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Fondazione LIRH
LEGA ITALIANA RICERCA HUNTINGTON E MALATTIE CORRELATE - ONLUS

Convegno annuale LIRH ONLUS

LA RICERCA *sulle malattie rare e* LE PROSPETTIVE *di cura per la malattia di* HUNTINGTON

Roma, sabato 2 Dicembre, 2017
Ore 9:30-16:00 Sala Loyola – Roma Eventi
Piazza della Pilotta 4 (Fontana di Trevi)

Developing Therapies to Selectively Silence Mutant Huntingtin

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Wave Life Sciences

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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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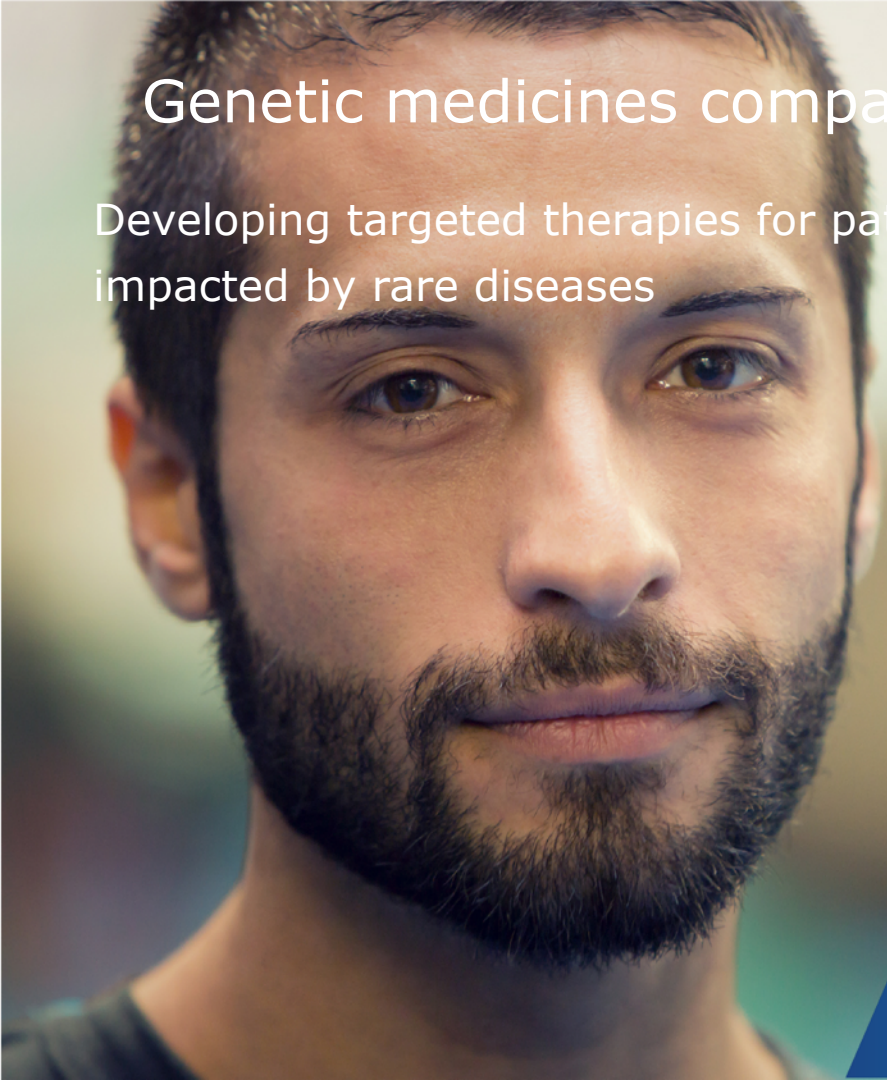

Genetic medicines company

Developing targeted therapies for patients impacted by rare diseases

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- Leadership and entire team is patient focused
- Rationally designed stereopure nucleic acid therapeutics
- Utilizing multiple modalities including antisense, exon skipping and RNAi
- Expertise and core focus in neurology
  - 2 Phase 1b/2a trials initiated in Huntington's disease
  - First Duchenne muscular dystrophy trial initiated
  - Clinical data readouts anticipated in 2019 for first 3 programs
- 90,000 sq feet of manufacturing space

Pipeline spanning multiple modalities, novel targets

	DISEASE	TARGET	BIOMARKER	ESTIMATED U.S. ADDRESSABLE PATIENTS *	MECHANISM	DISCOVERY	CANDIDATE	CLINICAL	NEXT ANTICIPATED MILESTONES
CNS	Huntington's disease ★	mHTT SNP1	mHTT	~10k / ~35k	A	●	●	Phase 1b/2a	Top line data 1H 2019
	Huntington's disease	mHTT SNP2	mHTT	~10k / ~35k	A	●	●	Phase 1b/2a	Top line data 1H 2019
	Amyotrophic lateral sclerosis	C9orf72	dipeptide	~1,800	A	●	●		Trial initiation Q4 2018
	Frontotemporal dementia	C9orf72	dipeptide	~7,000	A	●	●		Trial initiation Q4 2018
MUSCLE	Duchenne muscular dystrophy 51	exon 51	dystrophin	~2,000	E	●	●		Trial initiation Q4 2017
	Duchenne muscular dystrophy 53	exon 53	dystrophin	~1,250	E	●	○		Trial initiation Q1 2019
HEPATIC	Pfizer	APOC3			○	●	○		
	Pfizer	undisclosed			○	●	○		
	Pfizer	undisclosed			○	●	○		

A = allele-specific silencing. E = exon skipping.

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*Estimates of U.S. prevalence and addressable population by target based on publicly available data and are approximate.
*For Huntington's disease, numbers approximate manifest and pre-manifest populations, respectively

Creating a new class of oligonucleotides

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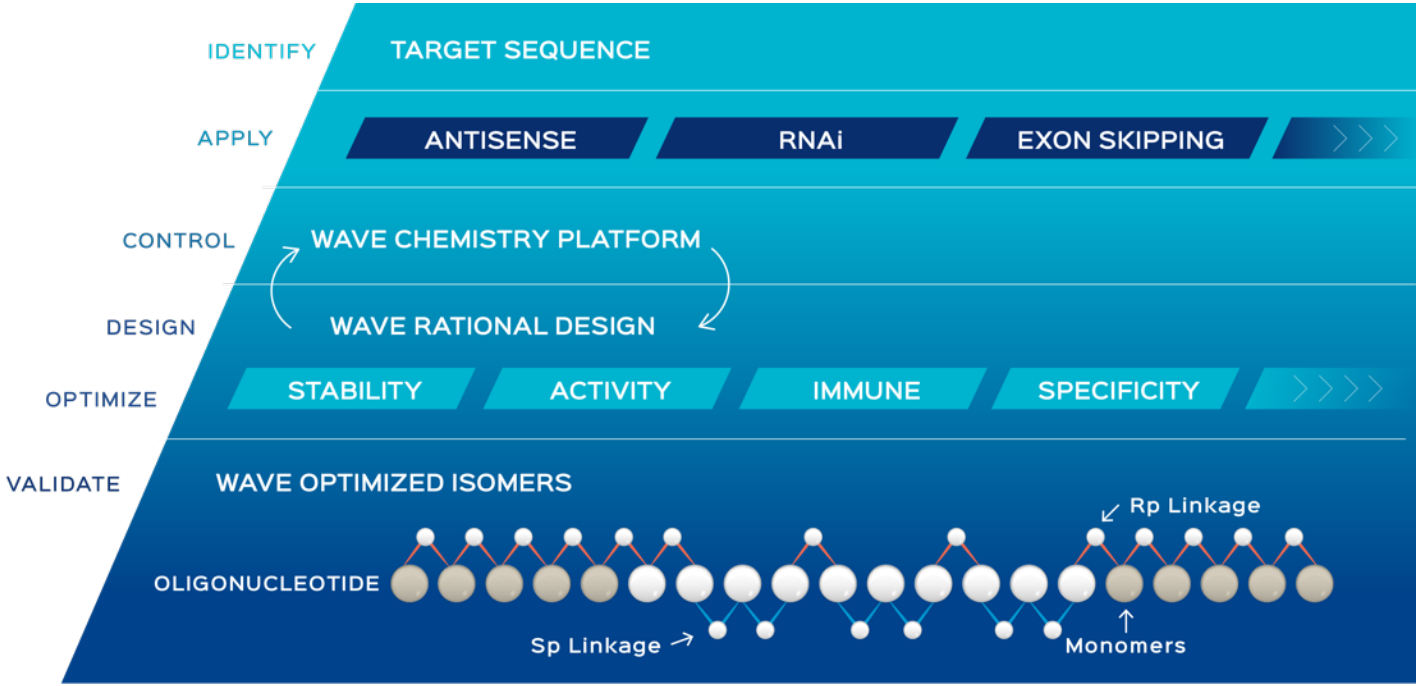


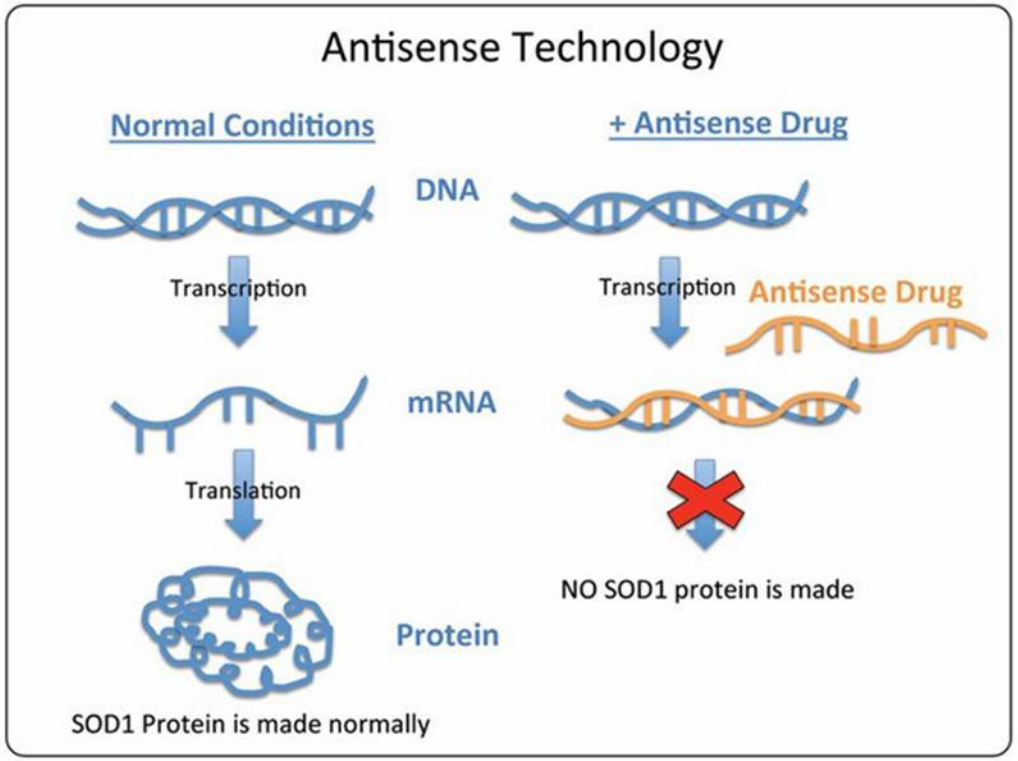
Source: Iwamoto N, et al. Control of phosphorothioate stereochemistry substantially increases the efficacy of antisense oligonucleotides. Nature Biotechnology. 2017.

What is Antisense?

- Antisense therapy is a form of treatment for genetic disorders or infections
- When the genetic sequence of a particular gene is known to cause a disease, it is possible to synthesize a strand of nucleic acid that will bind to the messenger RNA (mRNA) produced by that gene and inactivate it, or turn it off
- Antisense oligonucleotides (ASO's) are single strands of DNA or RNA that are complementary to a chosen sequence; In antisense gene therapy, short single-stranded pieces of chemically modified nucleotides, known as oligonucleotides are inserted into cells
- Oligonucleotides (oligos) have been under clinical development for approximately the past 30 years
- In treating HD, these strands would be complimentary to the MRNA that codes for the harmful huntingtin protein . After being inserted into the cell, oligos bind to the target mRNA and can inhibit the protein from being produced

Antisense Mechanism of Action

- Example



Antisense technology works to eliminate mutated protein by preventing it from being created.

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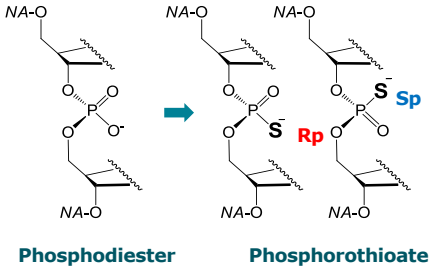
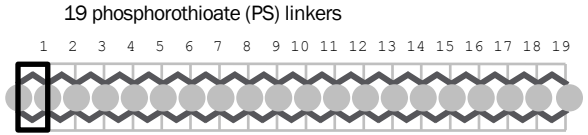
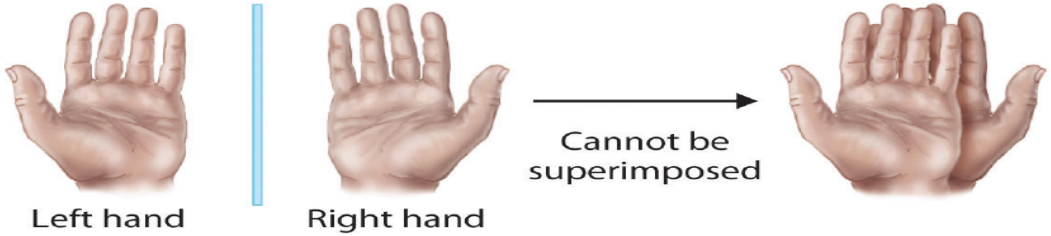
Chirality

- Phosphorothioate (PS) backbone modification is introduced into nucleic acid based therapies
  - Provides good stability and bio-availability
  - Adopts random three-dimensional arrangements during synthesis
  - Results in exponentially diverse drug mixtures with 2^N stereoisomers (N = number of PS)



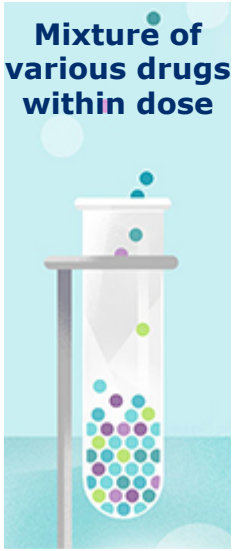


(2^{19} = 524,288)



Nucleic Acid Therapeutics

Traditional Method

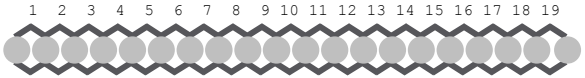


- Each nucleic acid therapeutic is made of strings of nucleotides held together by **chemical linkages**
- The **orientation of atoms at each linkage occurs randomly** using conventional synthesis, adopting either an "up" or "down" orientation
- These random orientations have implications for drug stability, efficacy, and safety

Wave Method

Uncontrolled

19 phosphorothioate (PS) linkers



(2^{19} = 524,288)

Controlled

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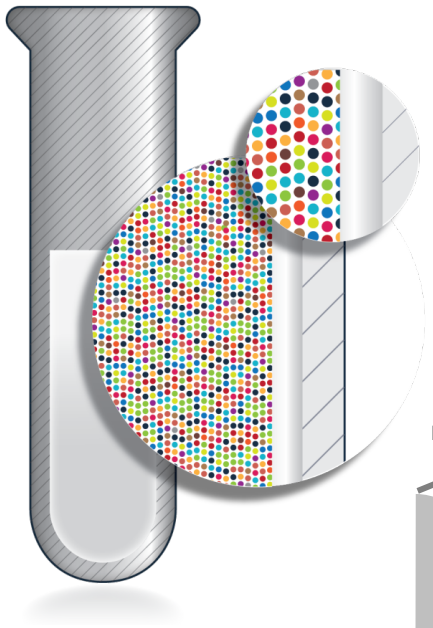
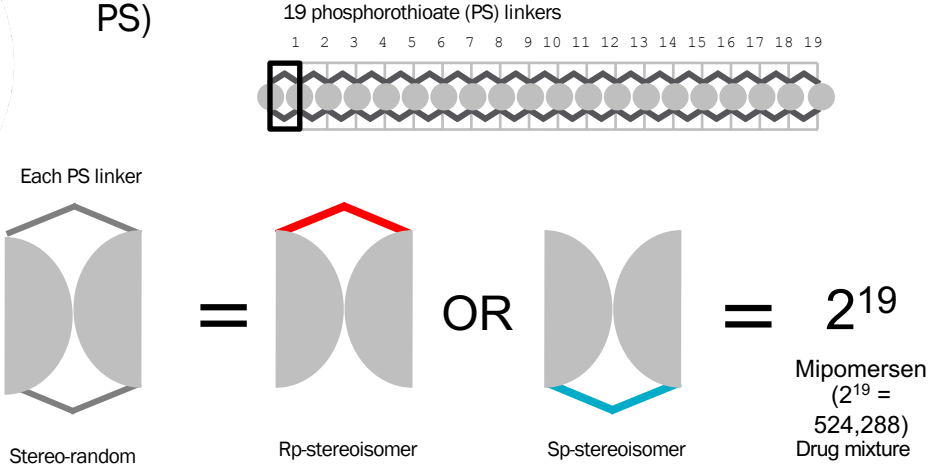
BACKGROUND



- Phosphorothioate (PS) chemical modifications introduced into nucleic acid based therapies adopt random three-dimensional arrangements during synthesis
- This results in exponentially diverse drug mixtures with 2^N stereoisomers (N = number of PS)



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Building the optimal, stereopure medicine

STANDARD OLIGONUCLEOTIDE APPROACHES

Pharmacologic properties include >500,000 permutations in every dose

Impact:
Unreliable therapeutic effects
Unintended off-target effects

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Stereochemistry enables precise control, ability to optimize critical constructs into one defined and consistent profile

Impact:
Potential for safer, more effective, targeted medicines that can address difficult-to-treat diseases

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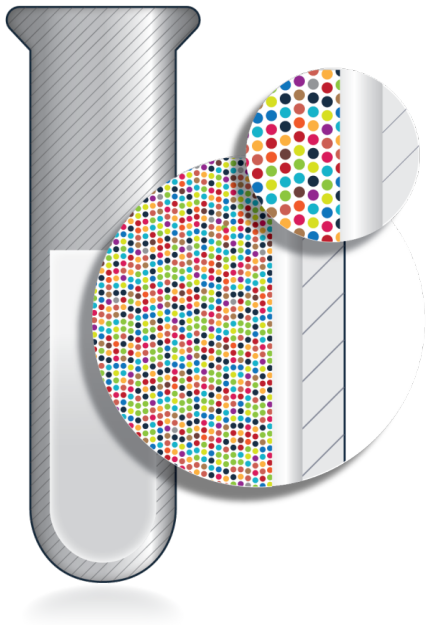
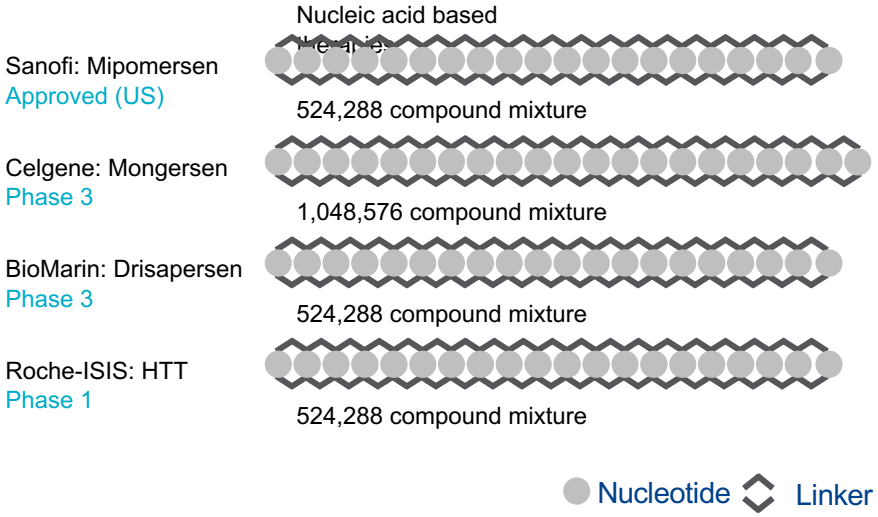
BACKGROUND



- Several nucleic acid based therapies have received FDA approval and many more are in development
- Only Wave's drugs are steropure isomers
- We believe that our technology can generate safer and more effective versions of these drugs



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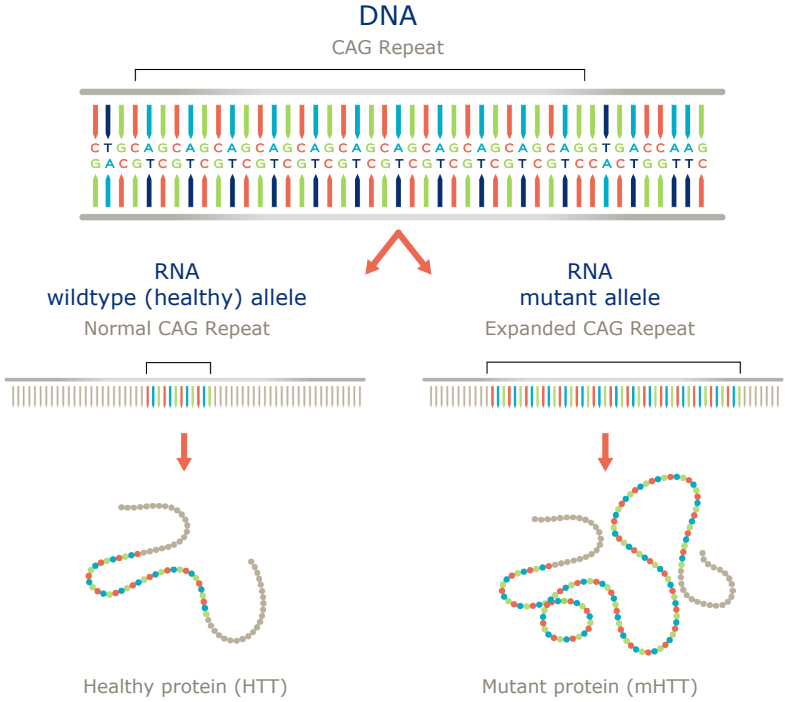
Huntington's Disease: a hereditary, fatal disorder

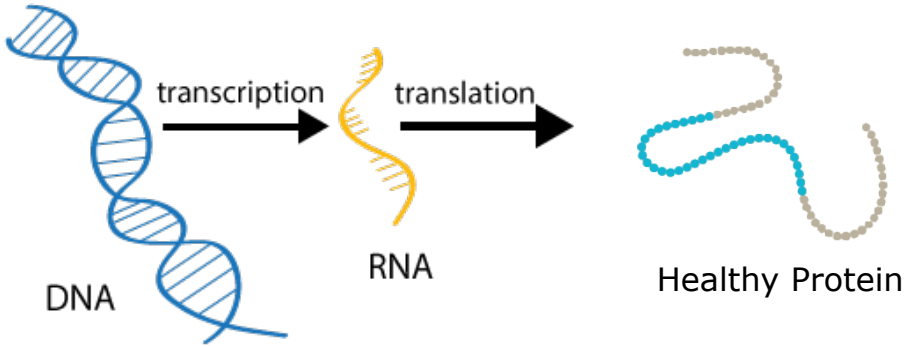
- Autosomal dominant disease, characterized by cognitive decline, psychiatric illness and chorea; fatal
- No approved disease-modifying therapies
- Expanded CAG triplet repeat in HTT gene results in production of mutant huntingtin protein (mHTT); accumulation of mHTT causes progressive loss of neurons in the brain
- Wildtype (healthy) HTT protein critical for neuronal function; suppression may have detrimental long-term consequences
- 30,000 people with Huntington's disease in the US; another 200,000 at risk of developing the condition



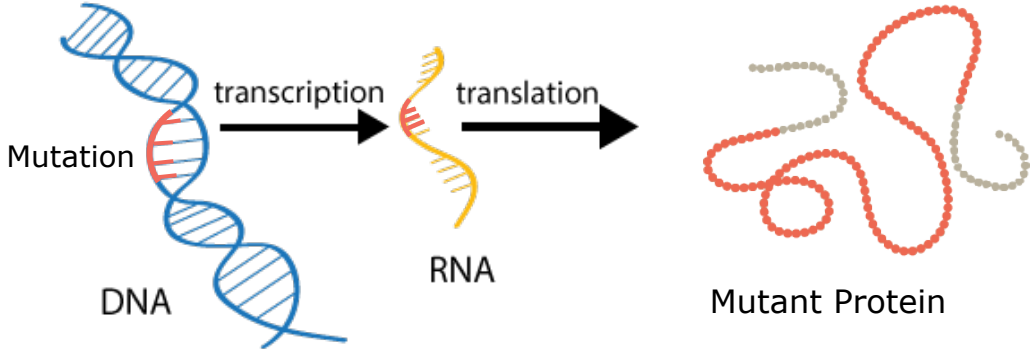
Sources: Auerbach W, et al. Hum Mol Genet. 2001;10:2515-2523. Dragatsis I, et al. Nat Genet. 2000;26:300-306. Leavitt BR, et al. J Neurochem. 2006;96:1121-1129. Nasir J, et al. Cell. 1995;81:811-823. Reiner A, et al. J Neurosci. 2001;21:7608-7619. White JK, et al. Nat Genet. 1997;17:404-410. Zeitlin S, et al. Nat Genet. 1995;11:155-163. Carroll JB, et al. Mol Ther. 2011;19:2178-2185.

Genetics of Huntington's Disease (HD)

Normal DNA



Mutated DNA



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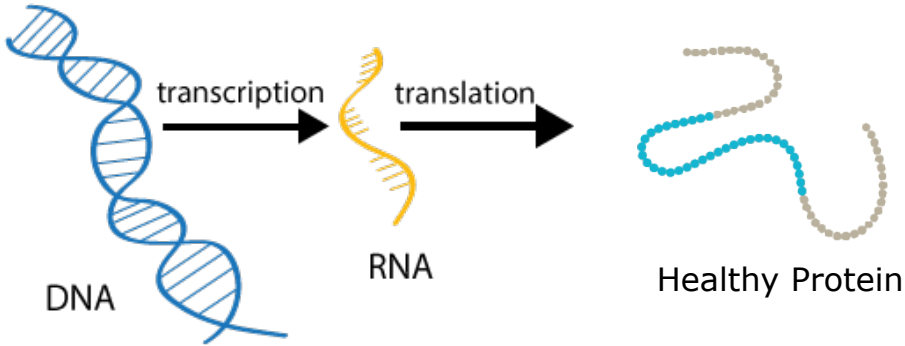
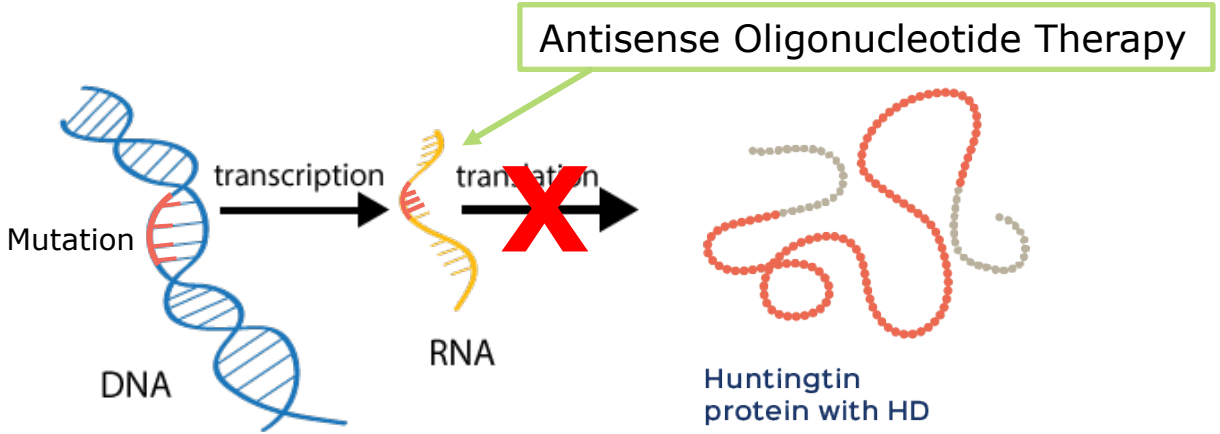
Antisense Oligonucleotides Therapies

Normal DNA



Mutated DNA



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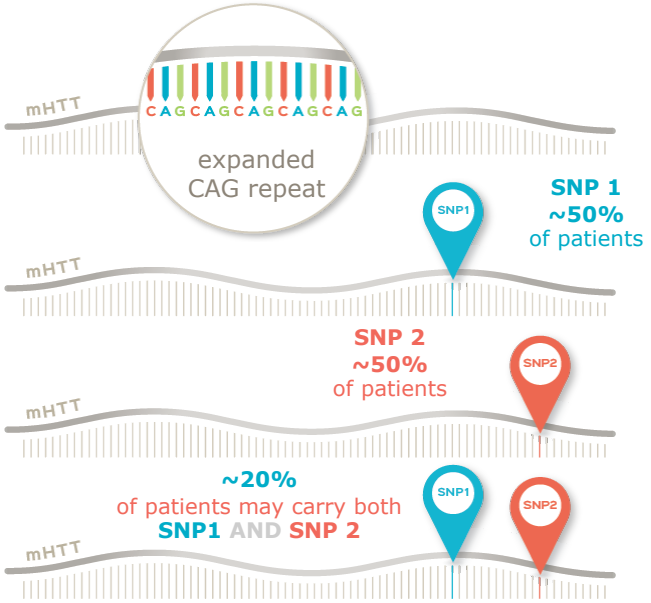
Wave approach: novel, allele-specific silencing

- Utilize association between single nucleotide polymorphisms (SNPs) and genetic mutations to specifically target errors in genetic disorders, including HD.
- Allele-specificity possible by targeting SNPs associated with expanded long CAG repeat in mHTT gene
- Approach aims to lower mHTT transcript while leaving healthy HTT relatively intact
- Potential to provide treatment for up to 70% of HD population (either oligo alone could address approximately 50% of HD population)



Total: Due to overlap, an estimated **~70%** of the total HD patient population carry SNP 1 and/or SNP 2

Source: Kaye, et al. Personalized gene silencing therapeutics for Huntington disease. Clin Genet 2014: 86: 29–36

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What is a SNP?

- SNP, pronounced like the word “snip,” stands for “single nucleotide polymorphism,” a scientific term for a copying error in our DNA.
- A SNP is a single building block of our DNA that is different than in the majority of people.
- SNPs occur normally, usually once in every 300 building blocks (or 10 million times in a person’s DNA), and we can inherit them from our parents.
- Most SNPs don’t impact our health.

  For example, one SNP linked to taste receptor proteins has been shown to cause a dislike of cilantro.

One SNP is linked to disliking cilantro

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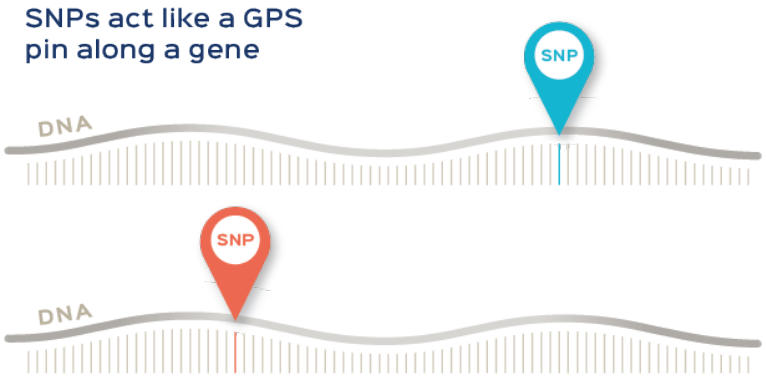
SNPs: A Genetic GPS

Since SNPs are located in very specific spots in our DNA, they can act like a pin on a map, helping find the exact gene that causes a disease, preference or trait.



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SNPs in Huntington's Disease (HD)

- Research has shown that certain SNPs are more frequently found on mutated *huntingtin* genes than on healthy ones.
- While there are hundreds of SNPs, common SNPs in HD include rs362301, rs362331, and rs7685686, which are found in over two-thirds of people with HD.

- These SNPs do not impact the severity or progression of the disease.

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Exploring the Potential of SNPs as a Targeting Tool

- The unique association between SNPs and genetic mutations opens up new possibilities for therapies that are intended to specifically target errors in many genetic disorders, including HD.

- Wave Life Sciences is exploring a new scientific approach that targets SNPs associated with mutations. The goal of our allele-silencing approach is to use the “GPS pins” to target genetic disorders including HD.

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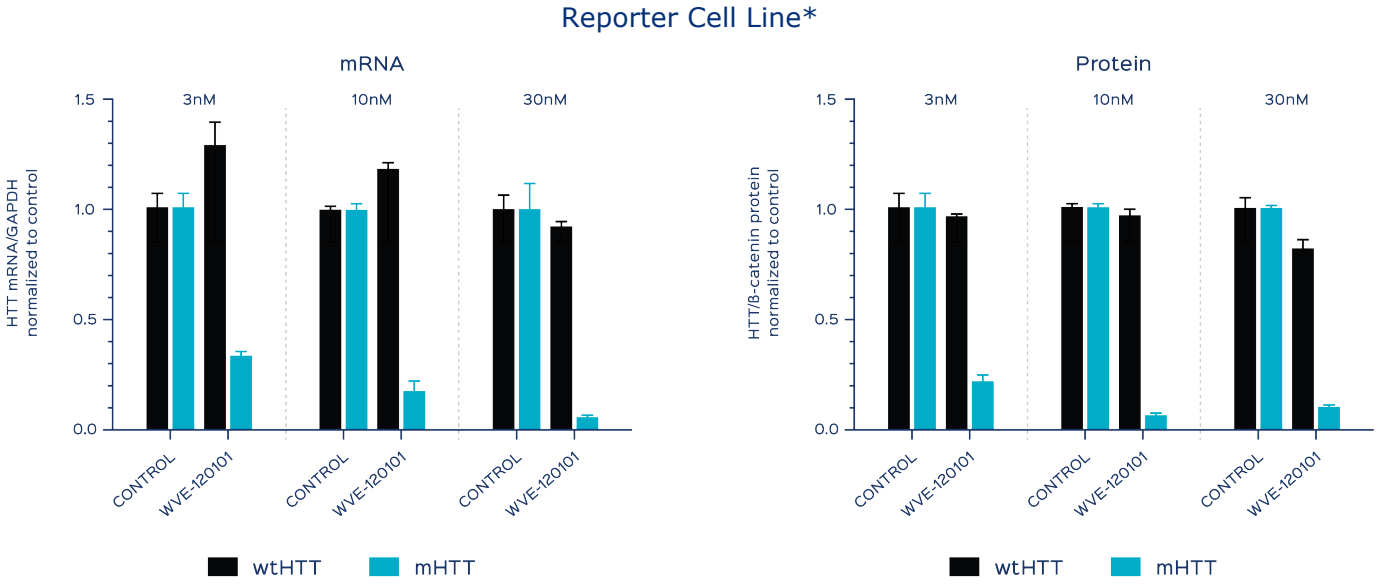
Selective reduction of mHTT mRNA & protein



*These results were replicated in a patient-derived cell line

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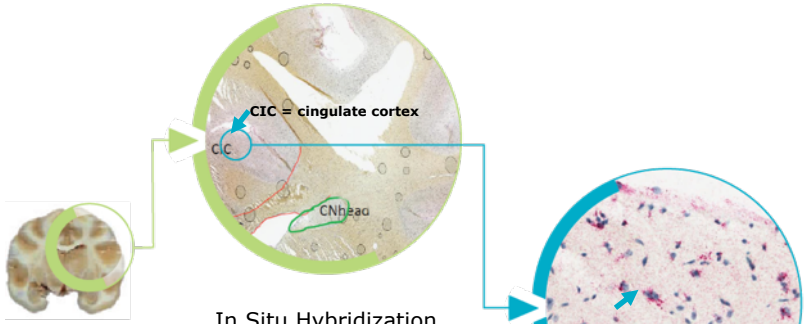
Demonstrated delivery to brain tissue

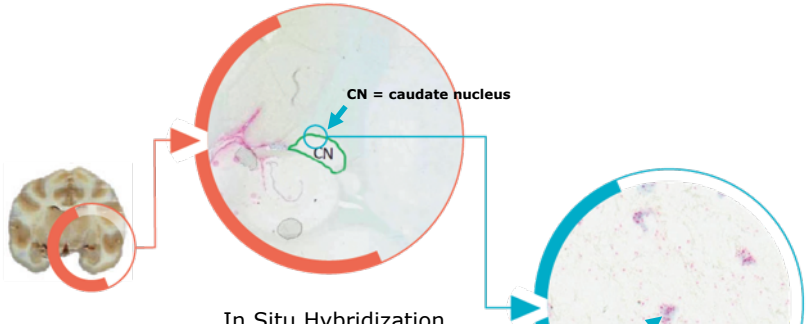
- WVE-120101 and WVE-120102 distribution in cynomolgus non-human primate (NHP) brain following intrathecal bolus injection



In Situ Hybridization ViewRNA stained tissue

Red dots are WVE-120101 oligonucleotide.

Arrow points to nuclear and perinuclear distribution of WVE- 120101 in cingulate cortex



In Situ Hybridization ViewRNA stained tissue

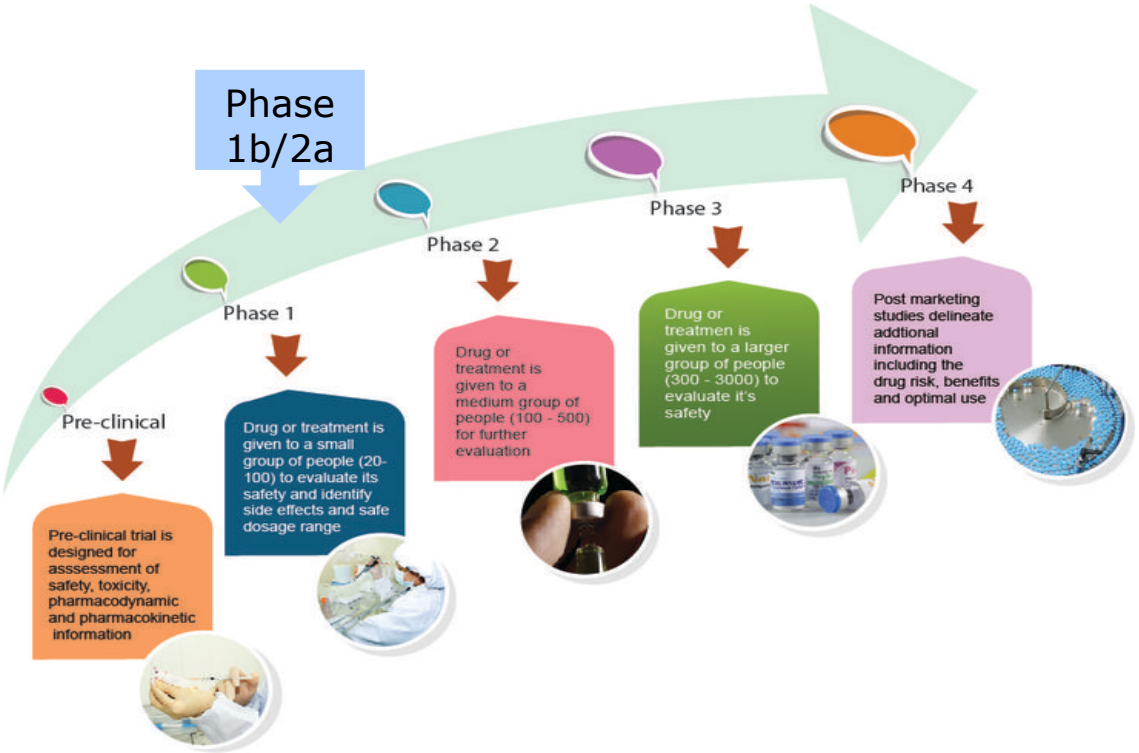
Red dots are WVE-120102 oligonucleotide.

Arrow points to nuclear and perinuclear distribution of WVE-120102 in caudate nucleus

CIC = cingulate cortex.
CN = caudate nucleus.

Clinical trials

A new investigational treatment goes through several clinical trial phases on the path to potential approval



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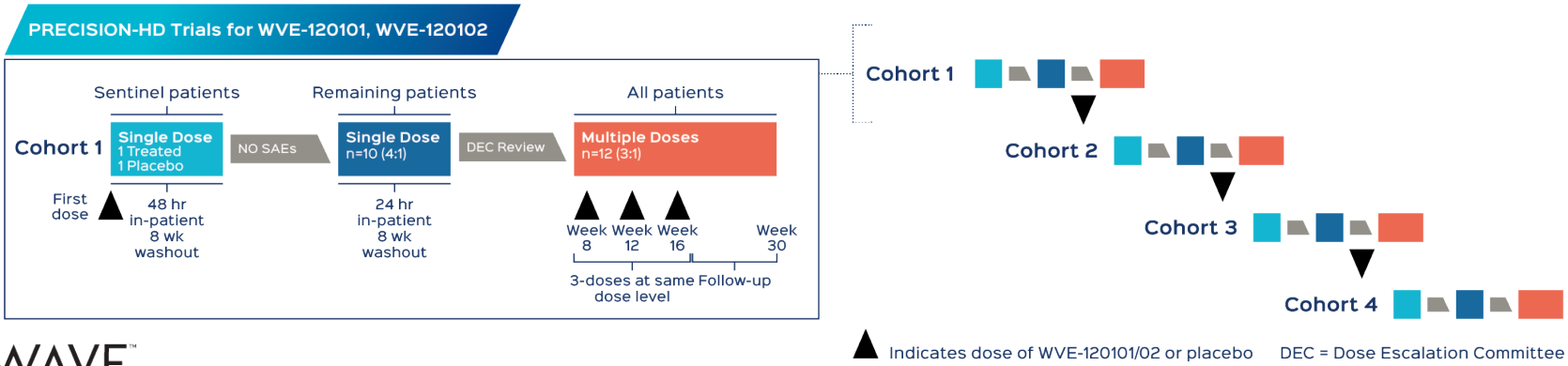
Two simultaneous Phase 1b/2a clinical trials

- Two parallel global placebo-controlled multi-ascending-dose trials for WVE-120101, WVE-120102
- Primary objective: assess safety and tolerability of intrathecal doses in early manifest HD patients
- Additional objectives: exploratory pharmacokinetic, pharmacodynamic, clinical and MRI endpoints
- Blood test to determine presence of SNP 1 or SNP 2 done at pre-screening
- Approximately 50 patients per trial
- Key inclusion criteria:
  age ≥25 to ≤65, stage I or II HD
- Top line data anticipated 1H 2019



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