TRIPLET THERAPEUTICS

Development of therapeutics to prevent onset and/or progression in Repeat Expansion Disorders

18 June 2021

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Somatic Expansion in Repeat Expansion Diseases and Role of DNA Damage Response Genes

Clinical Development of TTX-3360

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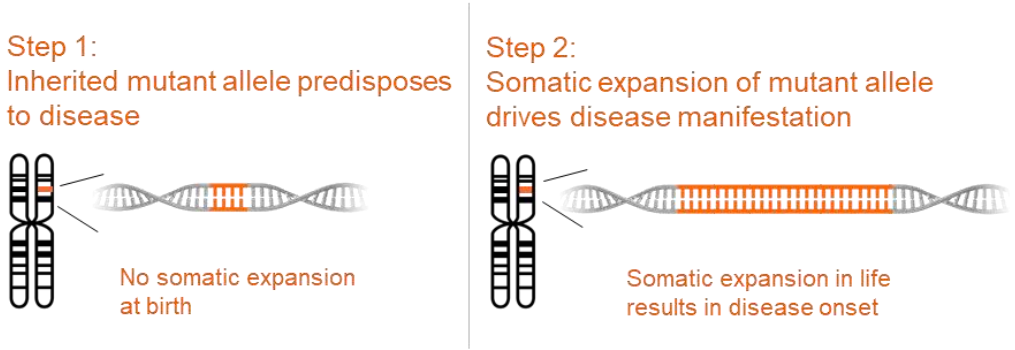
Many Repeat Expansion Disorders (REDs) affect the CNS and Represent a Significant Unmet Need

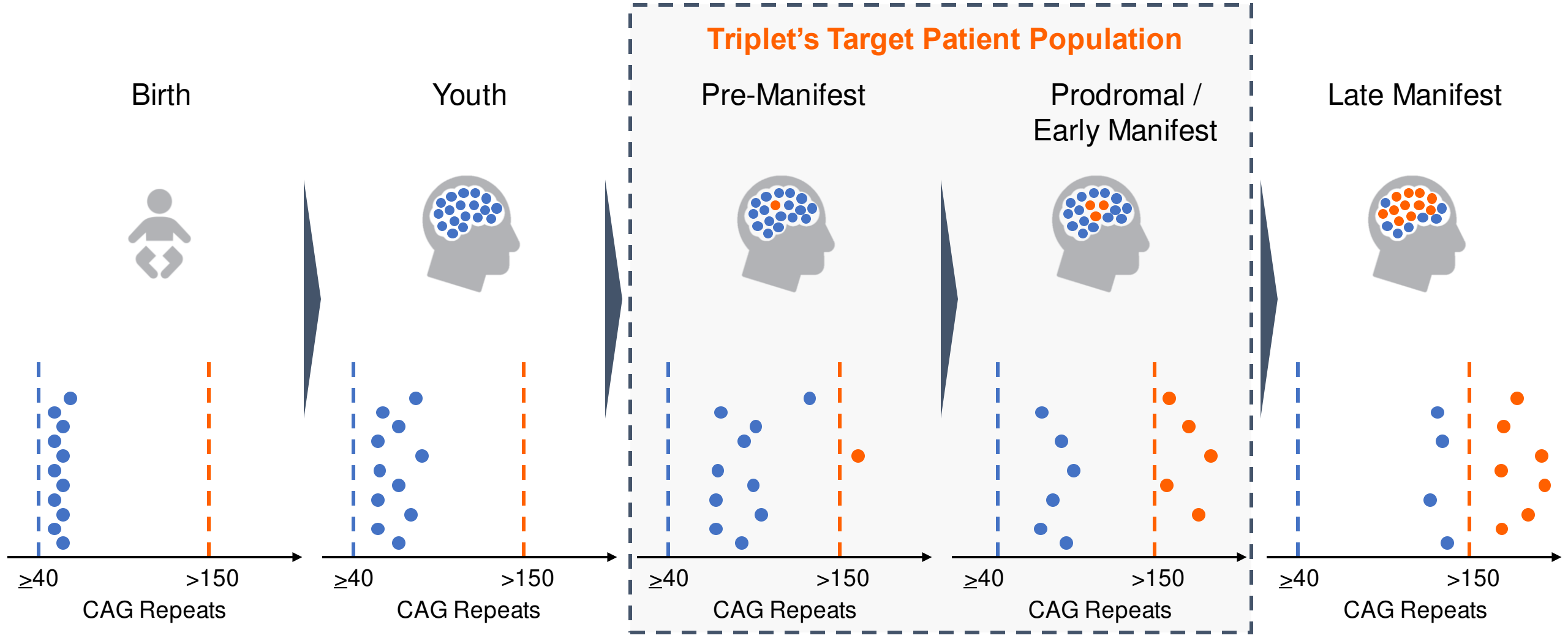
>50 known REDs
with more emerging

- Each caused by DNA repetitions in a single gene
- Mostly severe with no disease-modifying therapies
- 2-step hypothesis: Somatic Expansion (SE) required for symptom onset



Disease	Sequence	# of repeats in disease	Gene
Fragile X Syndrome (FXS)	CGG	>~200	FMR1 (5'UTR)
Friedreich's ataxia (FRDA)	GAA	>~70	FXN (intron)
Huntington's Disease (HD)	**CAG**	**>~36**	**HTT (exon)**
Myotonic dystrophy type 1 (DM1)	**CTG**	**>~50**	**DMPK (3' UTR)**
Progressive myoclonic epilepsy (PME)	CCCCGCCCCGCG	>~38	EPM1 (exon)
Spinocerebellar ataxia type 1 (SCA1)	**CAG**	**>~40**	**ATXN1 (exon)**
Spinocerebellar ataxia type 3 (SCA3)	**CAG**	**>~52**	**ATXN3 (exon)**
X-linked dystonia parkinsonism (XDP)	CCCTCT	>~30	TAF1 (intron)

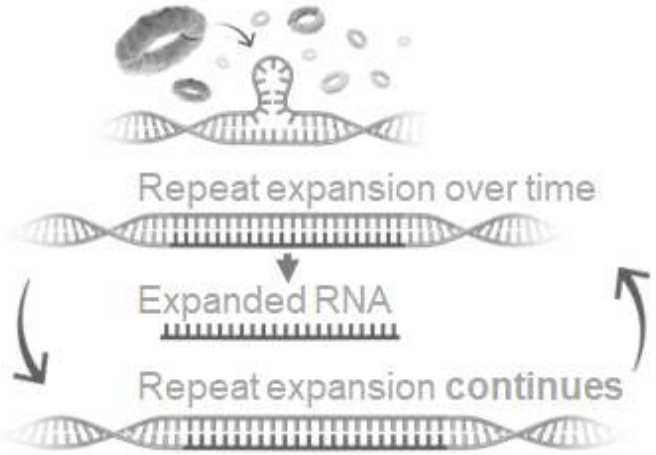
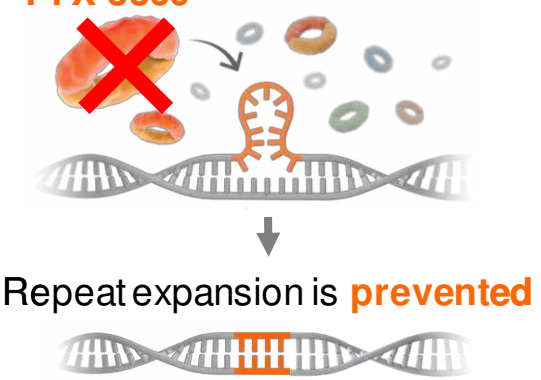
The 2-Step Hypothesis: Two Sequential Components Needed for Symptom Onset



Somatic expansion is cell autonomous and probability-driven

Modified from Kaplan et al. Plos Comp Biol 2007

Triplet's Approach Is Differentiated from HTT lowering and Targets Step 2: Somatic Expansion

	HTT-Lowering Antisense Oligonucleotide Approaches	Triplet's Approach
Target	HTT	MSH3 (DDR^ Protein)
Assumed Mechanism	Reduces levels of mHTT and/or wtHTT to lower protein/RNA toxicity; **DNA continues to expand** resulting in ever increasing toxicity; **exon 1 remains intact** 	Reduces levels of specific DDR protein/RNA to **stop somatic expansion** (HD mouse models) and halt disease onset & progression; **exon 1 production is halted** TTX-3360 
Required KD Level	~**75% mHTT selective lowering** may be required to abrogate toxicity	~**50%** based on patient-derived cell and animal models**
Disease Relevance	Only applicable to HD*	Potentially relevant in **30+ CNS REDs^^**
Delivery	Intrathecal (IT) injection	Intracerebroventricular (ICV) injection
Biodistribution	Cortex; **very limited exposure in striatum** (NHP)	Substantial distribution in **striatum and cortex** (NHP)
Targeted Patient Population	Manifest patients; critical role of HTT in brain development may pose **risk for younger patients***	**Premanifest** and manifest patients, patients aged 18 and older

**Based on current understanding of HTT's role in the brain; **Based on Q111 and R6/2 HD animal model data*

^DDR (DNA Damage Response), ^^REDs (Repeat Expansion Disorders (REDs)

Somatic Expansion in Repeat Expansion Diseases and Role of DNA Damage Response Genes

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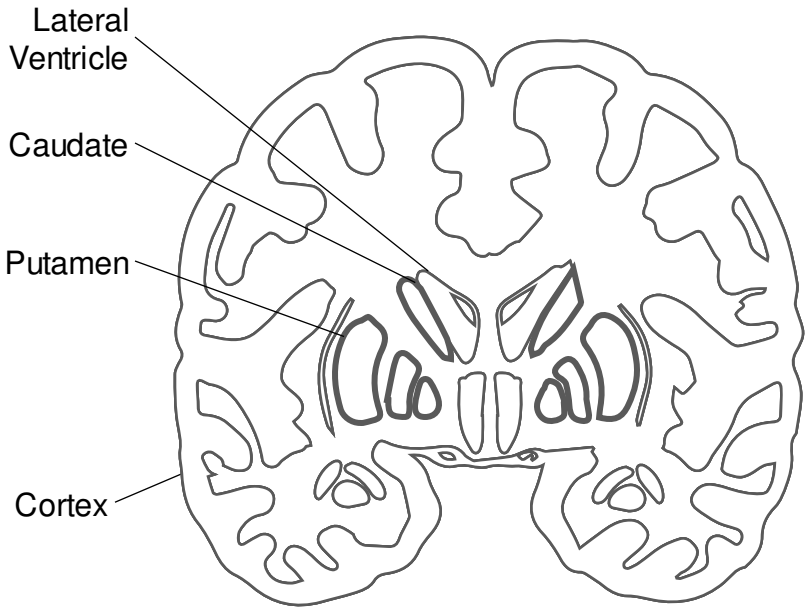
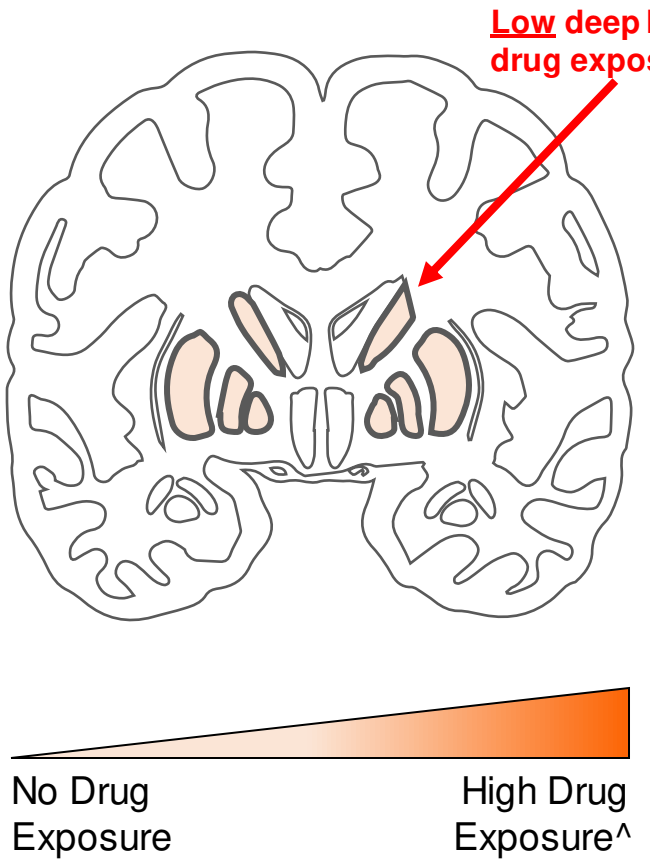
Route of Administration is Critical for Biodistribution of ASOs in HD-Relevant Brain Areas*

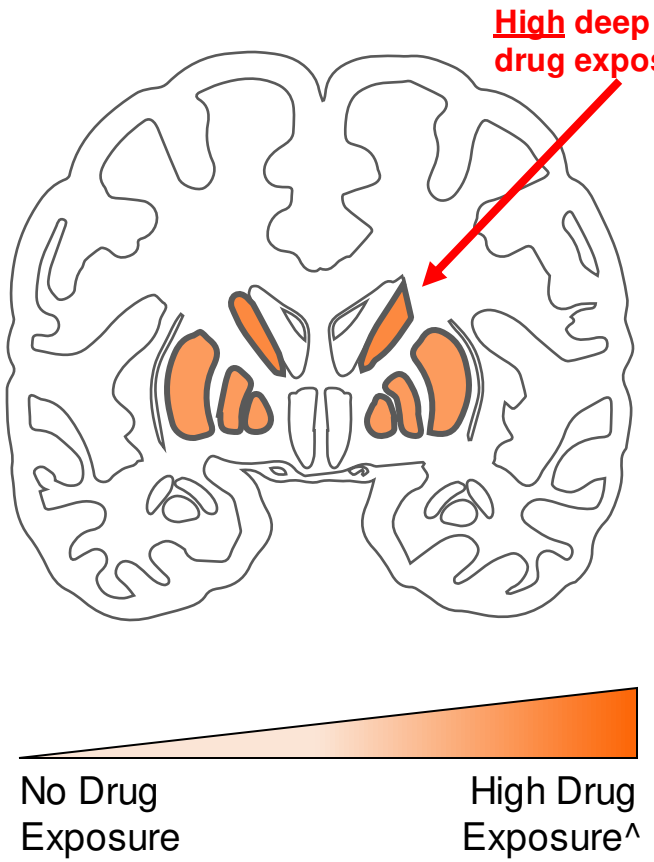
Key Brain Areas in HD



Drug Biodistribution via Intrathecal (IT) Injection



Drug Biodistribution via Intracerebroventricular (ICV) Injection



** Illustrative; Brain areas with unknown SE are colored white; ^ Based on published (Jafar-nejad et al 2020) and Triplet data*

Route-of-Administration: IT vs ICV

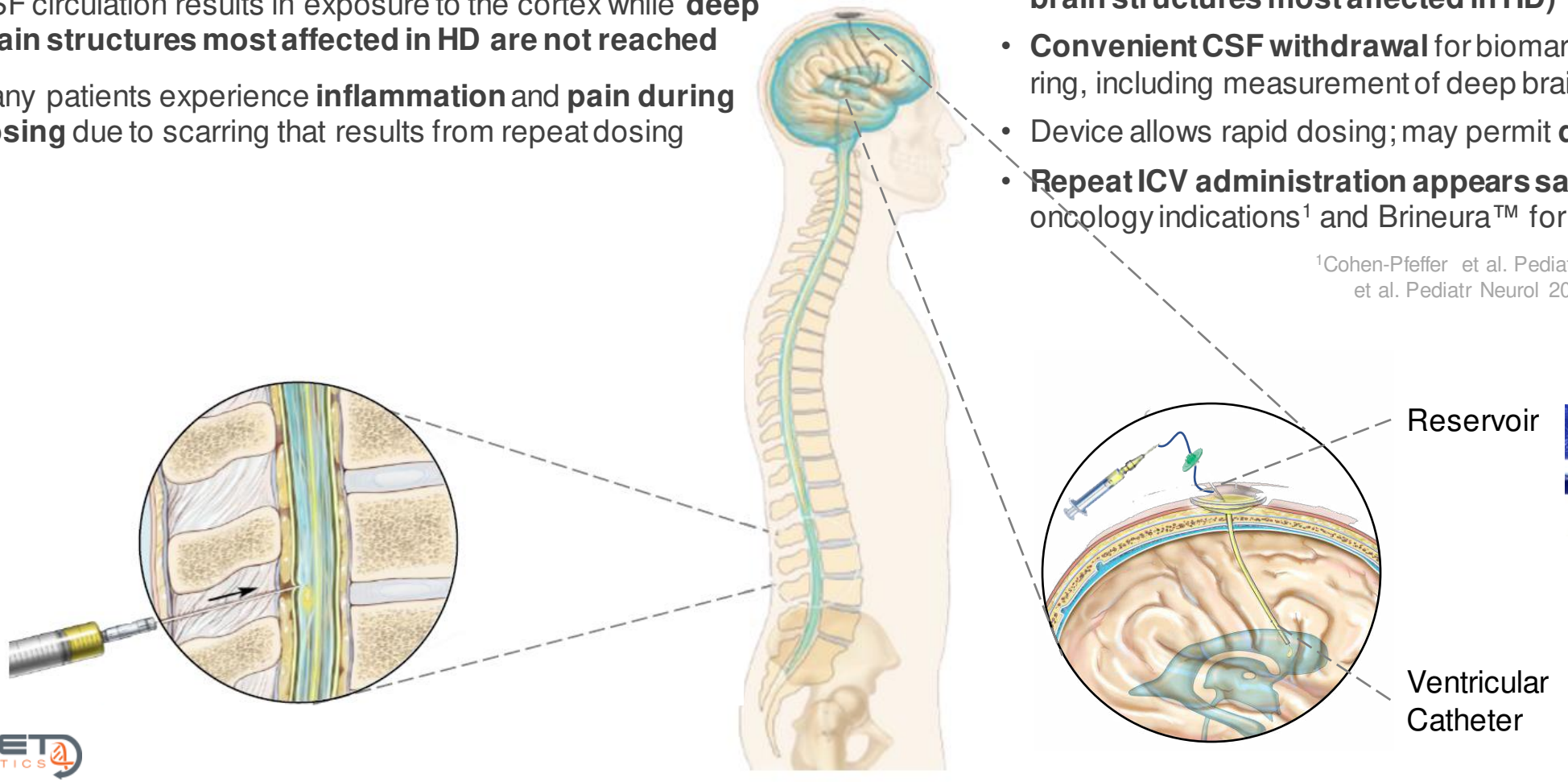
IT Delivery

- RoA popularized by success of Spinraza, an ASO for spinal muscular atrophy impacting motor neurons in spinal cord
- CSF circulation results in exposure to the cortex while **deep brain structures most affected in HD are not reached**
- Many patients experience **inflammation** and **pain during dosing** due to scarring that results from repeat dosing

ICV Delivery

- Implantation of port & catheter has been used for > 60 years
- Drug is delivered directly to the lateral ventricle **(next to deep brain structures most affected in HD)**
- **Convenient CSF withdrawal** for biomarkers and safety monitoring, including measurement of deep brain target engagement
- Device allows rapid dosing; may permit **dosing at home**
- **Repeat ICV administration appears safe longer-term** (CNS oncology indications[1] and Brineura™ for CLN2[2,3])

[1]Cohen-Pfeffer et al. Pediatr Neurol 2017; [2]de los Reyes et al. Pediatr Neurol 2020; [3]Schulz et al. NEJM 2018



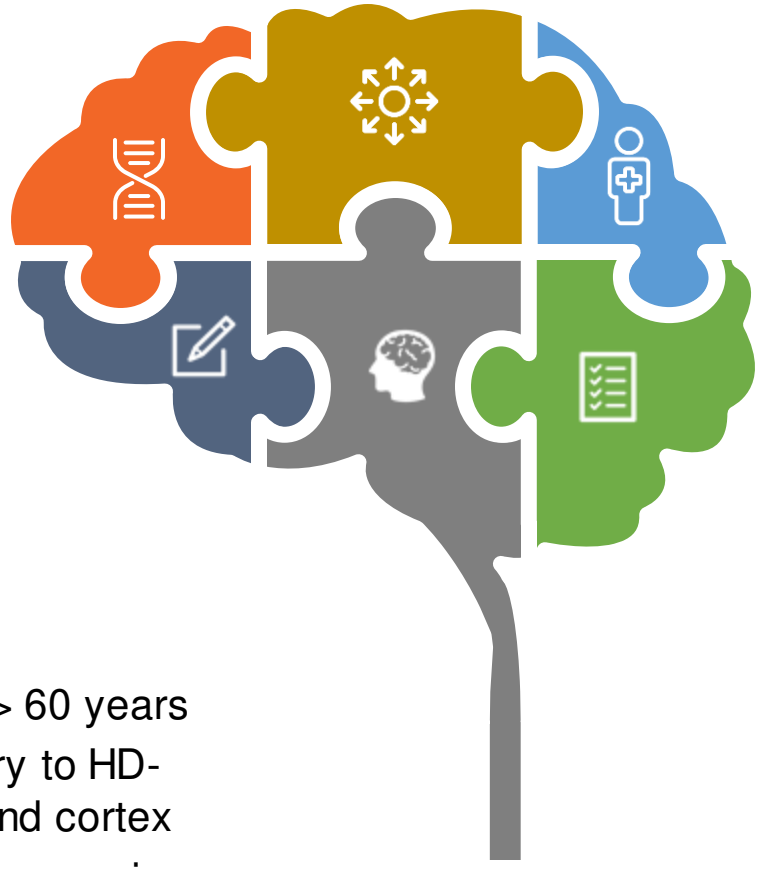
Size of a dime

SE in HD: 2-Step Hypothesis supported by accruing data:

- **MSH3 modulates SE in HD & other REDs**
- SE contributes to symptom onset and disease progression

Proof-Of-Mechanism:

- **Lowering MSH3** by ~50% in HD-relevant brain regions **halts SE** (HD mouse and cell models)



ICV Route of Administration:

- **Established procedure**, used for > 60 years
- Device implantation enables delivery to HD-relevant brain areas, *i.e.* striatum and cortex
- Repeat ICV dosing affords greater convenience than repeat IT dosing

Biodistribution in NHP:

- Single well-tolerated ICV injection of TTX-3360 lowered MSH3 broadly and proportionally in HD-relevant brain areas
- Lowering is sustained for ≥12 weeks
- **Opportunity for convenient clinical dosing regimen**

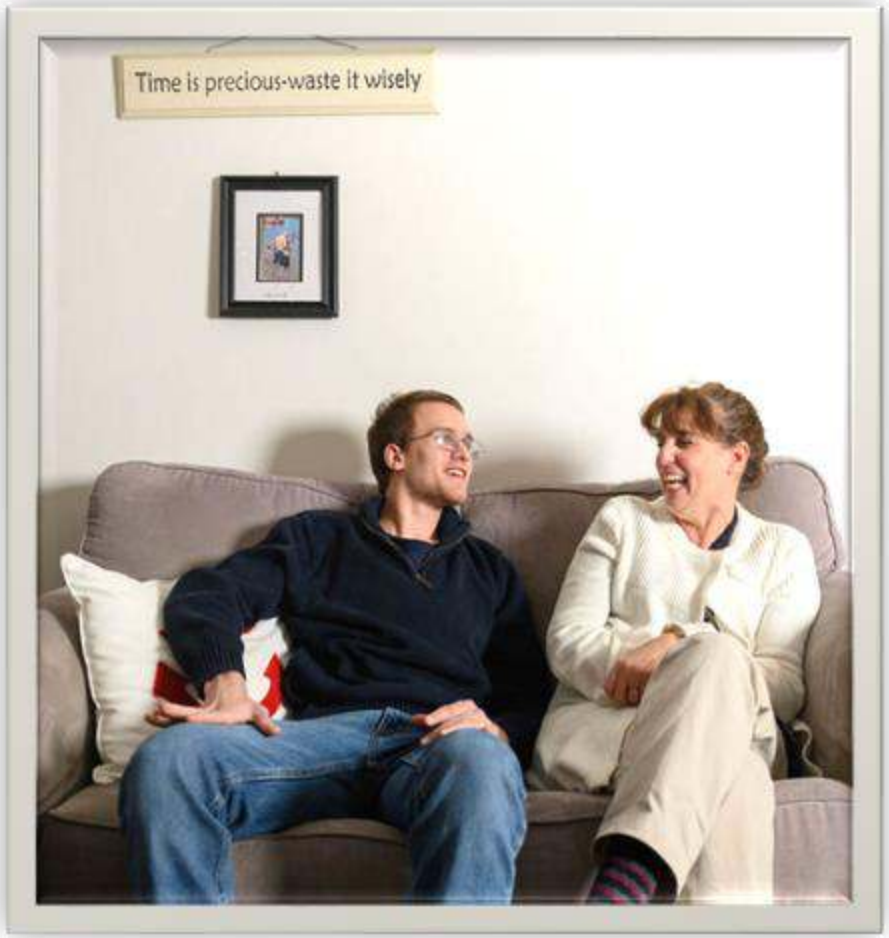
TTX-3360 is Safe and Well-Tolerated

- Preliminary clinical observations with TTX-3360 in NHP indicate good safety margin
- Data indicate **no difference in NfL after TTX-3360** vs. aCSF injections in NHP

Interventional Trials in HD & Beyond:

- **IND/CTA submission in H2 2021**
- Phase 1/2a at SHIELD HD sites and with SHIELD HD patients, and additional sites
- Trials to assess TTX-3360 in other REDs, such as SCA1 and 3 in consideration

Thank you! Acknowledging the Committed and Dedicated Triplet Team and Invaluable Advisors and Collaborators



Jonathan & Gina

CHDI
Rebecca Fuller
Cristina Sampaio

Enroll-HD
Juliana Bronzova
Tim McLean

HDSA
Leora Fox
Louise Vetter
George Yohrling

EHA
Astri Arnesen

HSC
Shelly Redman

Ataxia UK
Julie Greenfield

Clintrex
Karl Kieburtz
Andy McGarry

Sarah Tabrizi
Anne Rosser

Alexandra Durr
Mark Guttman
B. Landwehrmeyer
Ralf Reilmann
Carsten Saft
Ed Wild

Jeff Long
Julie Stout

Andres Lozano
Ludvic Zrinzo

Gill Bates
Jeff Carroll
Jim Gusella
Lesley Jones
Darren Monckton
Vanessa Wheeler

Seth Ament
Steven McCarroll

…and others

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