WVE-003: An investigational first-in-class allele-selective mutant huntingtin-lowering molecule in Huntington's Disease

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WAVE™ LIFE SCIENCES

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Disclosures

- Jane Atkins in an employee of Wave Life Sciences

WAVE LIFE SCIENCES HAS BEEN DEDICATED TO HD FOR MORE THAN A DECADE



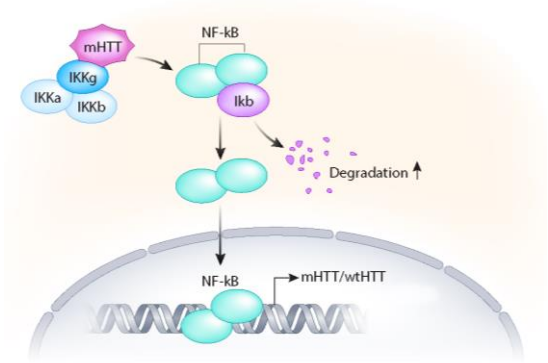
Allele-selective silencing of mHTT is a promising therapeutic strategy for HD

- Allele-selective silencing has the potential to impact multiple pathogenic mechanisms in HD
- WVE-003 robustly and durably lowered mutant huntingtin (mHTT) while sparing wild type huntingtin (wtHTT), exceeding our predefined criteria of ≥30% CSF mHTT lowering
- Wave's SELECT-HD clinical trial for WVE-003 demonstrated the first correlation between selective mHTT lowering and slowing of caudate atrophy
- Wave is planning a global, potentially registrational Phase 2/3 study of WVE-003 using caudate atrophy as a primary endpoint

mHTT is toxic and can interfere with normal wtHTT function

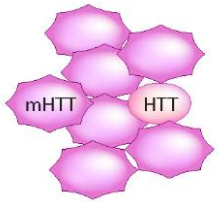
Aberrant mHTT complexes induce transcriptional dysregulation, impacting *HTT* gene expression

- By activating IKK complexes, mHTT disrupts physiological control over *HTT* gene expression; lowering mHTT should relieve its detrimental effect on wtHTT expression

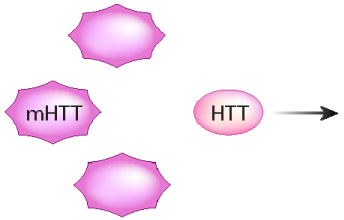


mHTT misfolds and forms aggregates with toxic properties, which can have a detrimental effect on wtHTT function

- Lowering mHTT is expected to restore availability of co-aggregated proteins, including wtHTT, to the cell where they can carry out their functions



Sequestered wild-type HTT



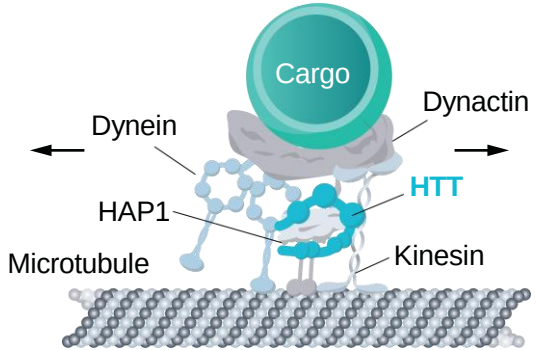
- Trafficking
- Gene expression
- DNA repair
- Neuronal repair & regeneration
- Ciliogenesis
- Mitosis
- CSF

Saudou & Humbert 2016 Neuron; Cason et al., 2022 Nat Rev Cell Biol; Laundos et al., 2023 Front Cell Dev Biol; Kaliszewski et al., 2015 Cell Death Diff; Keryer et al., 2011 J Clin Invest
Khoshnan & Patterson, 2011. Neurobiol Dis; Pogoda et al., 2021 Curr Med Chem; Hsiao et al., 2013 Hum Mol Genet

wtHTT is critical for normal brain function

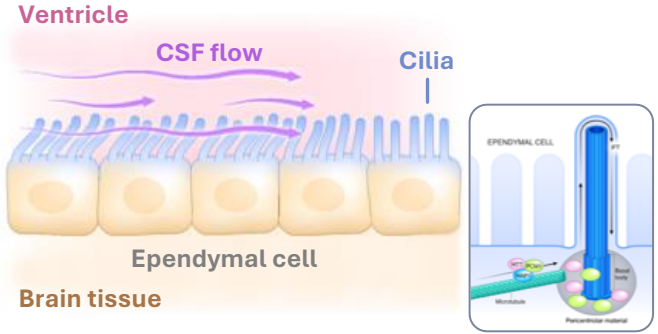
wtHTT supports health and function of neurons

- wtHTT (a scaffold protein) interacts with numerous protein partners, influencing various cellular processes, including vesicular and organelle trafficking, to support the health and function of neurons



wtHTT is crucial for cilia health

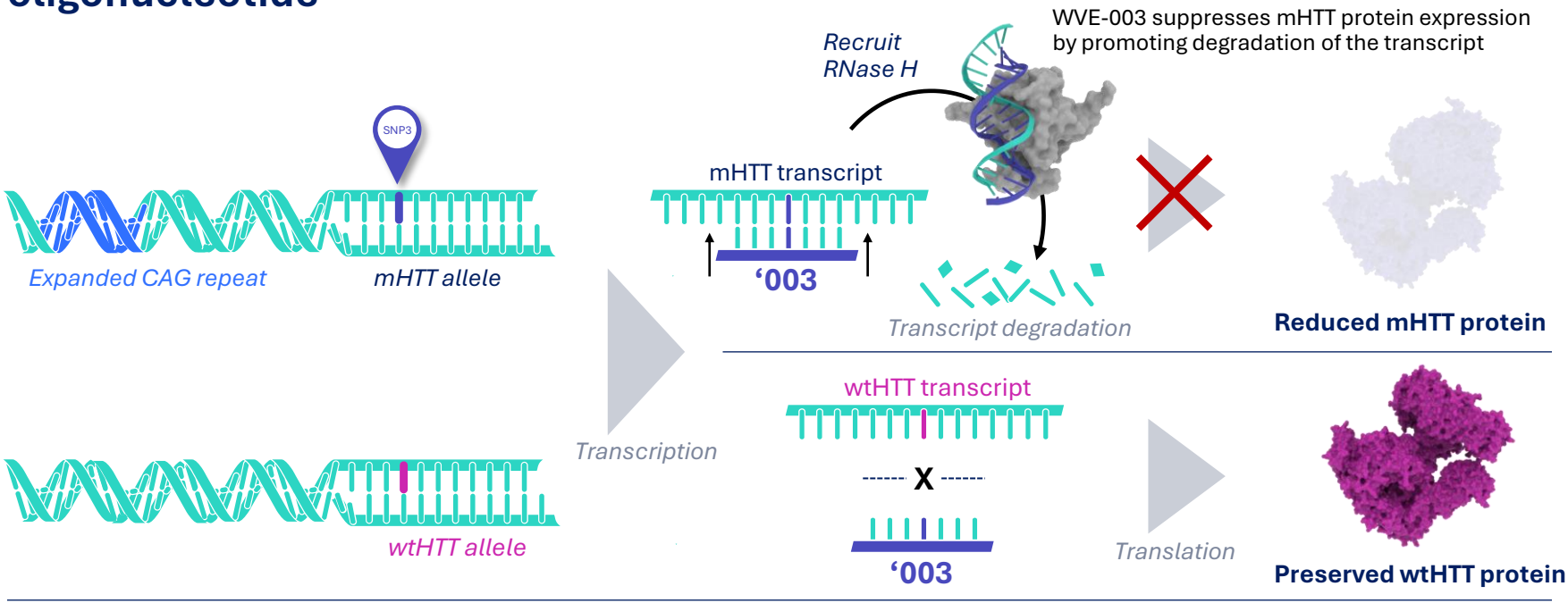
- In the absence of wtHTT, cilia formation and function is compromised, disrupting CSF flow, causing hydrocephalus



Only an allele-selective approach can address both gain-of-function and loss-of-function disruptions driven by mHTT

Saudou and Humbert 2016 Neuron; Colin et al., 2008 EMBO J; Gauthier et al., 2004 Cell; Gunawardena et al., 2013 Neuron; Srehlow et al., 2007 Hum Mol Gen; Kaliszewski et al., 2015 Cell Death Diff; Keryer et al., 2011 JCI; Haremaki et al., 2015 Dev Biol; Liu and Zeitlin, 2011 JCI; Ibanez-Tallon et al., 2002 Hum Mol Gen; Dietrich et al., 2009 Hum Mol Gen

WVE-003: Investigational first-in-class allele-selective mHTT lowering oligonucleotide



Molecular Therapy Nucleic Acids

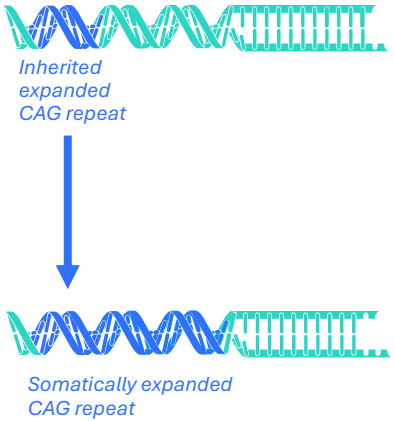
Preclinical data published in *Molecular Therapy Nucleic Acids*

Iwamoto *et al.*, *Mol Ther Nuc Acids* 2024 DOI: 10.1016/j.omtn.2024.102246

An allele-selective approach will address the second step of somatic expansion by reducing levels of potential pathogenic drivers

STEP 1: Length of CAG repeat increases over time

- Role for DNA repair (e.g. MSH3, PMS1), transcriptional read-through, DNA replication

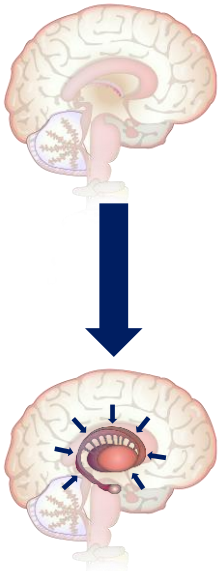


pathogenic process

- Molecular driver(s) not yet identified
- mHTT mRNA and protein are potential contributors

STEP 2: Neurodegeneration

- Somatic expansion associated with caudate atrophy



Hong et al., 2021 J Hunt Dis; Matlik et al., 2024 Nat Genet; Aldous et al., 2024 Brain; Handsaker et al 2025 Cell; Mouro Pinto et al., 2025 Nat Genet; Bunting et al., 2025 SciTM; Scahill et al., 2025 Nat Med

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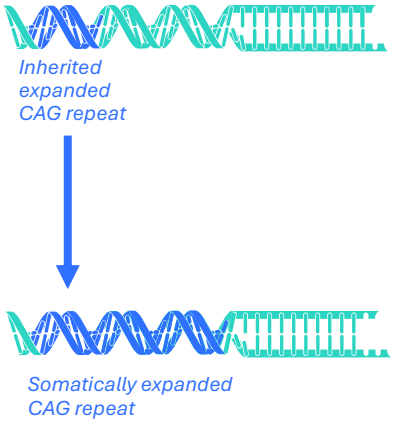

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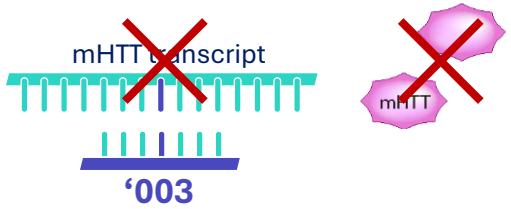

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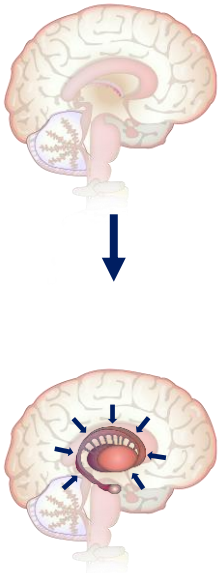

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Multiple 30 mg doses of WVE-003 demonstrated a favorable safety profile and confirmed the allele-selective mechanism of action

- SELECT-HD was an adaptive Ph1b/2a randomized, placebo-controlled, double-blind clinical trial designed to rapidly assess WVE-003 in HD

- First clinical demonstration of allele-selective lowering of mHTT, exceeding our predefined criteria of ≥30% CSF mHTT lowering (see poster #54)
  - Mean mHTT reductions up to 46% compared with placebo (30mg Q8W, P=0.0007)
  - Durable mHTT reduction, with mean 44% lowering maintained for at least 12 weeks after dosing
  - wtHTT levels were preserved throughout single and multidose phases
  - Modeling of single and multidose data support Q12W dosing

Poster #54

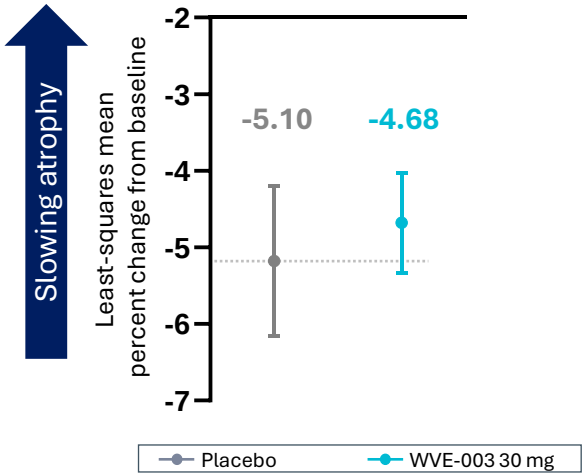
- Some CSF NfL elevations observed, not correlated with severity or number of AEs

- 30 mg WVE-003 Q8W was generally safe and well-tolerated*
  - AEs were balanced across cohorts, mild or moderate in intensity
  - Imbalance in treatment-related AEs, mild or moderate in intensity

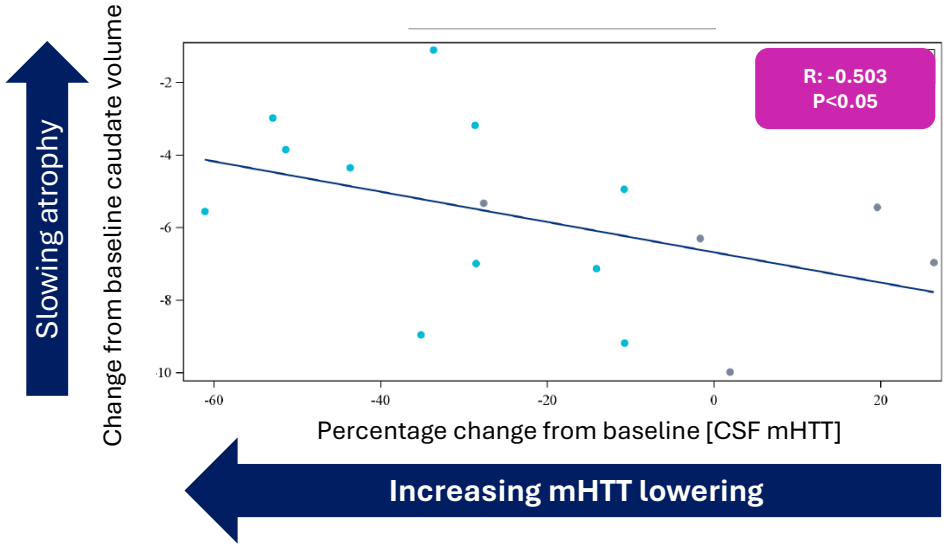
*Safety data are from completed study results presented on June 25, 2024. Five months after a patient completed their final safety visit, an SAE was reported that we assessed to be not-related to WVE-003. Q8W: every 8 weeks; AE: adverse event; SAE: serious adverse event; CSF: cerebrospinal fluid; NfL: neurofilament light

Slowing of caudate atrophy associated with mHTT lowering, WVE-003 exposure

Normalized caudate volume



mHTT lowering associated with slowing caudate atrophy



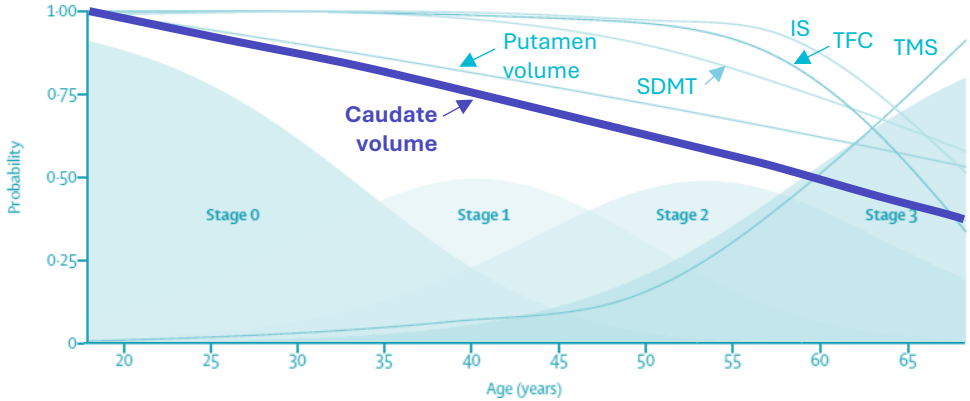
Similar association observed between slowing atrophy and increasing WVE-003 CSF concentration

Baseline MRI single-dose day 1-3 MRI; final MRI multidose day 169; Volumes derived through Jacobian integration after normalization in MNI space
Results are from mixed model repeated measures (MMRM) analysis; CSF mHTT concentration: single-dose baseline, multidose day 141

Preservation of caudate volume is expected to predict clinical benefit in HD

- Medium spiny neurons, the primary neurons of the caudate and putamen, are sensitive to mHTT-induced toxicity and death in HD[1]
- Caudate and putamen vMRI consistently provide the earliest biomarkers for brain atrophy, with annualized striatal volume loss ~3-5%[2]
- Loss of caudate volume is a landmark for classification in Stage 1 in the HD-ISS [2]
- Caudate volume is associated with cognitive, motor, and functional measures[3]

HD-ISS stage probability and predicted clinical landmark changes as a function of age



Adapted from Tabrizi 2022

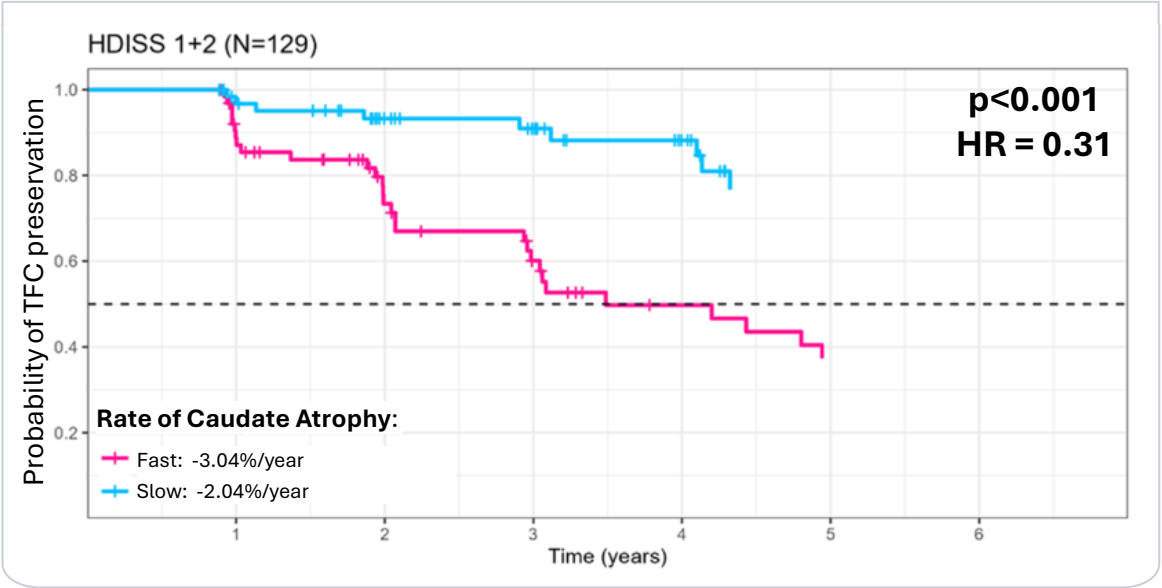
1. Saudou et al., 2016 Neuron; Handsaker et al., 2025 Cell; Matlik et al., 2024 Nat Genet; 2. Tabrizi et al., 2022 Lancet, Liu et al., 2023 Brain Comm, Tabrizi et al., 2012 Lancet Neurol; Scahill et al., 2025 Nat Med; 3. Papoutsi et al., 2024 CHDI poster, Tabrizi et al., 2012 Lancet, Dominguez et al., 2016 British J Psych vMRI: volumetric MRI; CSF: Cerebrospinal fluid

Internal analysis of natural history data demonstrates a 1% difference in rate of atrophy is associated with a delayed onset of disability by ≥7.5-years

TRACK-HD, PREDICT-HD

- HD-ISS 1 + 2
- CAG ≥ 42
- TFC = 13 at baseline
- 3T MRI
- Freesurfer 6.0
- Cox Model to predict time-to-TFC loss based on log caudate volume change

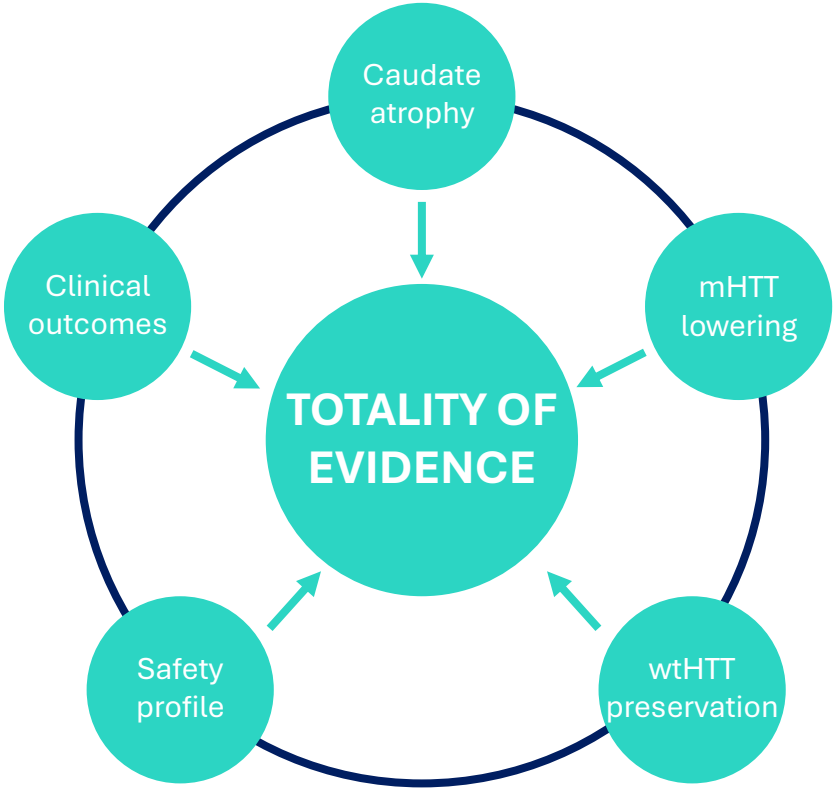
Slower decline in caudate volume associated with probability of TFC preservation in HD natural history data



TRACK-HD (n=366) and PREDICT-HD (n=1,078) are longitudinal HD natural history studies that include MRI brain imaging, clinical outcome assessments. Paulson et al., Neurosci.2014, Tabrizi et al., Lancet Neurol 2009, Tabrizi et al., Lancet Neurol 2012, Tabrizi et al., Lancet Neurol. 2013
TFC: Total Functional Capacity

Use of biomarkers as endpoints to support drug approval has the potential to rapidly bring disease-modifying medicines to patients

- There remains a high unmet need for disease-modifying medicines for people living with HD
- We need to work with urgency to design safe and efficient studies
- We intend to use caudate atrophy as a primary endpoint, together with other biomarkers, to rapidly advance WVE-003 for the treatment of HD

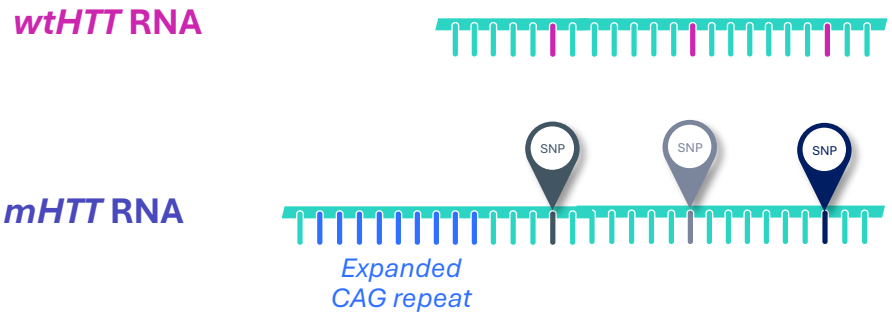


Advancing Wave's allele-selective approach for the treatment of HD

Next steps for WVE-003: Ph2/3 study

- Planning underway, including key aspects of study design, for a global, potentially registrational Phase 2/3 study in adults with SNP3 and HD
- Using caudate atrophy as a primary endpoint
- Expect to submit IND application in 2H 2025

Next steps for allele-selective silencing: Targeting additional SNPs on *mHTT*



Development of additional SNP-targeted candidates can bring allele-selective silencing to a broader population of people living with HD

SNP: single nucleotide polymorphism; wtHTT: wild type huntingtin; mHTT: mutant huntingtin;

Acknowledgements

THANK YOU to SELECT-HD participants and their families

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- Ray Dorsey
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Wave Colleagues and Study Team

SELECT-HD Investigators

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