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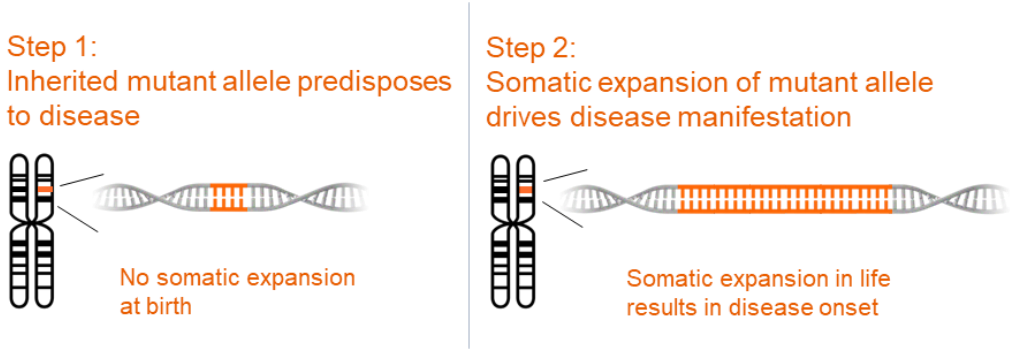
Many Repeat Expansion Disorders (REDs) affect the CNS and Represent a Significant Unmet Need

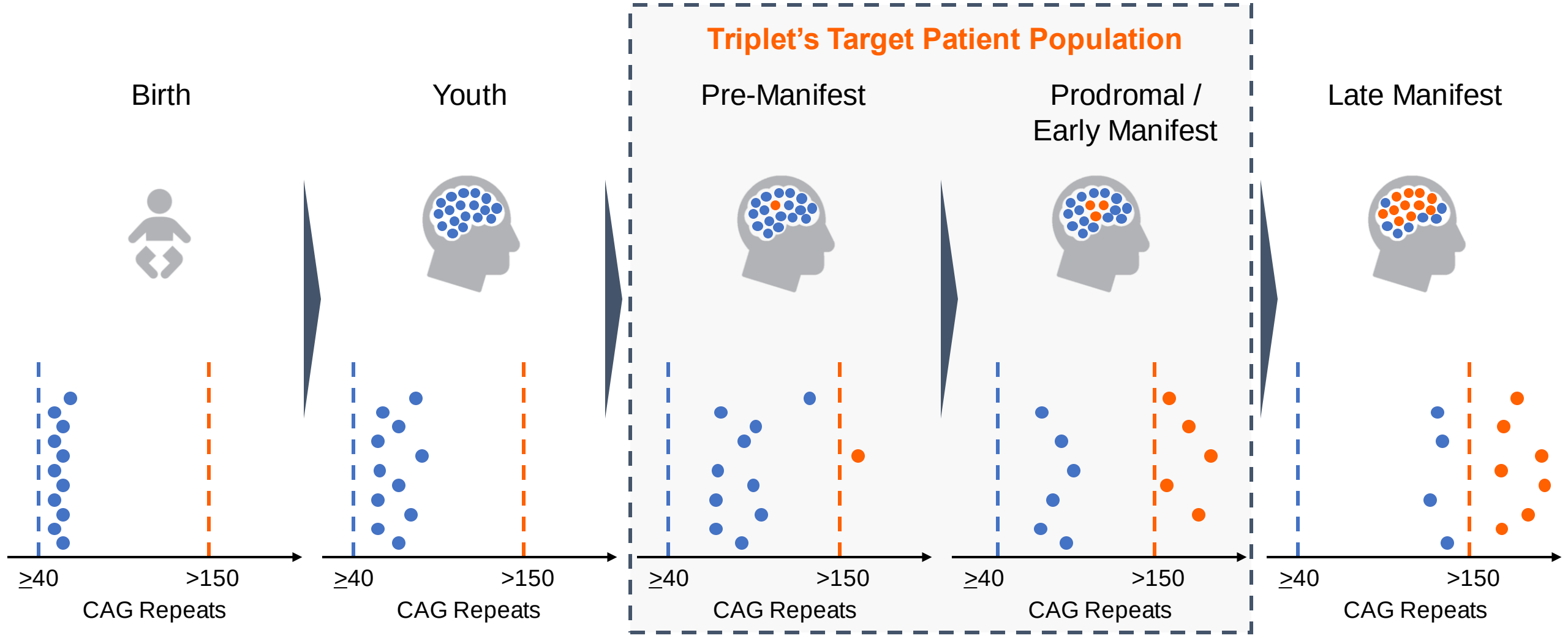
>50 known REDs
with more emerging

- 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)

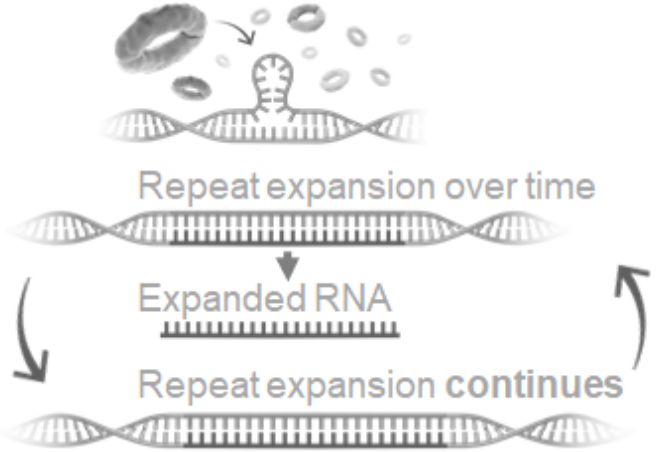
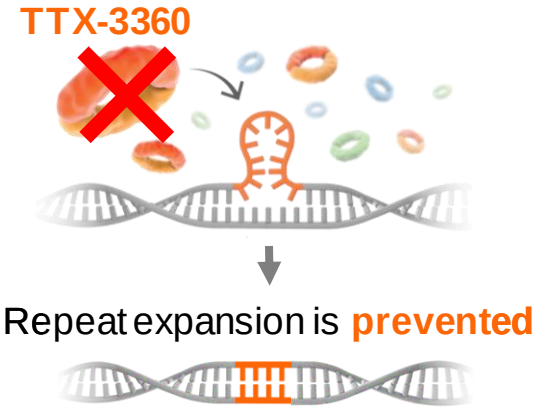
The 2-Step Hypothesis: Two Sequential Components Needed for Symptom Onset



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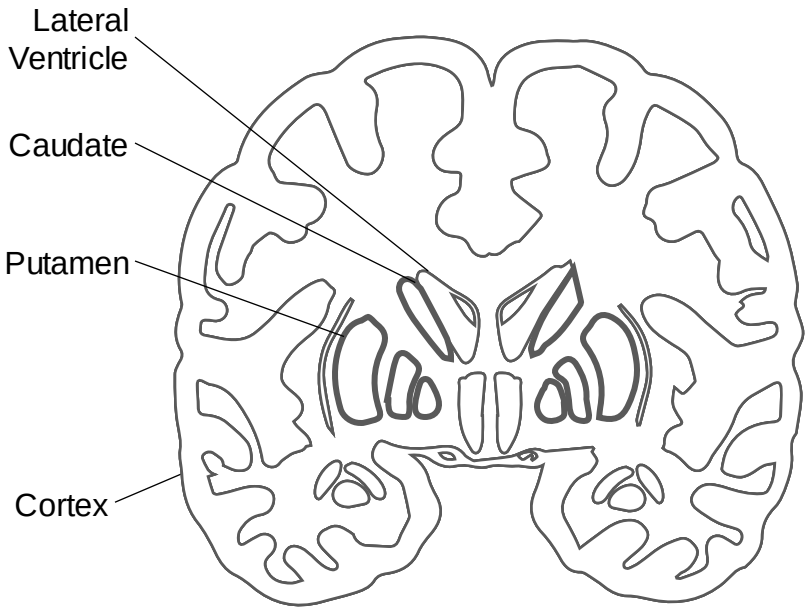
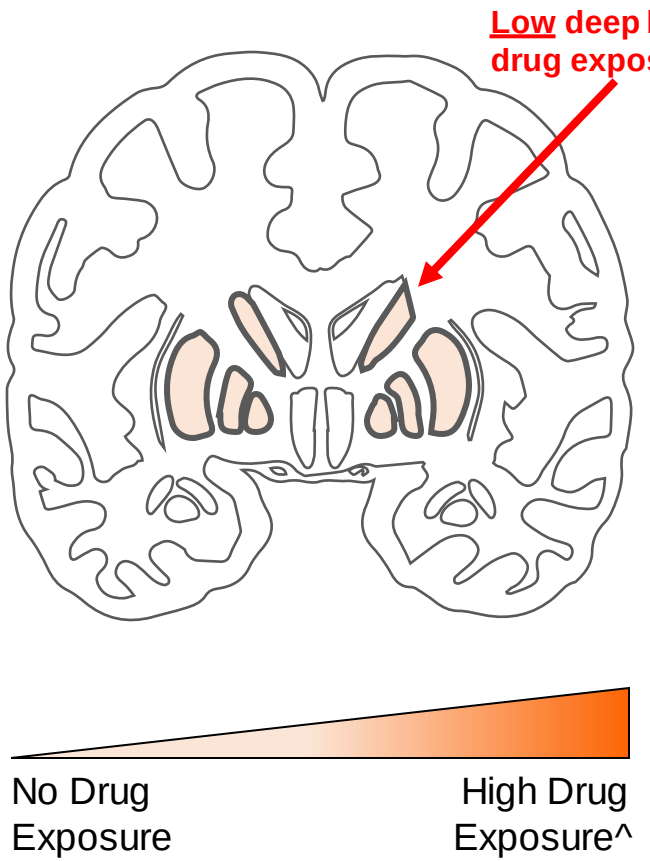
Route of Administration is Critical for Biodistribution of ASOs in HD-Relevant Brain Areas*

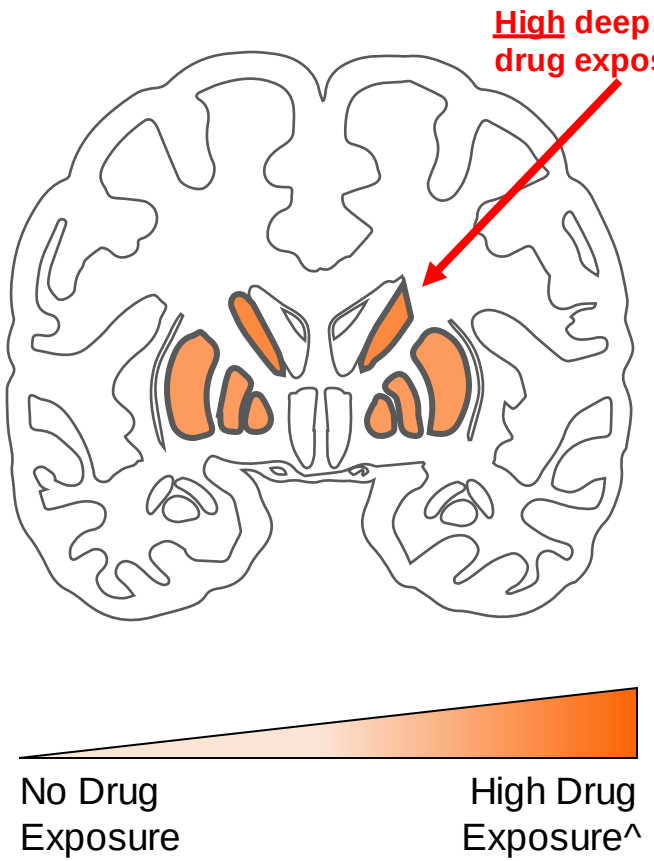
Key Brain Areas in HD



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

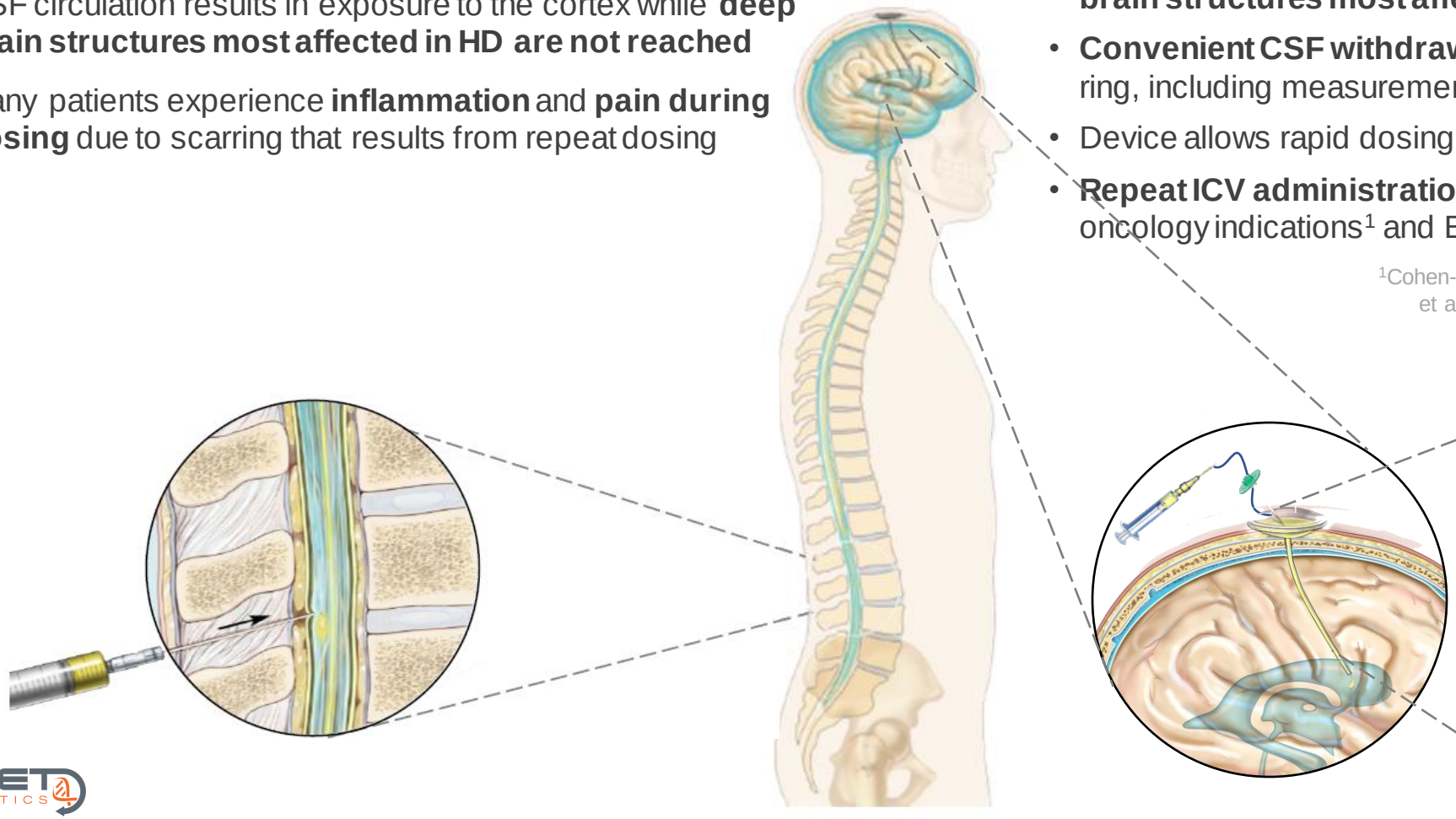
IT Delivery

- 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



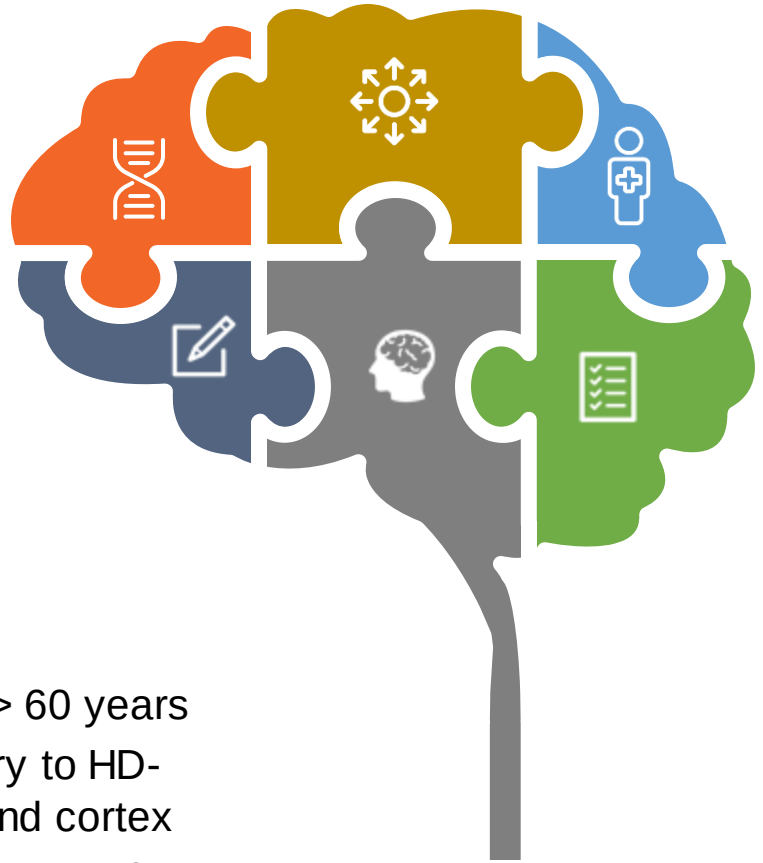
Size of a dime

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

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