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Innovations that led to SELECT-HD, a phase 1b/2a clinical trial of an allele-selective therapy for Huntington's Disease

Michael A. Panzara, MD, MPH

Chief Medical Officer, Head of Therapeutics Discovery and Development

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Forward-looking statements

This document contains forward-looking statements. All statements other than statements of historical facts contained in this document, including statements regarding possible or assumed future results of operations, preclinical and clinical studies, business strategies, research and development plans, collaborations and partnerships, regulatory activities and timing thereof, competitive position, potential growth opportunities, use of proceeds and the effects of competition are forward-looking statements. These statements involve known and unknown risks, uncertainties and other important factors that may cause the actual results, performance or achievements of Wave Life Sciences Ltd. (the "Company") to be materially different from any future results, performance or achievements expressed or implied by the forward-looking statements. In some cases, you can identify forward-looking statements by terms such as "may," "will," "should," "expect," "plan," "aim," "anticipate," "could," "intend," "target," "project," "contemplate," "believe," "estimate," "predict," "potential" or "continue" or the negative of these terms or other similar expressions. The forward-looking statements in this presentation are only predictions. The Company has based these forward-looking statements largely on its current expectations and projections about future events and financial trends that it believes may affect the Company's business, financial condition and results of operations. These forward-looking statements speak only as of the date of this presentation and are subject to a number of risks, uncertainties and assumptions, including those listed under Risk Factors in the Company's Form 10-K and other filings with the SEC, some of which cannot be predicted or quantified and some of which are beyond the Company's control. The events and circumstances reflected in the Company's forward-looking statements may not be achieved or occur, and actual results could differ materially from those projected in the forward-looking statements. Moreover, the Company operates in a dynamic industry and economy. New risk factors and uncertainties may emerge from time to time, and it is not possible for management to predict all risk factors and uncertainties that the Company may face. Except as required by applicable law, the Company does not plan to publicly update or revise any forward-looking statements contained herein, whether as a result of any new information, future events, changed circumstances or otherwise.

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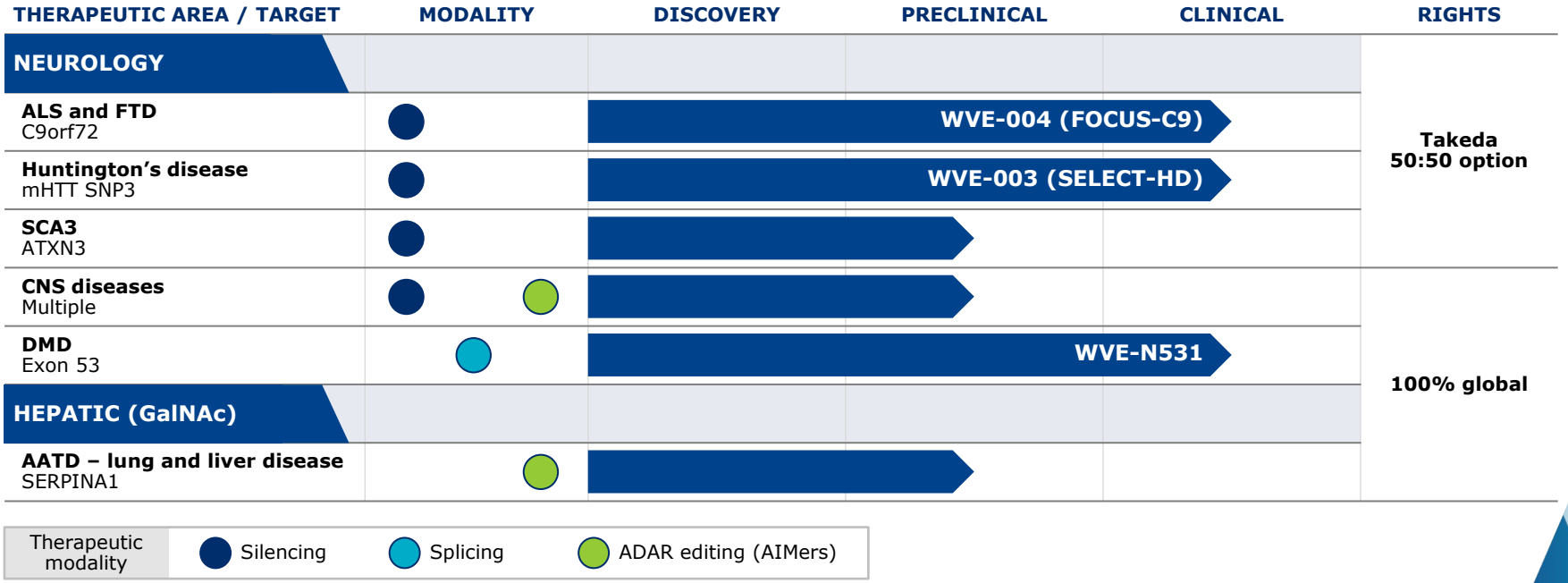
Wave Life Sciences

We are a genetic medicines company focused on delivering transformational therapies for people with serious, genetically-defined diseases



ALS: Amyotrophic lateral sclerosis; FTD: Frontotemporal dementia; SCA3: Spinocerebellar ataxia 3; CNS: Central nervous system; DMD: Duchenne muscular dystrophy; AATD: Alpha-1 antitrypsin deficiency

Leveraging learnings from PRECISION-HD studies

PRECISION HD1 & PRECISION HD2

- mHTT results from PRECISION-HD trials did not support further development of WVE-120102 or WVE-120101
- No worsening of disease progression in treated participants versus expected based on natural history

- Genotyping assay to improve efficiency of patient identification
- Biomarker assay to measure wild-type HTT protein in CSF
- Clinical experience of sites from PRECISION-HD1 and PRECISION-HD2 trials
- Starting dose informed by preclinical *in vivo* models
  - WVE-003 development includes insights on PK/PD relationships in multiple species

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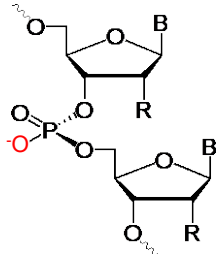
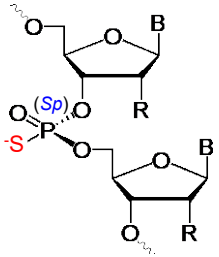
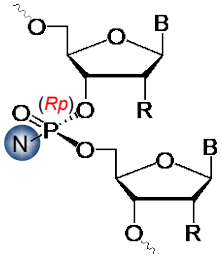
WVE-003 contains novel PN backbone chemistry

PRISM™ backbone linkages

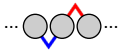
PO	PS	PN





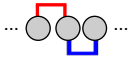


Chirality
None



Chirality

PS backbone *Rp*
PS backbone *Sp*



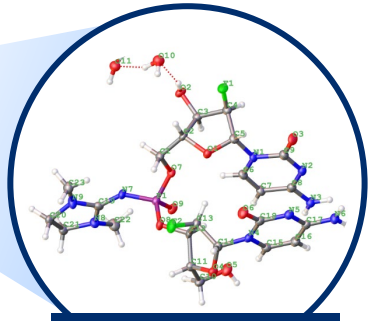
Chirality

PN backbone *Rp*
PN backbone *Sp*

Negative charge

Negative charge

Neutral charge



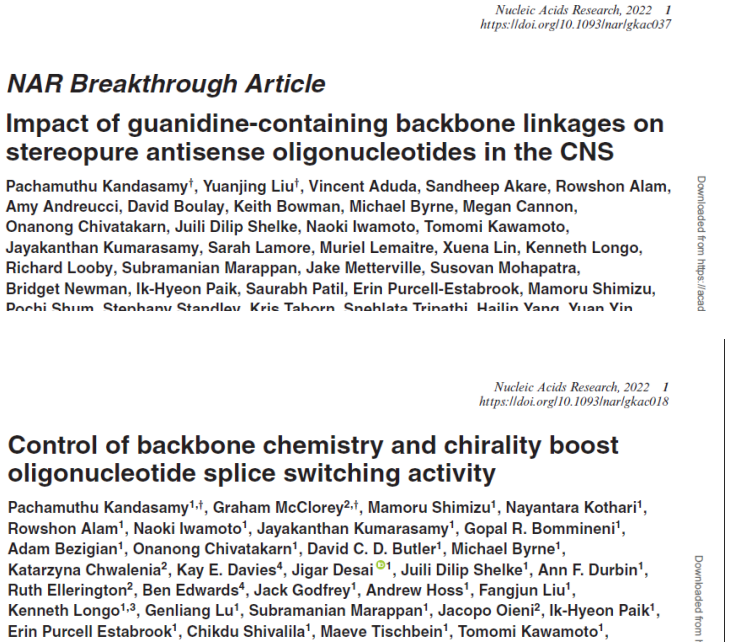
Phosphoryl guanidine x-ray structure

example

PO: phosphodiester PS: phosphorothioate PN: phosphoryl-guanidine

PN chemistry substantially improves oligonucleotide pharmacology in preclinical studies

Breakthrough Articles from NUCLEIC ACIDS RESEARCH



Nucleic Acids Research, 2022 1
https://doi.org/10.1093/nar/gkac037

NAR Breakthrough Article

Impact of guanidine-containing backbone linkages on stereopure antisense oligonucleotides in the CNS

Pachamuthu Kandasamy†, Yuanjing Liu†, Vincent Aduda, Sandheep Akare, Rowshon Alam, Amy Andreucci, David Boulay, Keith Bowman, Michael Byrne, Megan Cannon, Onanong Chivatakarn, Juili Dilip Shelke, Naoki Iwamoto, Tomomi Kawamoto, Jayakanthan Kumarasamy, Sarah Lamore, Muriel Lemaitre, Xuena Lin, Kenneth Longo, Richard Looby, Subramanian Marappan, Jake Metterville, Susovan Mohapatra, Bridget Newman, Ik-Hyeon Paik, Saurabh Patil, Erin Purcell-Estabrook, Mamoru Shimizu, Pochi Shum, Stephany Standley, Kris Taborn, Snehlata Tripathi, Hailin Yang, Yuan Yin

Nucleic Acids Research, 2022 1
https://doi.org/10.1093/nar/gkac018

Control of backbone chemistry and chirality boost oligonucleotide splice switching activity

Pachamuthu Kandasamy[1,†], Graham McClorey[2,†], Mamoru Shimizu[1], Nayantara Kothari[1], Rowshon Alam[1], Naoki Iwamoto[1], Jayakanthan Kumarasamy[1], Gopal R. Bommineni[1], Adam Bezigian[1], Onanong Chivatakarn[1], David C. D. Butler[1], Michael Byrne[1], Katarzyna Chwalenia[2], Kay E. Davies[4], Jigar Desai[1], Juili Dilip Shelke[1], Ann F. Durbin[1], Ruth Ellerington[2], Ben Edwards[4], Jack Godfrey[1], Andrew Hoss[1], Fangjun Liu[1], Kenneth Longo[1,3], Genliang Lu[1], Subramanian Marappan[1], Jacopo Oieni[2], Ik-Hyeon Paik[1], Erin Purcell Estabrook[1], Chikdu Shivalila[1], Maeve Tischbein[1], Tomomi Kawamoto[1],

Benefits of PN chemistry in CNS

- ✓ Increased potency in neurons
- ✓ Well-tolerated in multiple *in vitro* & *in vivo* assays
- ✓ Increased potency & extended durability of silencing in mice
- ✓ Enhanced tissue exposure in mice

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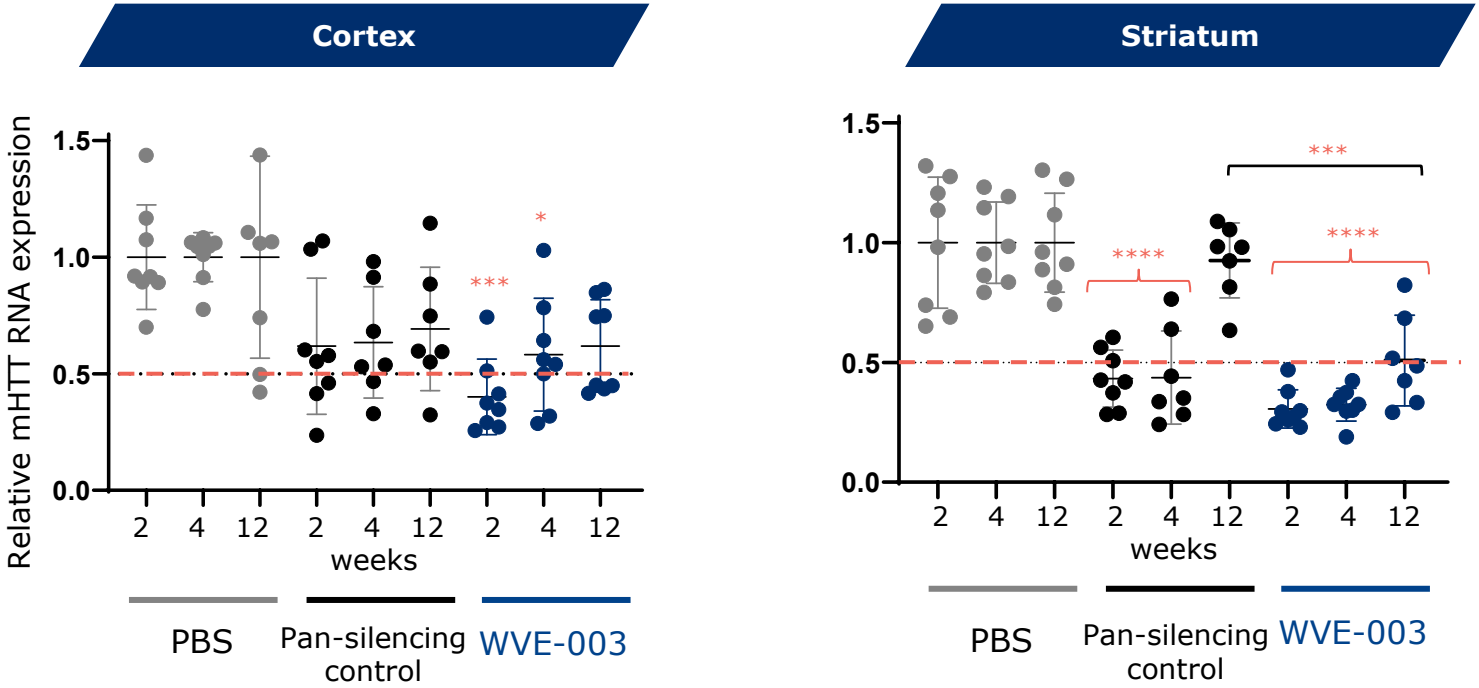
Papers published in *Nucleic Acids Research*: Kandasamy et al., 2022 doi: 10.1093/nar/gkac037; Kandasamy et al., 2022 doi: 10.1093/nar/gkac018

WVE-003 has potent and durable effects in mouse cortex and striatum

Maximum knockdown of 75% with ~50% knockdown persisting for at least 3 months

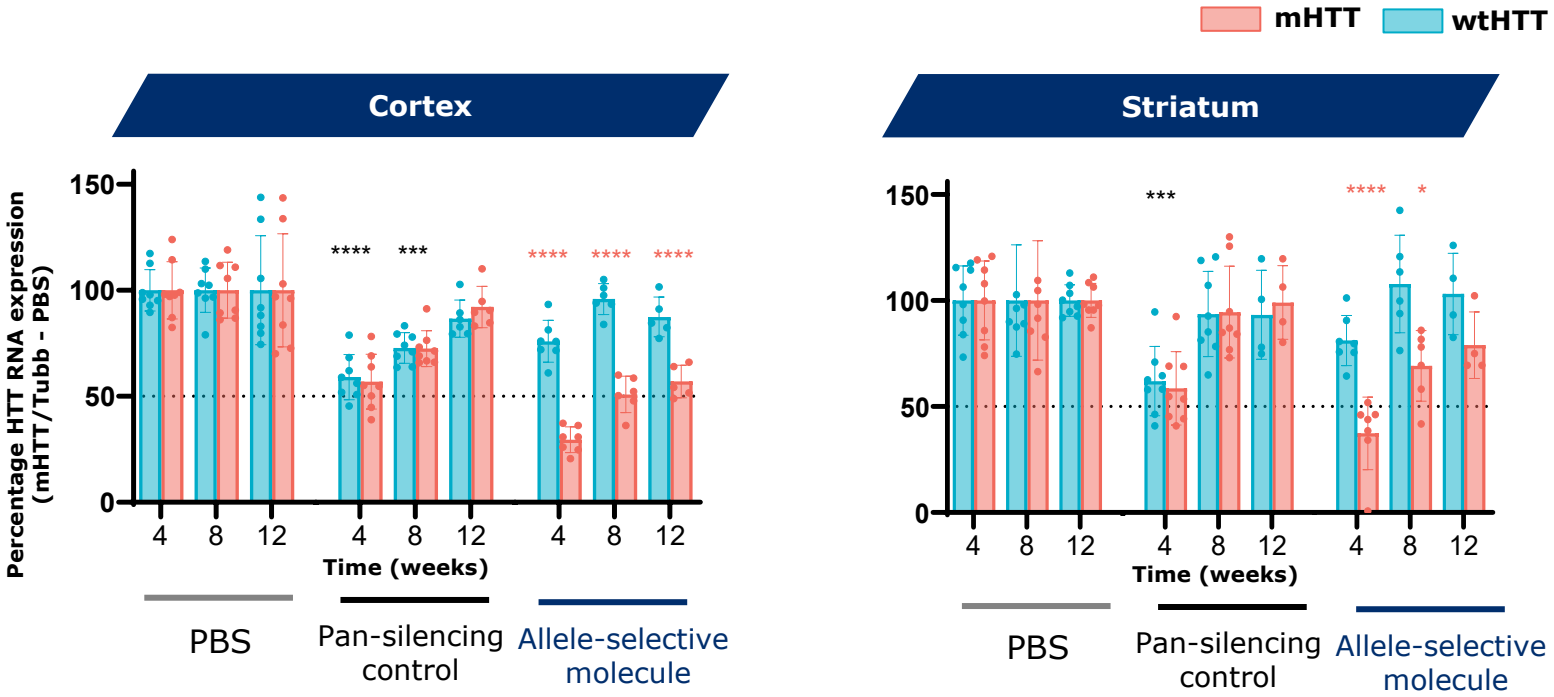


BACHD mouse

BACHD mice administered 3x100 μg intracerebroventricular doses PBS or oligonucleotide. (Left) Relative mHTT RNA in cortex at 2, 4 and 12-weeks post-dosing. (Right): Relative mHTT in striatum at same time points as cortex. BACHD contains SNP3 only in some mHTT transgenes. Data are mean ± SD, n=8. *P<0.0332, ***P<0.0002, ****P<0.0001 versus PBS unless otherwise noted). P values were calculated via 1-way analysis of variance. mHTT, mutant HTT; Tubb, tubulin

Allele-selective activity in CNS of Hu97/18 mice

Allele-selective molecule decreases mHTT, spares wtHTT, whereas pan-acting molecule uniformly decreases wtHTT and mHTT



Hu97/18 mouse

Hu97/18 mice administered 3x100 μg intracerebroventricular doses PBS or oligonucleotide. Relative mHTT RNA in cortex (left) striatum (middle) or hippocampus (right) at 4, 8 and 12-weeks post-dosing. Data are mean ± SD, n=8. Stats: ns non-significant, *P<0.05, **P<0.01, ***P<0.0001, ****P<0.0001 versus PBS by 1-way ANOVA. mHTT, mutant HTT; wtHTT, wild-type HTT; Tubb, tubulin

Preclinical pharmacological modeling available to inform clinical starting dose

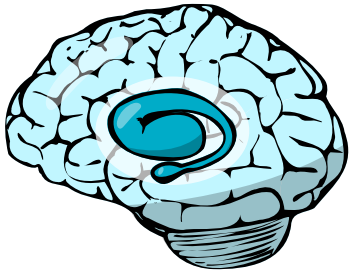
BACHD

Ascending dose studies
- PK & mHTT knockdown data
- IC_{50} determination

NHP

Concentrations in **cortex** and **striatum** sufficient for target engagement (administration by LP)

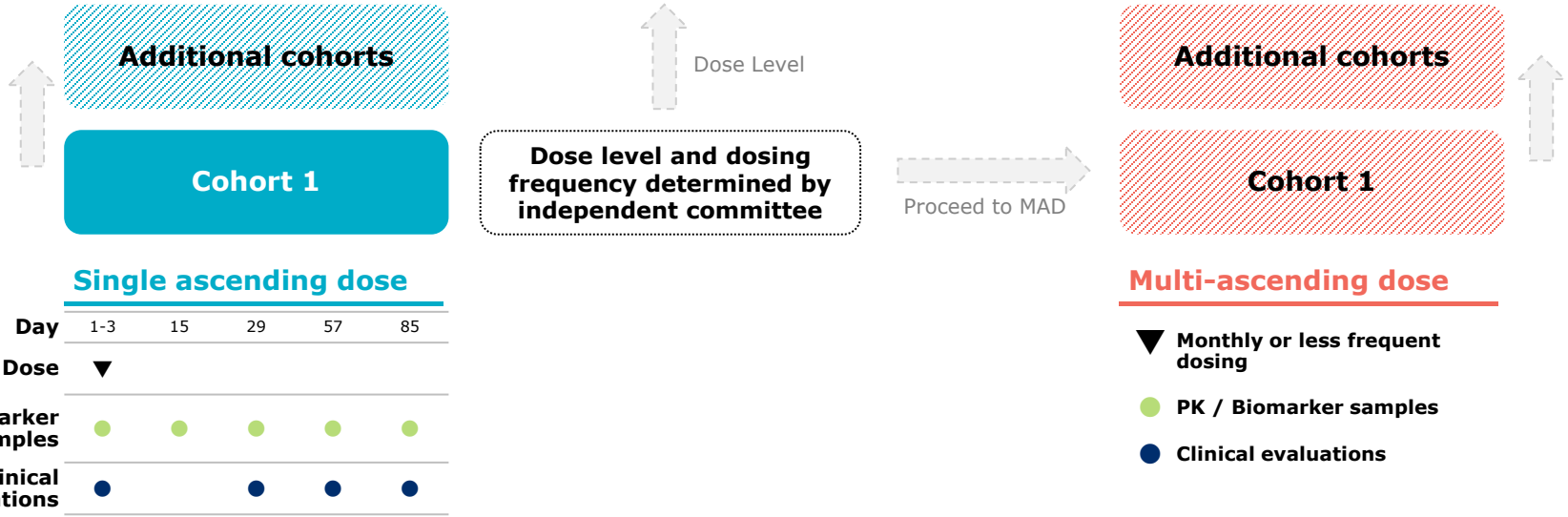
Human
(cortex, striatum)



Anticipated mHTT knockdown in **cortex** and **striatum**

PK: pharmacokinetic PD: pharmacodynamic IC_{50}: the concentration of observed half of the maximal effect mHTT: mutant huntingtin protein

SELECT-HD: Adaptive trial design enables data-driven refinement of dosing regimen



SELECT HD

Clinicaltrials.gov identifier: NCT05032196

Clinical evaluations
- Safety and tolerability
- UHDRS

Key biomarkers:
- Mutant HTT
- Wild-type HTT
- NfL

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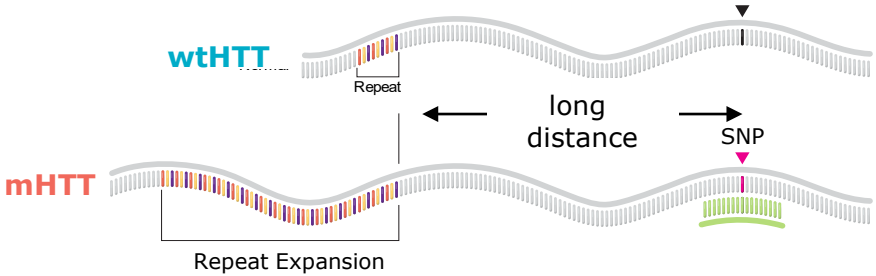
Adaptive cohorts

PK: pharmacokinetic mHTT: mutant HTT wtHTT: wild-type HTT NfL: neurofilament light chain

Innovations facilitate enrollment of genetically defined patient population



Allele selectivity by SNP targeting

- SNP located far from CAG repeat
- Confirm presence of SNP variant
- Confirm location of SNP variant *only* on mHTT

	PRECISION-HD Phasing Assay	SELECT-HD Phasing Assay
Equipment	Long-range sequencer PCR & CE system	PCR & CE system
Time	**Months**	**Days-weeks**
Sample	~20 mL whole blood	~10 mL whole blood

- ✓ More accessible equipment & processing power
- ✓ Faster turnaround
- ✓ Lower patient burden (less sample needed)

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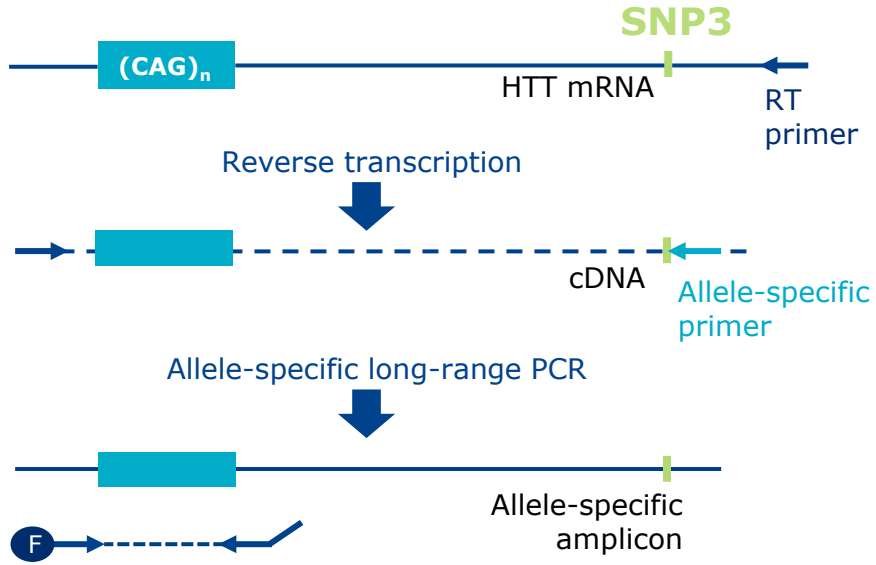
mHTT, mutant huntingtin; SNP, single nucleotide polymorphism; PCR, polymerase chain reaction; CE, capillary electrophoresis;, mL, milliliter

Rapid patient identification

Investigational assay enables SNP genotyping and phasing with CAG-repeat expansion



AmplideX® PCR/CE *HTT* assay

- CAG length, SNP zygosity and phasing information from a single assay
- PCR-based assay using *in vitro* diagnostic device ready capillary electrophoresis (CE) platform
- CLIA validated
- 1-2 weeks turn around time

SNP single nucleotide polymorphism; PCR polymerase chain reaction; CLIA Clinical Laboratory Improvement Amendments
Cartoon adapted from poster presented at AMP 2020 by Sarah Statt (Asuragen)

Assessment of wtHTT protein in CSF

Improvements to tHTT assay & depletion of mHTT key to quantification of wtHTT

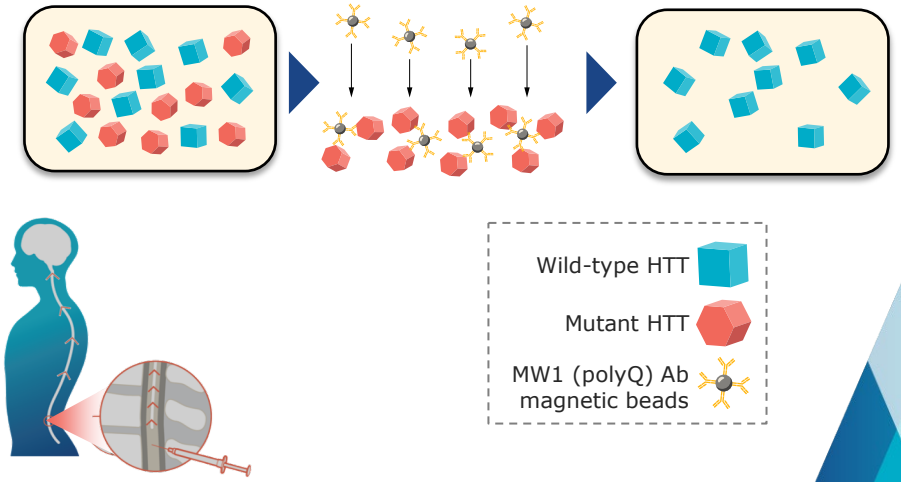
Parameters	Initial	Improved
LLoQ	1.3 fM (floating)	7.3 fM
Assay range	1.3 – 2,000 fM	2.92 – 1,500 fM
QC sample accuracy & precision	X	√
Stability	X	√

Acceptance criteria for tHTT updated to support wtHTT protein quantification method
- QC to calibrate low, mid and high concentration ranges
- QC to calibrate immunoprecipitation

Step 1:
- Quantify tHTT (improved 2B7-D7F7 assay)
- If tHTT ≥20 fM, go to step 2

Step 2:
Immunodeplete mHTT with polyQ Ab magnetic beads

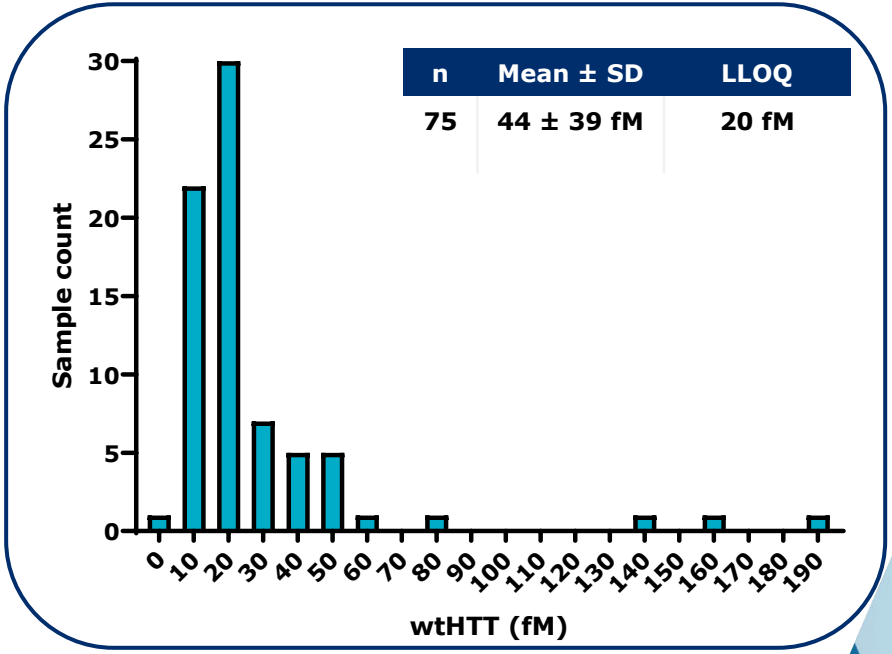
Step 3:
- Re-test sample with tHTT assay
- Remaining HTT is surrogate of wtHTT protein



Ab, antibody; CSF, cerebrospinal fluid; mHTT, mutant HTT protein; wtHTT wild-type HTT; polyQ, polyglutamine; tHTT, total HTT
MW1: Wild et al., J Clin Invest, 2015.

wtHTT quantification method performs reliably

- Evaluated precision, spike recoveries, assay range and sensitivity in CSF
  - Free MW1 Ab dilution of ≥1:200 minimizes interference with tHTT assay
  - Depletion with MW1 has an acceptable level of specificity when tHTT levels are ≥20 fM
  - MW1-mediated depletion of mHTT is efficient across mHTT:wtHTT ratios tested
- Method applied to quantify wtHTT in CSF samples from patients with HD



CSF, cerebrospinal fluid; Ab, antibody; fm, femtamolar; m, mutant; wt, wild-type; t. total

Wave remains committed to an allele-selective approach in HD

- **Innovations led to SELECT-HD, a Phase 1b/2a clinical trial**
  - **Advances in oligonucleotide chemistry & design:** Wave's novel PN backbone chemistry
  - **Preclinical pharmacological modeling**: informed clinical starting dose
  - **Rapid patient identification:** improved phasing assay
  - **New biomarker:** development & qualification of a new wtHTT protein quantification method
  - **Adaptive trial design:** enable data-driven changes to dose level & frequency while trial ongoing

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Acknowledgements

On behalf of Wave, thank you to all the patients, families, advocacy organizations, healthcare providers, and regulators with whom we have collaborated, particularly the study participants and families in PRECISION-HD and SELECT-HD

- **SELECT-HD Investigators**
- **SELECT-HD Clinical Advisory Committee**
  - Daniel Claassen
  - Mary Edmondson
  - Ray Dorsey
  - Ralf Reilmann
- **CHDI**
- **Asuragen**
- **EVOTEC**
- **IRBM**
- **Wave's scientists and Study Team**

For additional information on SELECT-HD contact clinicaltrials@wavelifesci.com or visit clinicaltrials.gov (NCT05032196)

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