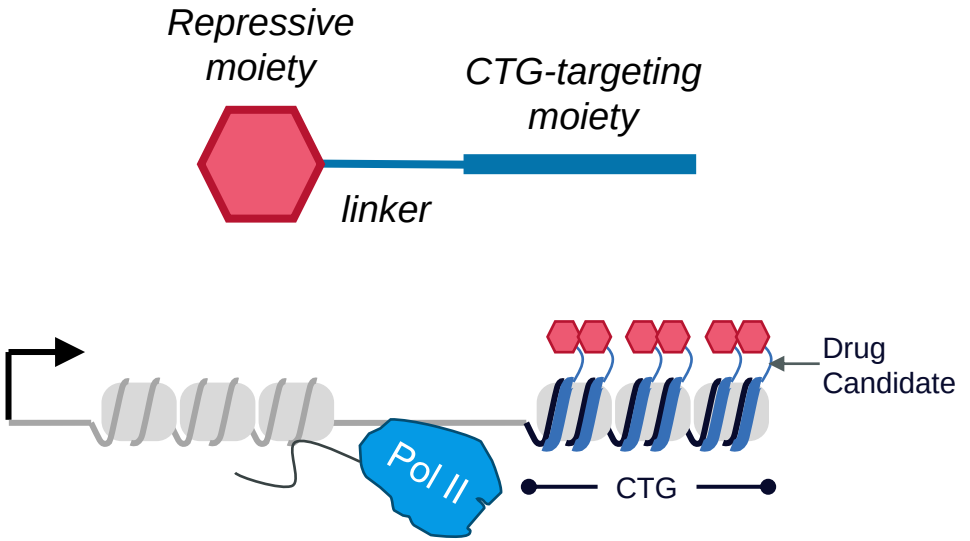


Fautsch (2021) *Prog Ret Eye Res*

Design Therapeutics has pioneered a new approach for FECD



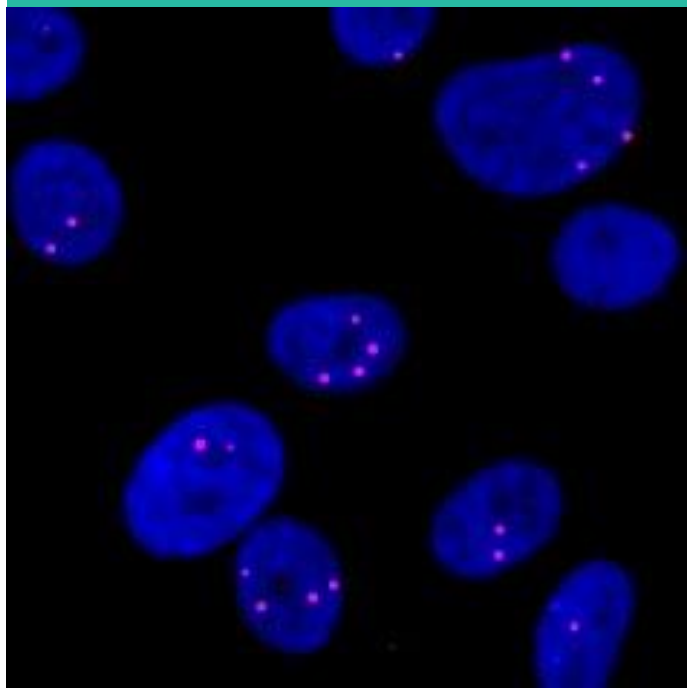
FECD GeneTAC™ Molecule



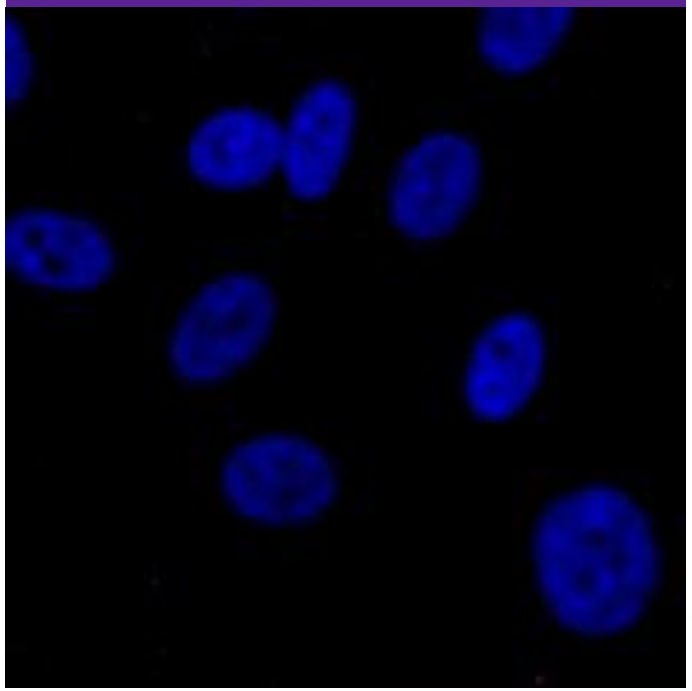
Our molecules are designed to block transcription specifically through the mutant locus

FECD GeneTAC™ molecules reduced toxic *TCF4* foci in CECs isolated from patients with FECD with IC_{50}<10nM

FECD CECs + Vehicle

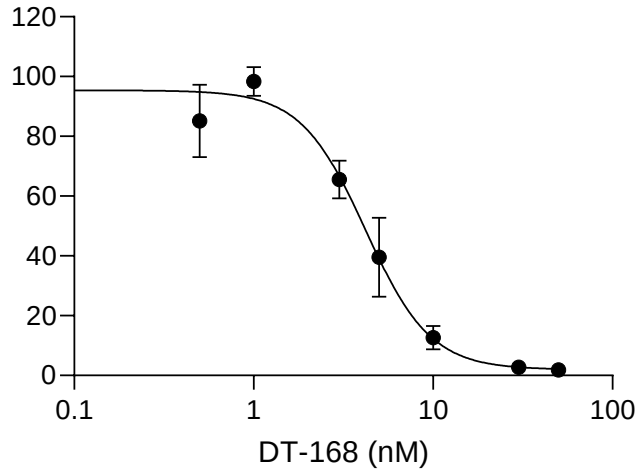


FECD CECs + FECD GeneTAC™ Molecule (100nM)



Nucleus / **Foci**

Primary corneal endothelial cells from FECD patients treated daily for 14 days with DT-168

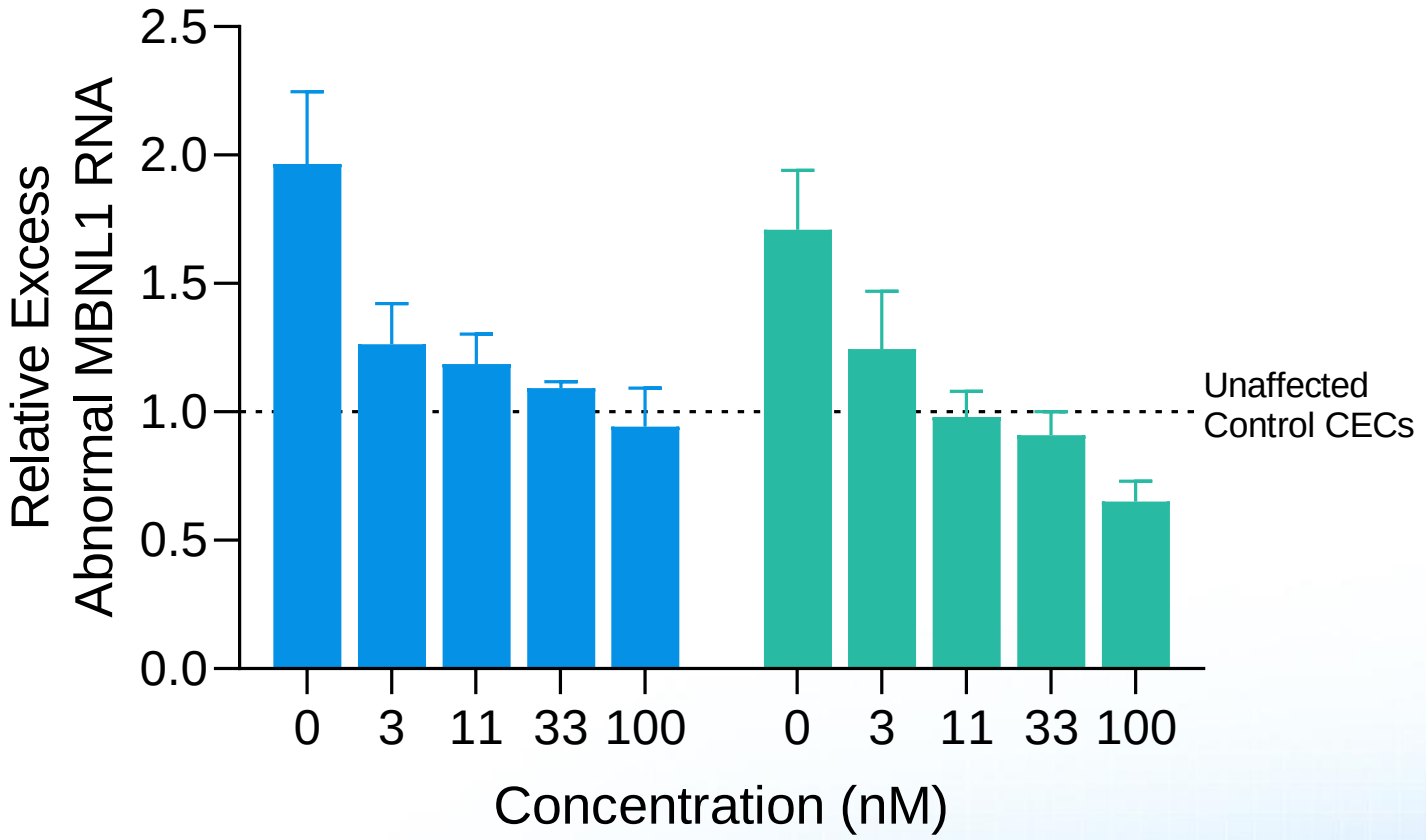


GeneTAC™ molecules corrected aberrant splicing events in CECs isolated from patients with FECD

Correction of Aberrantly Spliced *MBNL1* RNA in FECD CECs

9-day continuous treatment with FECD GeneTAC™ molecule

CEC 1 CEC 2



DT-168 declared a FECD GeneTAC™ development candidate

An eye drop that potentially addresses the genetic root cause of FECD

- Designed to suppress the expression of mutant *TCF4* gene that contains expanded CTG repeats
- Convenient self-administration facilitates wide adoption
- Well-tolerated following topical administration for 2 weeks in preclinical animal studies
- Negligible systemic exposure
- **IND-enabling studies ongoing, IND expected in 2H 2023**

Myotonic Dystrophy Type 1 (DM1)

Dominant repeat expansion drives disease

DM1 patients have an expanded CTG repeat in the 3’ UTR intron of one copy of their DMPK gene.

Normal

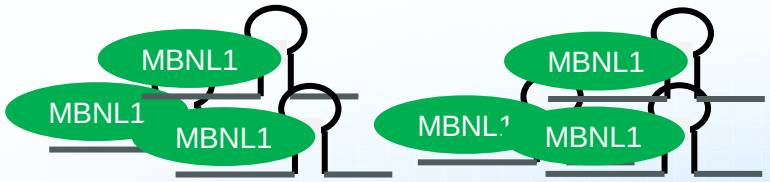
<50 repeats

Diseased (one copy)

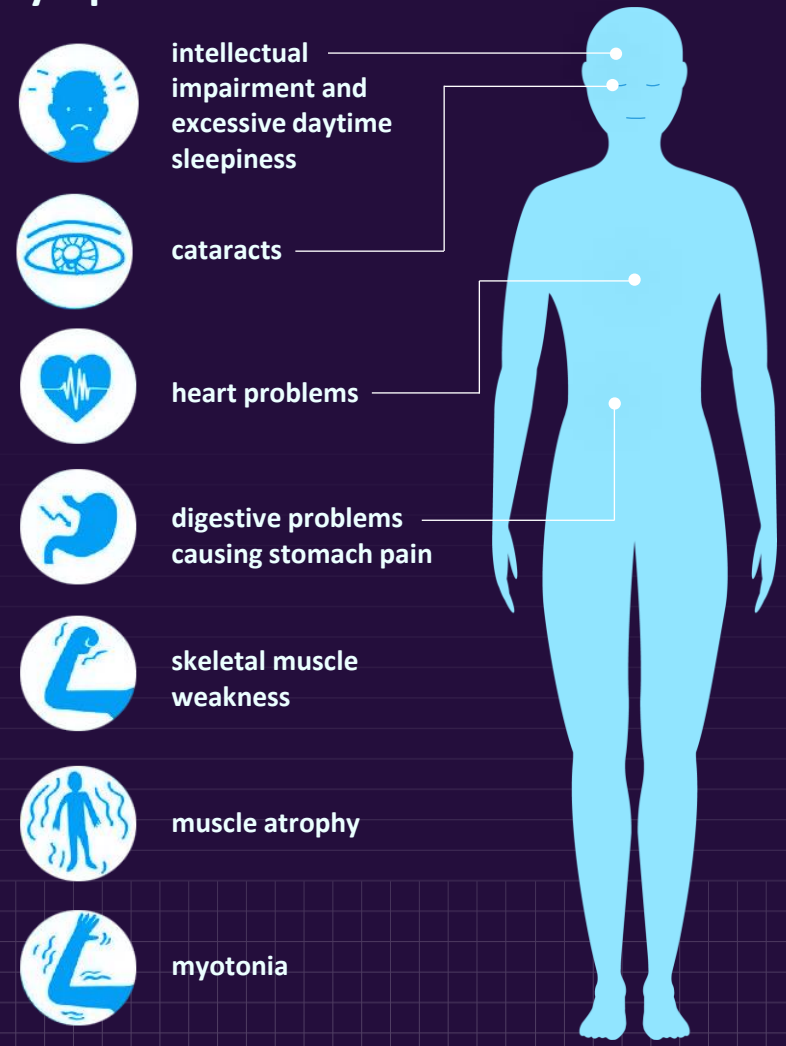
>50 to 1000+ repeats

Toxic gain of function

Expanded CTG repeats in the DMPK mRNA trap MBNL1 splicing factors in CUG foci. Reduced MBNL1 activity leads to improperly spliced genes and cellular dysfunction



Symptoms



70,000+ individuals affected in the U.S.
90,000+ individuals affected in Europe

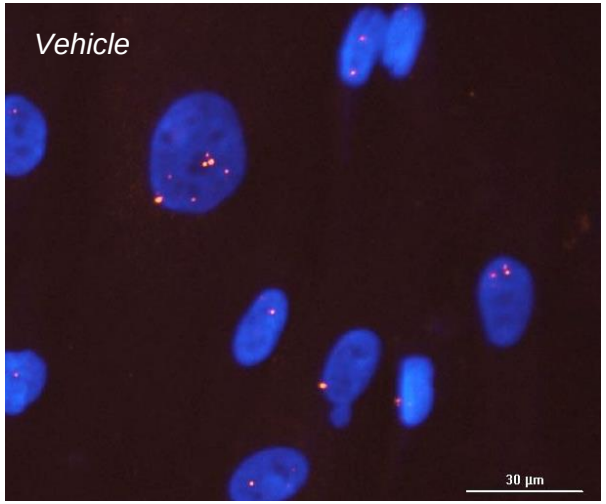
Advanced Programs Focus on DM1 Symptoms or Congenital DM1

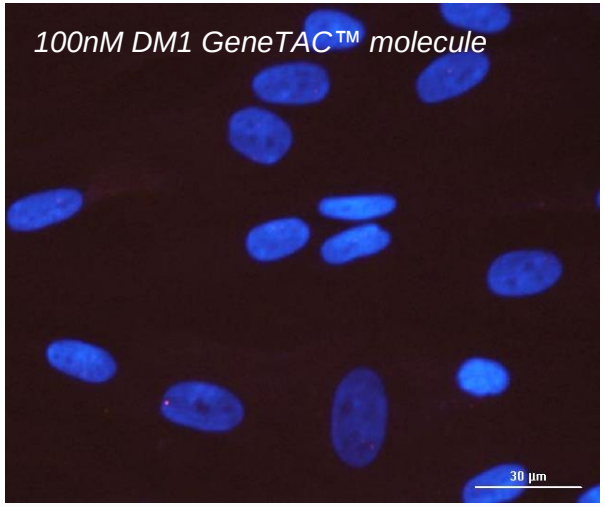
	PHASE 2		PHASE 1		Preclinical
	AMO PHARMA	HARMONY BIOSCIENCES	AVIDITY BIOSCIENCES	Dyne THERAPEUTICS	astellas GENE THERAPIES
	Tideglusib (AMO-02)	**Pitolisant**	**AOC 1001**	**TBD**	**AT-466**
Potential MOA	Inhibits GSK3-Beta kinase to phosphorylate CUGBP1 and restore mis-regulation of its myogenic targets	Histamine 3 receptor antagonist/inverse agonist for EDS symptoms	TfR1 targeting **mAb** conjugated with siRNA to reduce DMPK mRNA levels	**ASO** conjugated to TfR1 targeting Fab	**AAV** vector to deliver antisense exon skipping or RNA knockdown
Foci Data	N/A	N/A	• **"Quantifiable reduction" in nuclear foci** observed in patient DM1 cells	• **"Approximately 40% reduction in nuclear foci"** in DM1 cells	N/A
	Only congenital DM1	*Only Excessive Daytime Sleepiness*	*Non-selective knockdown of DMPK*	*Non-selective knockdown of DMPK*	

Source: Company websites, Corporate filings, https://www.pedneur.com/article/S0887-8994(20)30274-5/fulltext (AMO Pharma)
Note: Additional candidates not included due to limited DM1 specific clinical R&D: Nexien (sublingual cannabinoid formulation) to manage myotonia symptoms, Lupin's mexiletine (approved) to manage myotonia symptoms. Other potential 2022 INDs not included due to limited recent updates: Arthex Biotech and LocanaBio.

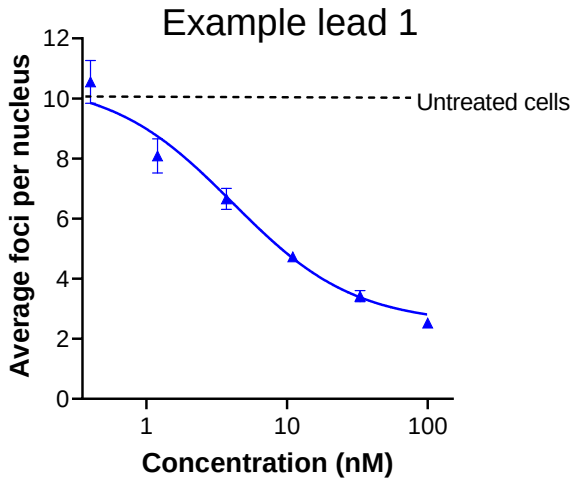
Ongoing characterization of potent DM1 GeneTAC™ lead molecules that result in foci resolution in DM1 patient cells

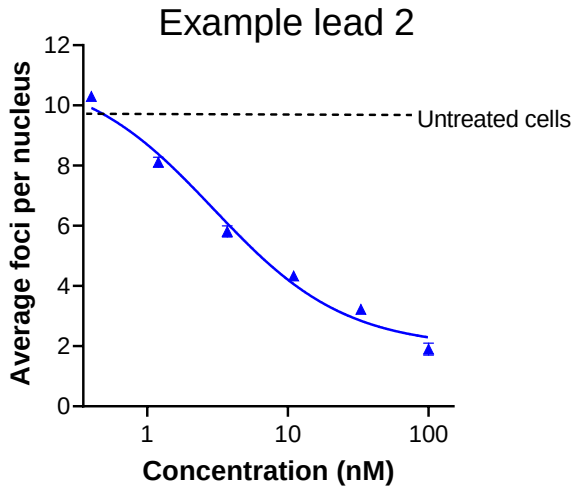
DM1 patient fibroblasts treated for 3 days





DM1 patient myotubes treated for 7 days

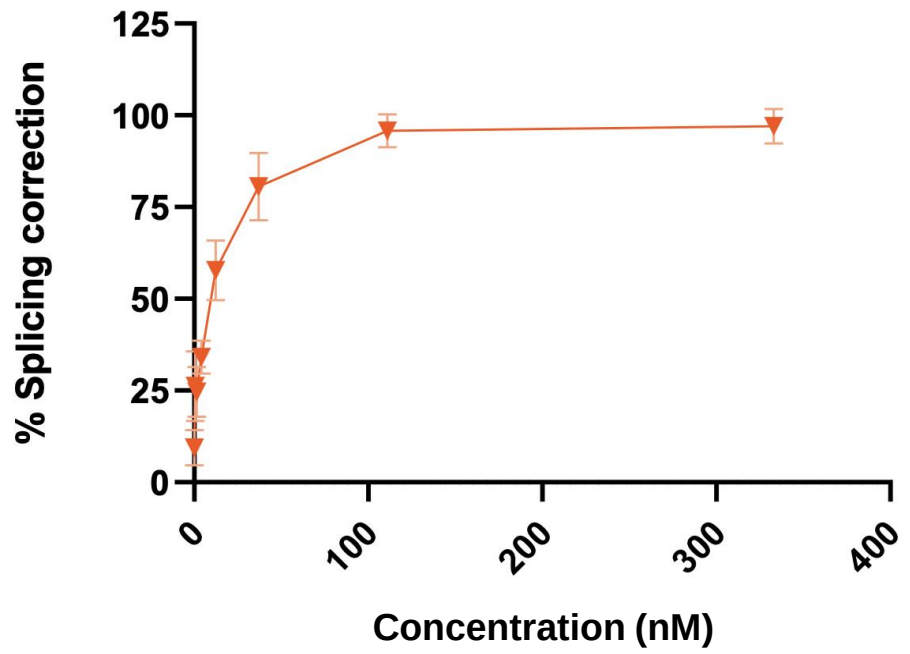




Note: Bars represent standard errors.

DM1 GeneTAC™ Molecules Demonstrated High Potency in Correcting Splicing Defects in DM1 Patient Myoblasts

% Splicing Correction for MBNL1 Exon 7 Inclusion in DM1 patient fibroblasts



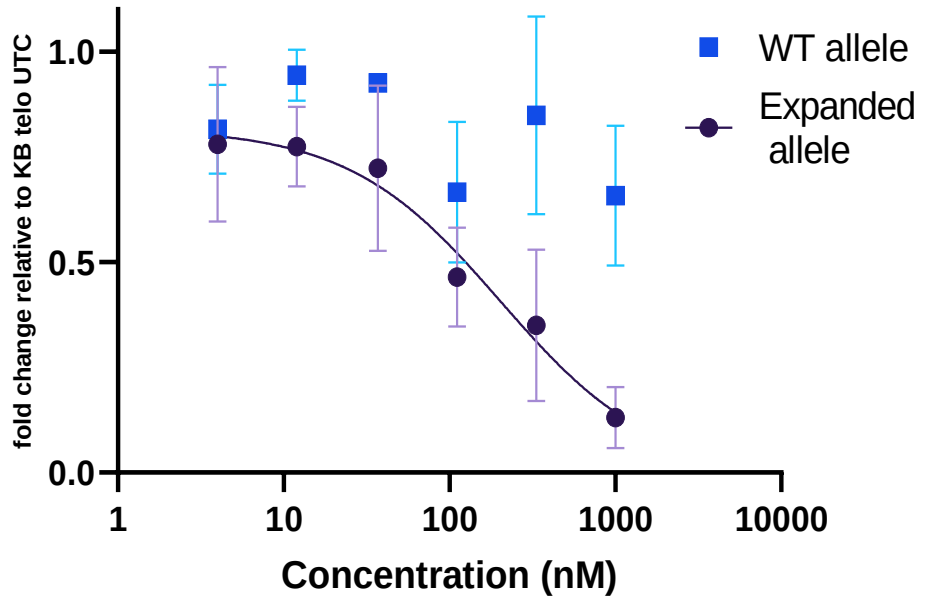
- DM1 patient myoblasts were treated with GeneTAC™ molecules for 6 days. Wildtype myoblasts were plated in tandem as a control
- MBNL1 exon 7 inclusion mRNA was measured via qRT-PCR
- MBNL1 exon 7 inclusion mRNA expression was normalized to GAPDH mRNA expression
- % splicing correction is defined as:

$$\frac{\text{(Average untreated DM1 myoblasts – } \textit{GeneTAC}^{TM} \textit{ molecule treated DM1 myoblasts)}}{\text{(Average untreated DM1 myoblasts – average untreated WT)}} \times 100 = \textbf{\% MBNL1 Exon 7 Inclusion splicing restoration}$$

DM1 GeneTAC™ Treatment Resulted in Allele Selective Knockdown of muDMPK in DM1 Patient Myoblasts

ddPCR

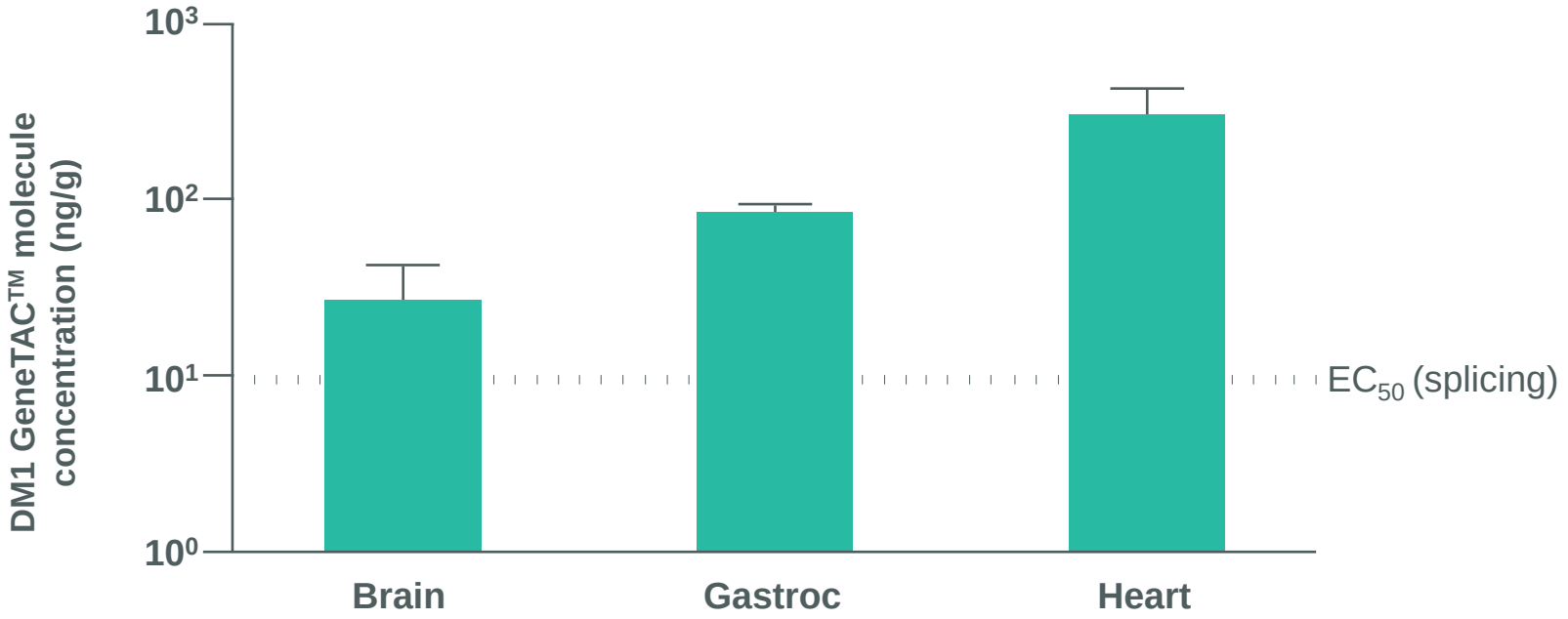
Allele Selective Reduction of DMPK in DM1 Patient Derived Myoblasts after DM1 GeneTAC™ treatment (72h)



- Telo-MyoD-KB cells harbor rs57221 G>C SNP which is associated with mutant DMPK allele (400 CTG repeats)
- SNP can also be quantitively measured via ddPCR using TaqMan probes which discriminate for each SNP

GeneTAC™ Molecules Targeted Tissue Distribution Sufficient to Drive Biological Effects

Tissue Biodistribution



10 mg/kg single dose
Tissue concentrations measured 24 hours post last dose

Three clinical GeneTAC™ programs expected in the next three years

DEVELOPMENT PROGRAMS	NEXT ANTICIPATED MILESTONE	EXPECTED TIMING
Friedreich ataxia (FA; GAA) – DT-216	Data from MAD trial	Mid-2023
	Initiate phase 2	2H 2023
Fuchs endothelial corneal dystrophy (FECD; CTG) – DT-168	IND	2H 2023
Myotonic dystrophy type 1 (DM1; CTG)	IND	2024
RESEARCH PROGRAMS	**ESTIMATED US PREVALENCE**	
Fragile X syndrome (FXS; CGG)	~80,000	
Huntington disease (HD; CAG)	~40,000	
C9orf72-amyotrophic lateral sclerosis/ frontotemporal dementia (ALS/FTD; GGGGCC)	~7,000	
Other CTG-expansion diseases	~25,000	