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Analyst and Investor Research Day

OCTOBER 7, 2019
BOSTON, MASSACHUSETTS

Welcome

Paul Bolno, MD, MBA
President and CEO
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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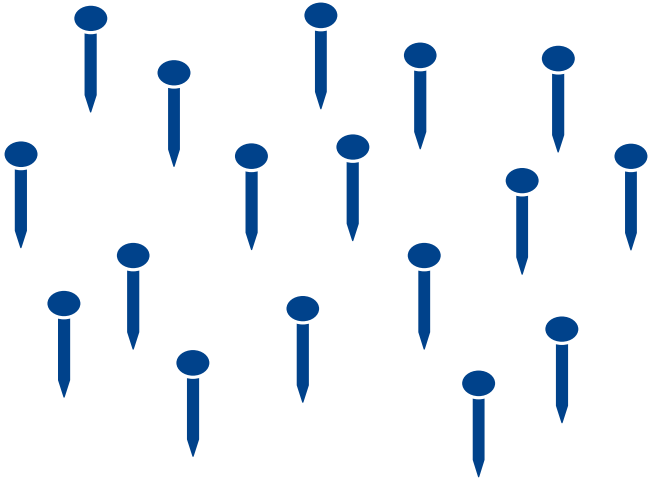
Our purpose at Wave

Genetic medicines company committed to delivering life-changing treatments for people battling devastating diseases

I **Building a genetic toolbox for a lifetime of treatment**



One tool appears suitable from a distance

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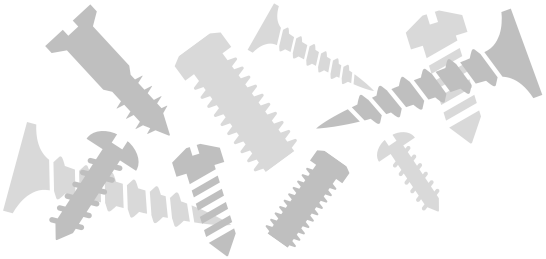
Our purpose at Wave

Genetic medicines company committed to delivering life-changing treatments for people battling devastating diseases

I Building a genetic toolbox for a lifetime of treatment

Target variability requires a comprehensive toolkit



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Our purpose at Wave

Genetic medicines company committed to delivering life-changing treatments for people battling devastating diseases

I Building a genetic toolbox

- Splicing, silencing, editing
- Non-viral delivery to nucleus
- Optimized, stereopure oligonucleotides

II Designing precision medicines for complex diseases

- Restoring functional protein
- Selectively reducing toxic protein
- Pursuing broad distribution

III Committed to patients in need

- Advancing innovative drug development approaches
- Scaling manufacturing expertise and capacity
- Building commercial infrastructure
- Developing novel payor strategies

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Today's Agenda

	**Paul Bolno, MD, MBA** President & CEO | Wave Life Sciences	**Opening Remarks**
	**Gregory Verdine, Ph.D.** Co-founder / Board Member | Wave Life Sciences	**Chirality Matters in Biology**
	**Chandra Vargeese, Ph.D.** SVP, Head of Drug Discovery | Wave Life Sciences	**PRISM**
	**Elena Cattaneo, Ph.D.** University of Milano	**Biology of Huntingtin (HTT)**
	**Frédéric Saudou, M.Sc., Ph.D.** Grenoble Institute of Neurosciences (GIN)	**Biology of Huntingtin (HTT)**
	**Chandra Vargeese, Ph.D.** SVP, Head of Drug Discovery | Wave Life Sciences	**Advancing HD Portfolio with mHTT SNP3**
	**Michael Byrne, Ph.D.** Director *In Vivo* Biology & Ophthalmology | Wave	**Lead Inherited Retinal Disease Program: USH2A**
	**Paul Bolno, MD, MBA** President & CEO | Wave Life Sciences	**Closing Remarks**

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PRISM | Huntington's disease | Ophthalmology

Chirality Matters in Biology

Gregory Verdine, Ph.D.
Co-founder and Board Member
Wave Life Sciences

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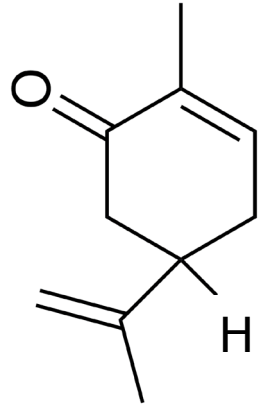
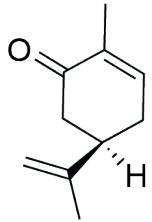
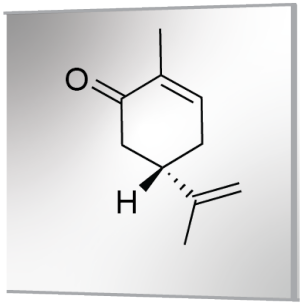
Chirality in biology



carvone





R-carvone *S*-carvone

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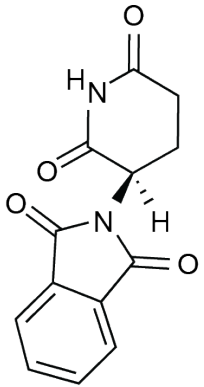
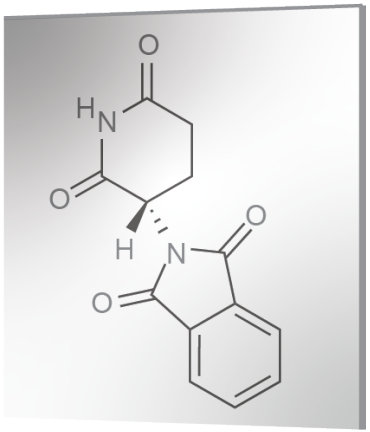
Stereochemistry Matters in Drugs – Case of Thalidomide

- Thalidomide was prescribed for the treatment of morning sickness in pregnant women.
- Between 1957 and 1962, thalidomide caused severe birth defects in >10,000 children.
- Thalidomide is a mixture of two stereoisomers.
- One stereoisomer (*R*) is responsible for the therapeutically beneficial effects.
- The other (*S*) isomer causes birth defects.
- Drugs should be stereochemically pure.



(*R*)

Anti-emetic



(*S*)

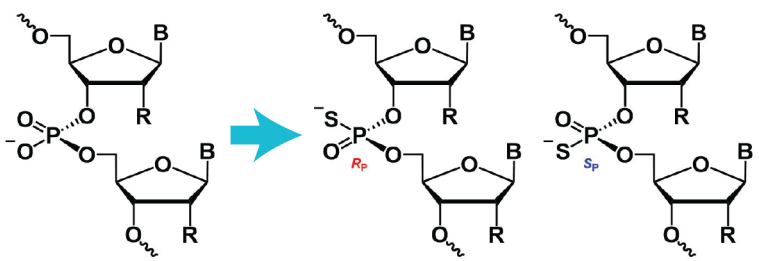
Teratogen

Vargesson et al., 2015. Thalomide-induced teratogenesis: History and mechanisms. Birth Defects Res C Embryo Today 105:140-156.
ACS Molecule of the week archive: Sept. 1, 2014.

Oligonucleotides

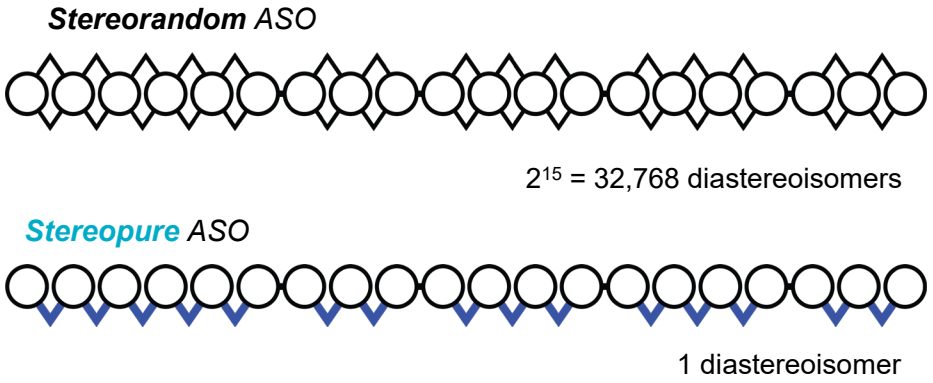
Phosphorothioate (PS) modifications introduce chiral centers

Enormous number of permutations exist (2^n) → Resulting in **thousands of different molecules** in <u>every dose</u>



Phosphodiester (prochiral)

Chiral Phosphorothioate



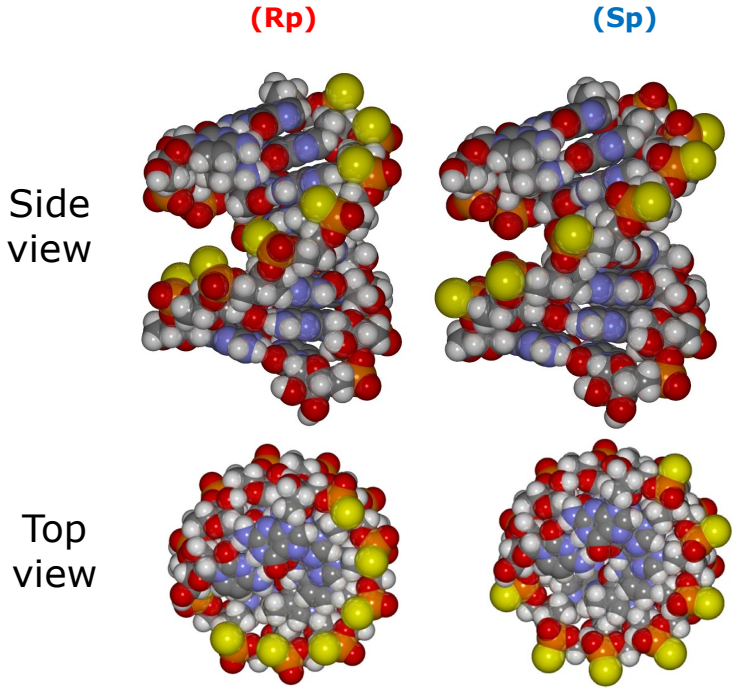
Phosphorothioate (PS)

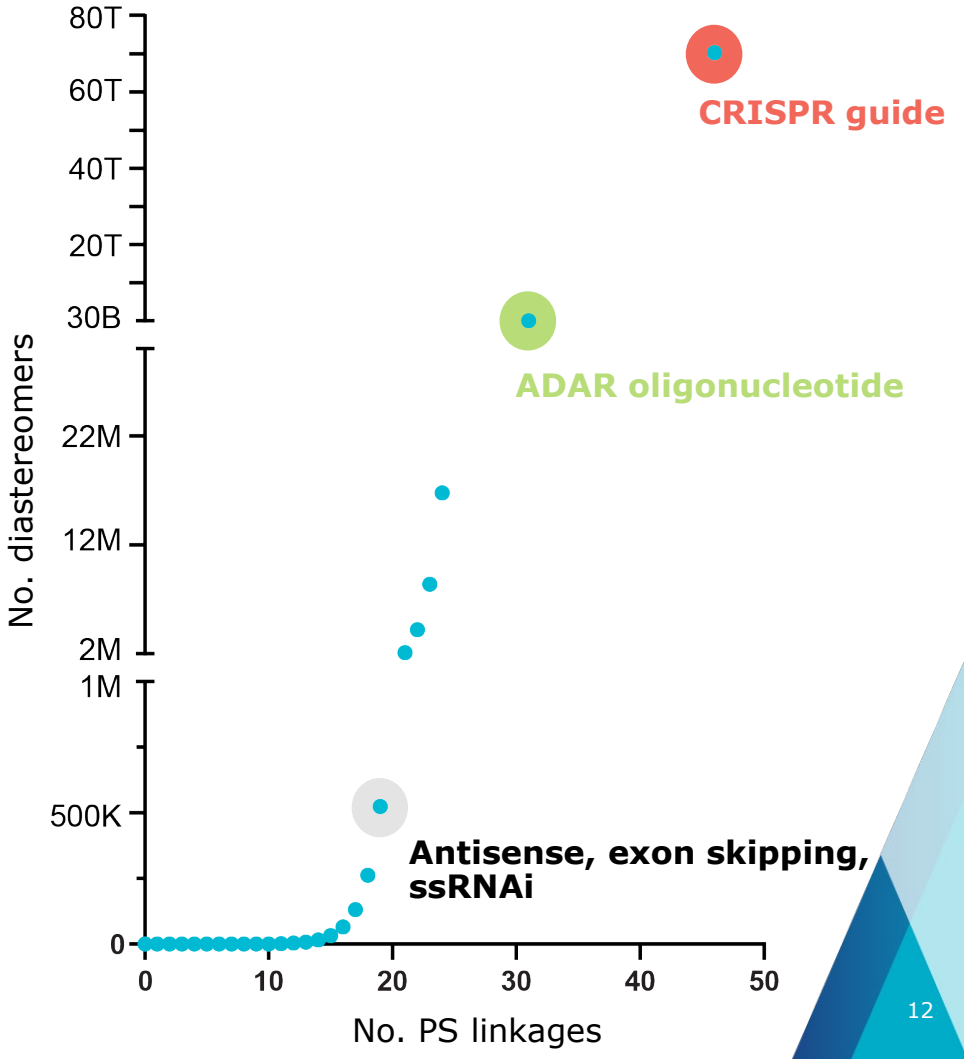
WAVE LIFE SCIENCES — Phosphodiester

Rp / Sp — Stereorandom — Nucleoside

Stereochemical diversity

- Exponential diversity arises from uncontrolled stereochemistry





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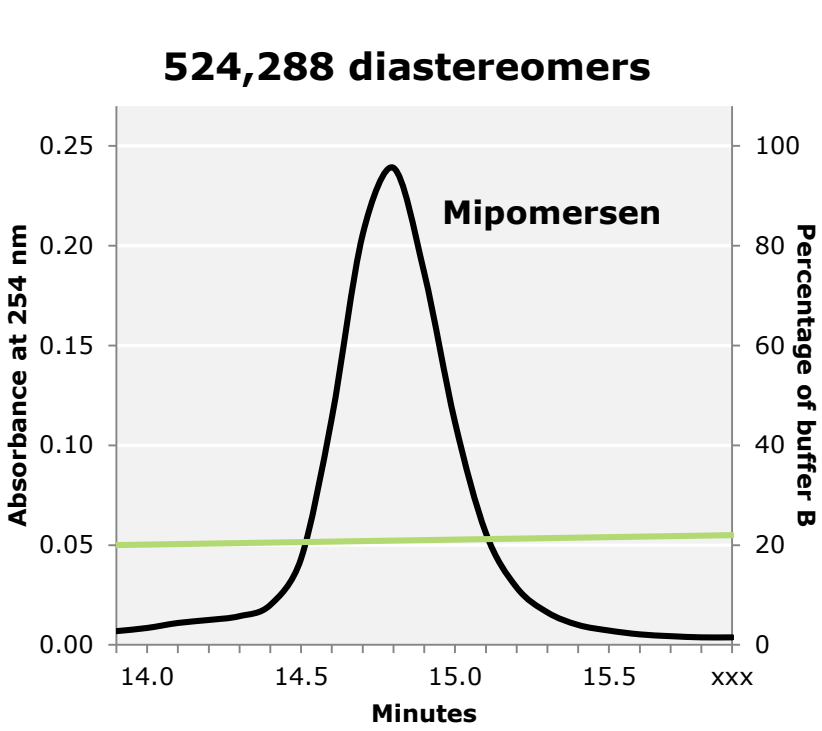
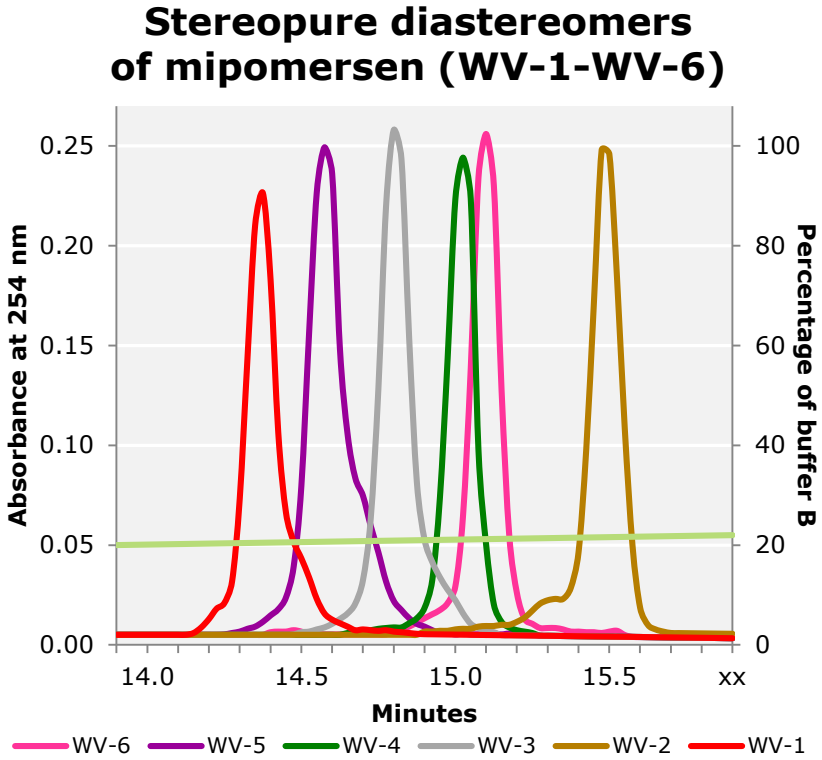
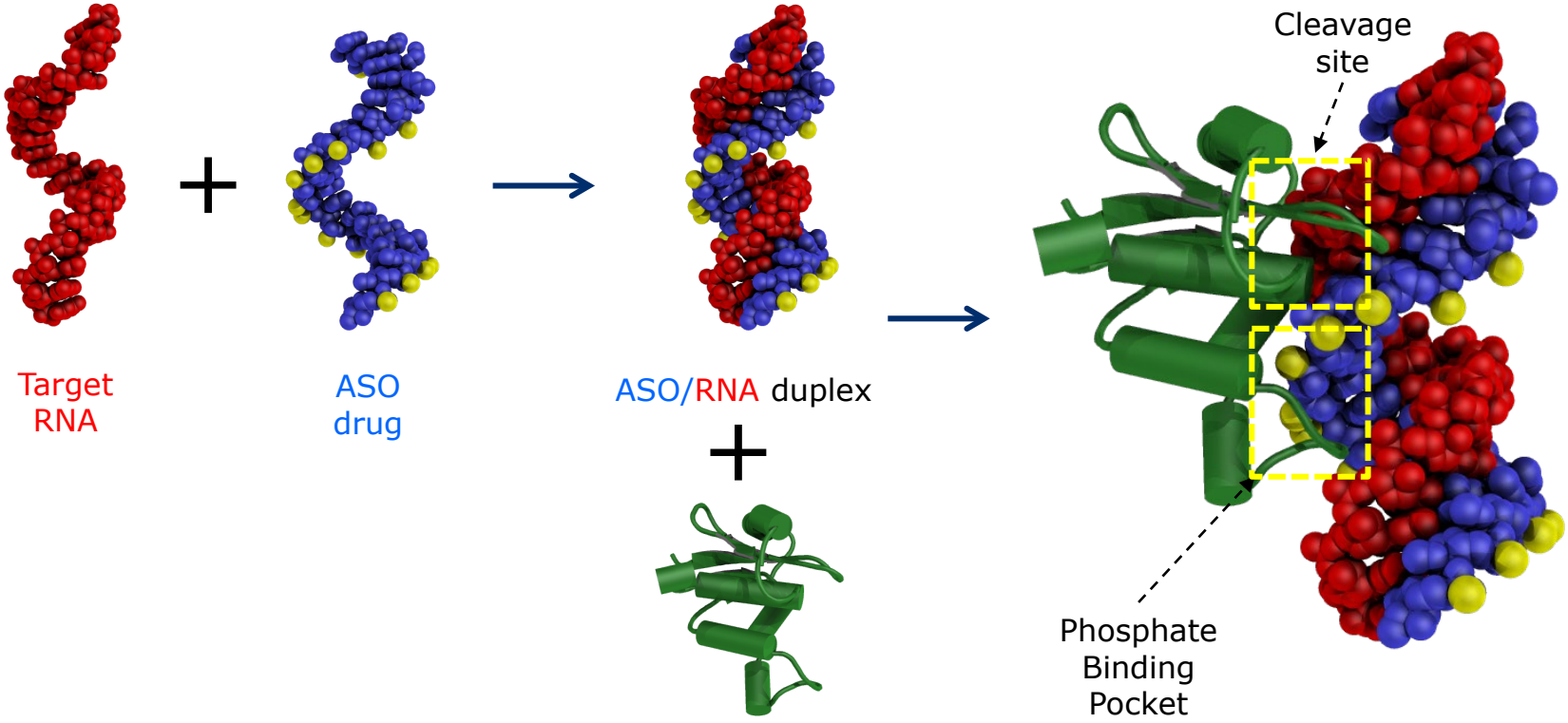
Mipomersen





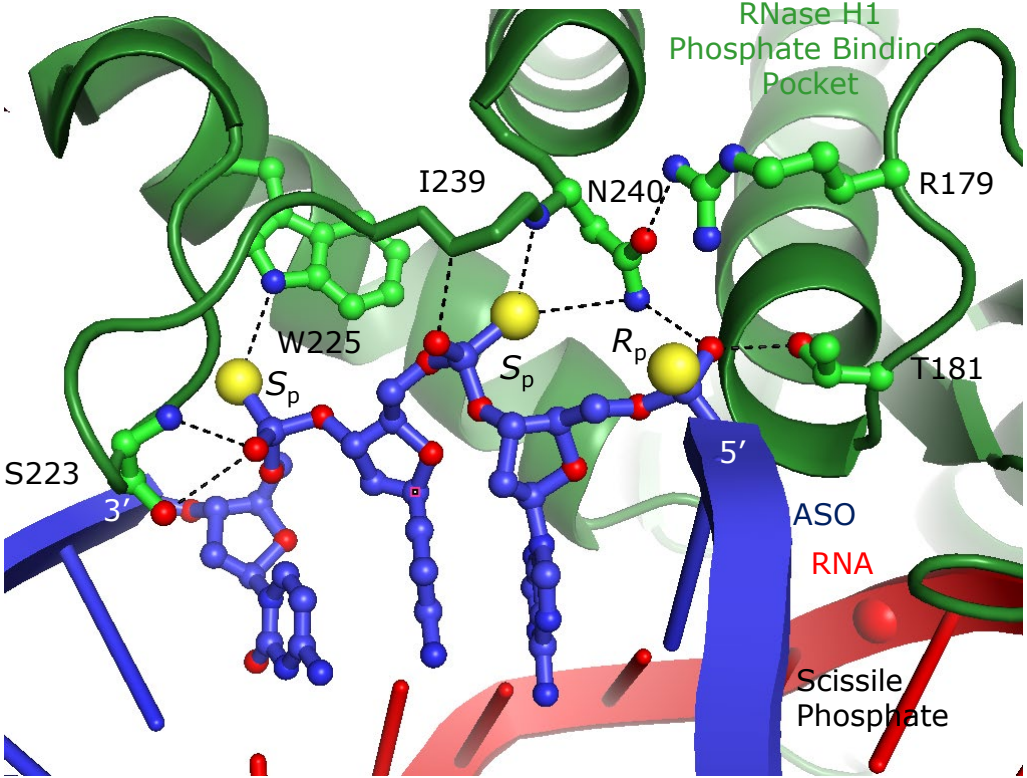
Iwamoto et al., 2017. Control of phosphorothioate stereochemistry substantially increases the efficacy of antisense oligonucleotides. *Nat. Biotechnol.* 35:845-851.

Overall ASO/RNA/RNase H complex structure



Yellow spheres represent 'S' atoms

Phosphate binding pocket

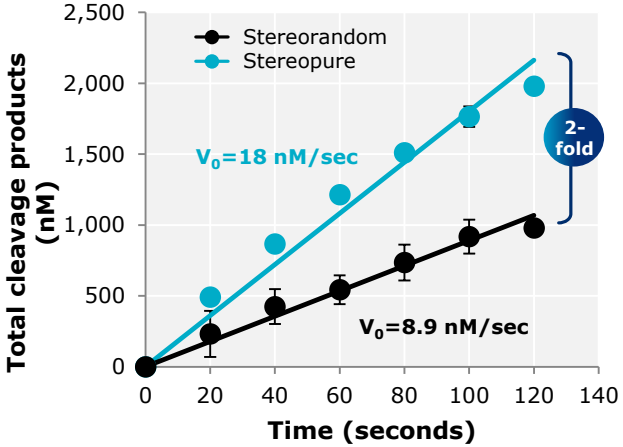


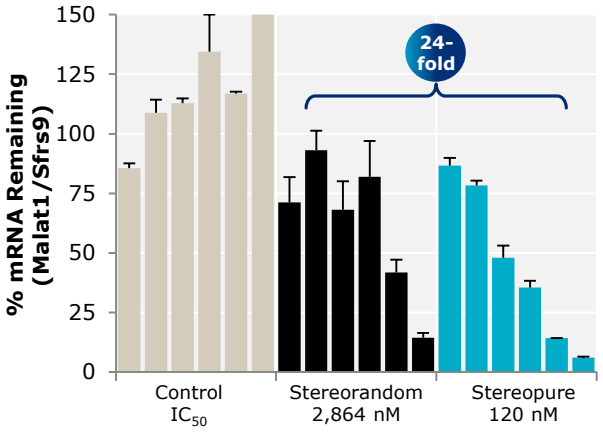
1.3 Å resolution

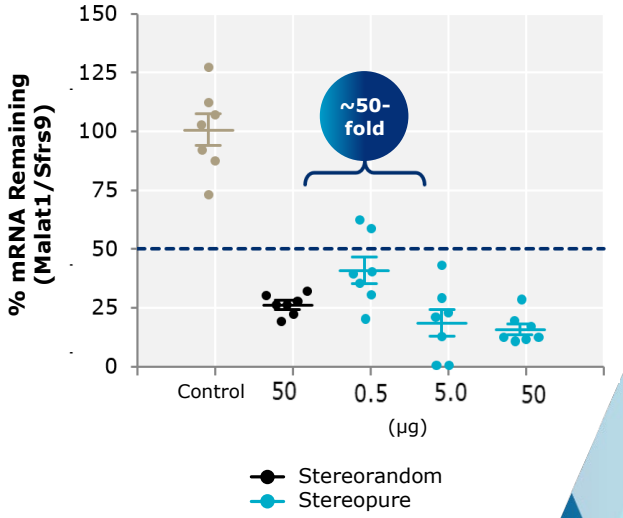
Precision RNase H-mediated RNA degradation

PRISM

Improved rate and amount of cleavage → **Increased potency *in vitro*** → **Translatable potency shift *in vivo* (eye)**







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In RNase H1 assay, ASOs were pre-annealed to surrogate MALAT1 mRNA (1:1, Cf=5 mM). RNase H (250:1, E:S) was added and quenched with EDTA at the indicated times. Products were quantified, and V0 was calculated from the best-fit line (n=3 per time point). In iCell neurons, 10, 30, 100, 300, 1,000 or 3,000 nM ASO was added to iCell neurons under free-uptake conditions. 4-days post-treatment, RNA was harvested and processed. MALAT1 mRNA expression was determined by qPCR (n=2 per concentration). Control is non-targeting oligonucleotide. In two separate experiments, mice received a single IVT injection of 1 µL in both eyes. One-week post-injection, eyes were enucleated, flash frozen, bisected into anterior and posterior and processed for RNA. MALAT1 mRNA expression was determined by qPCR (each dot represents one eye).

PRISM

Chandra Vargeese, Ph.D.
SVP, Head of Drug Discovery
Wave Life Sciences

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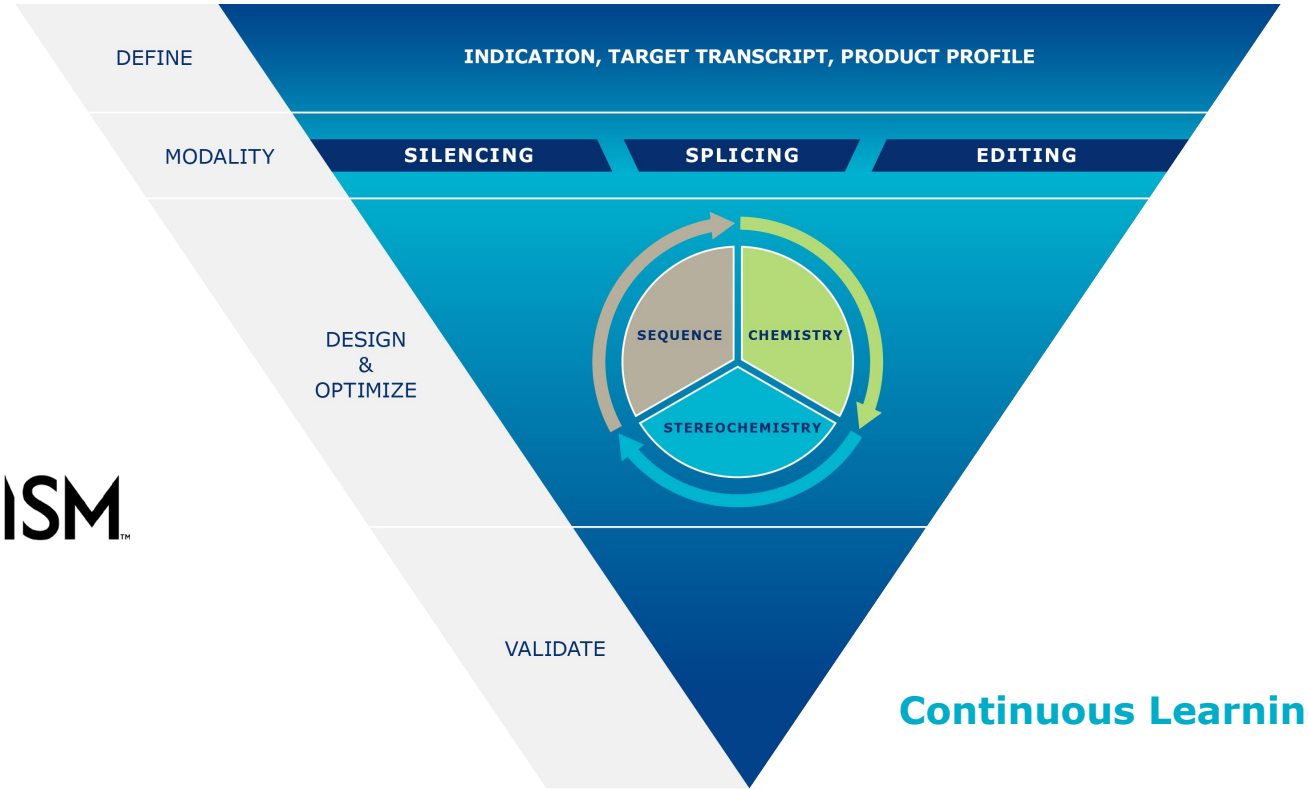
PRISM: Wave's proprietary discovery and drug development platform

Platform progress

Applied learnings

New modality: ADAR-mediated RNA editing

PRISM platform enables rationale drug design



PRISM™

Continuous Learning

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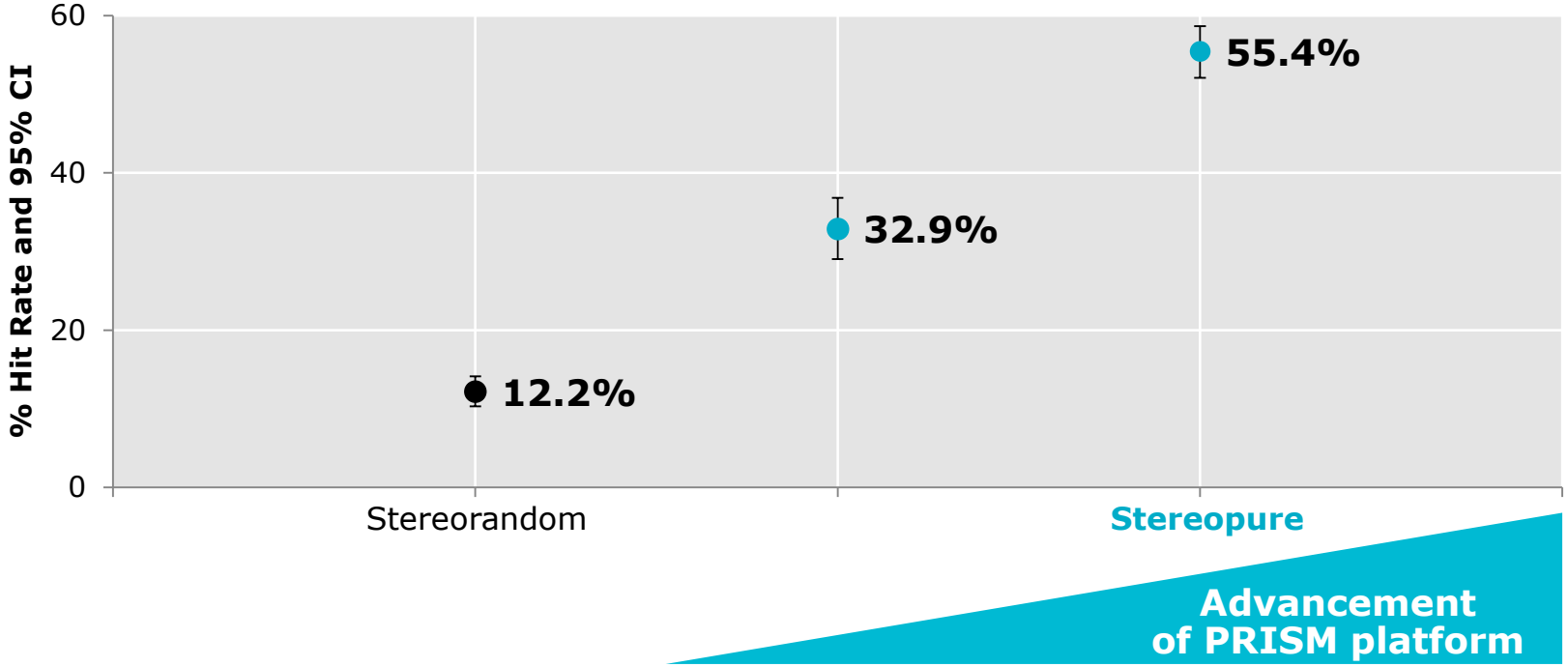
PRISM platform advancing



~5-fold improvement in primary screen hit rates

All screens used iPSC-derived neurons; Data pipeline for improved standardization

PRISM: Wave's proprietary discovery and drug development platform

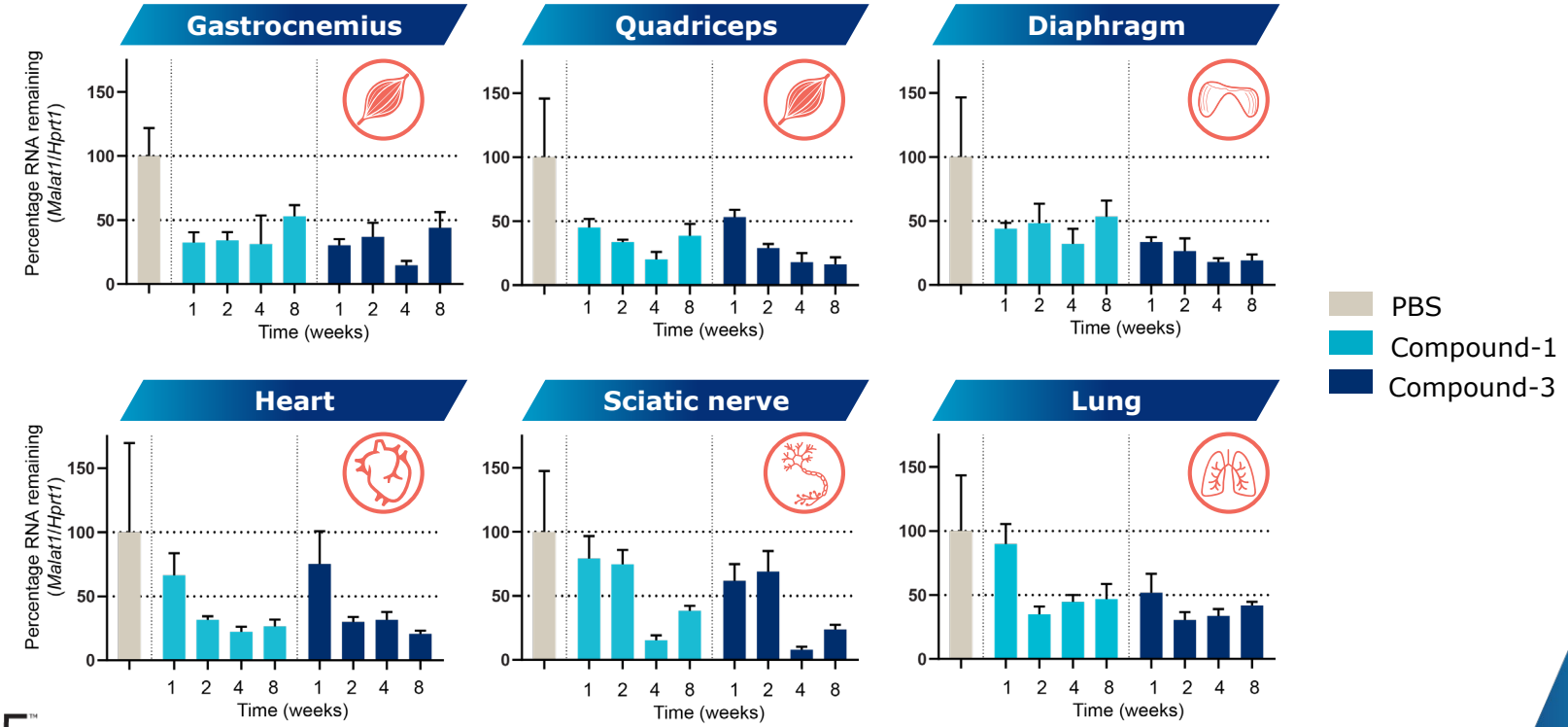
Platform progress

Applied learnings

New modality: ADAR-mediated RNA editing

Broad tissue distribution and durable target engagement

Single IV injection of Wave compounds targeting *MALAT1* (human equivalent of 1.6 mg/kg)



Mice were dosed with a single IV injection (25 mg/kg) of *MALAT1*-targeting compound, and tissues were assessed for RNA expression 1-, 2-. 4-, and 8-weeks post-dose. Relative percentage of *MALAT1* RNA to PBS-treated mice (n=5 per group). *MALAT1* RNA levels are normalized to Hprt1.

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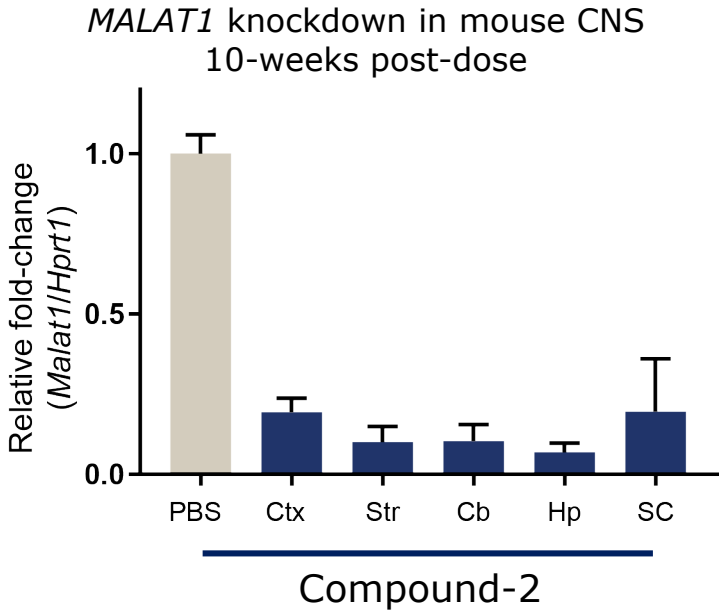
CNS: Potent and durable targeting with PRISM designed oligonucleotides

In vivo durability



- Broad distribution
- >80% knockdown of *MALAT1* in multiple regions and cell types
- Knockdown observed 10-weeks after single 100µg dose

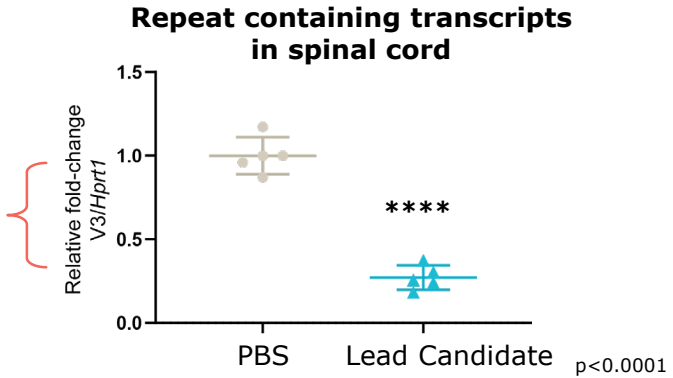
Mice received a single 100 µg ICV injection (n=3 per group). Relative fold-change in *MALAT1* expression is shown for the indicated tissues 10-weeks post-dose. *MALAT1* expression levels are normalized to *Hprt1*. PBS, phosphate buffered saline; Ctx, cortex; Str, striatum; Cb, cerebellum; Hp, hippocampus; SC, spinal cord.

CNS: Allele-selective silencing of expanded C9orf72 repeat containing transcripts

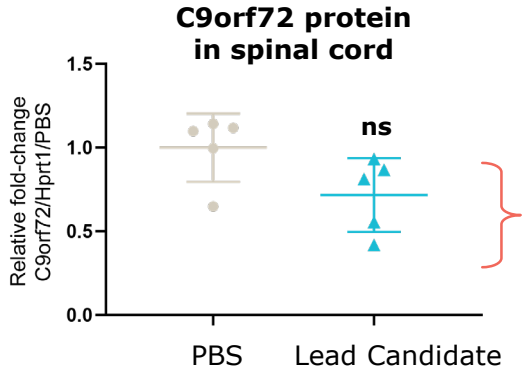
- C9orf72 genetic mutations are the strongest genetic risk factor found to date for the more common, non-inherited (sporadic) forms of Amyotrophic Lateral Sclerosis (ALS) and Frontotemporal Dementia (FTD); GGGGCC repeat drives the formation and accumulation of dipeptide repeat proteins that accumulate in brain tissue
- **Wave's approach:** Selectively silence the GGGGCC repeat containing transcript while minimizing the impact on normal C9orf72 protein

Selective silencing of C9orf72 *in vivo* (transgenic mouse)

Reduction of repeat containing transcripts



p<0.0001



Protein preservation

Clinical development expected to initiate in 2H 2020

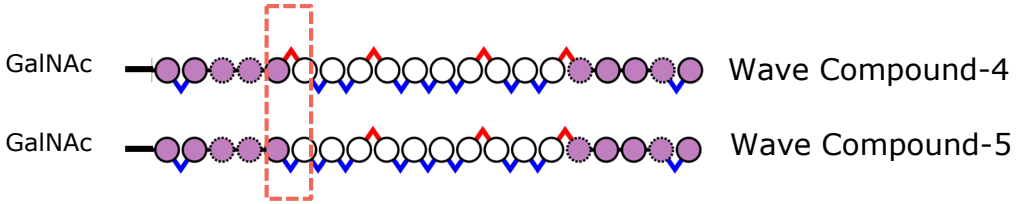
Experimental description: 2 x 50 ug on day 1 and day 8; mRNA Samples were analyzed using quantitative PCR (Taqman assay), Protein samples were measured by Western Blot.

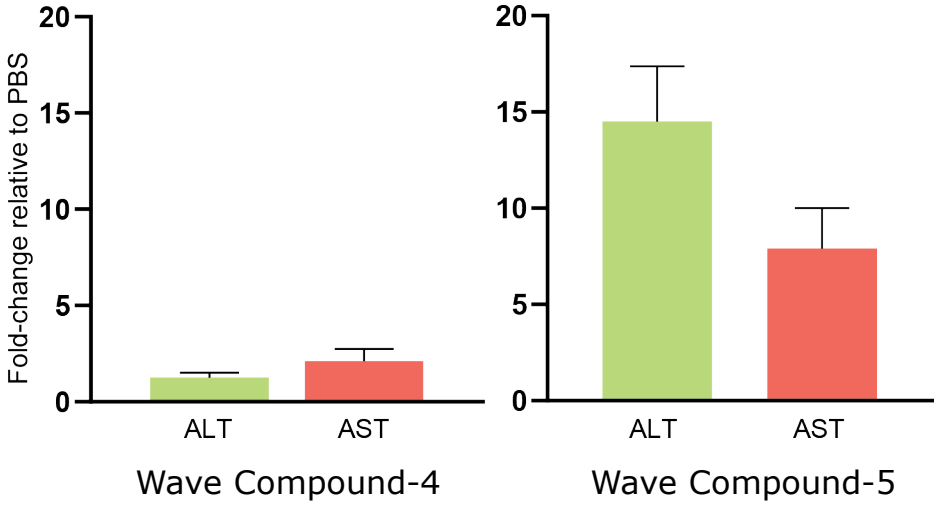
PRISM enables resolution of different stereoisomer toxicity profiles

Single *Rp* to *Sp* shift increases biomarkers for hepatotoxicity

Compound-4 and **Compound-5** have identical:

- Sequence
- Chemical modifications
- Backbone modifications
- *In vitro* potency
- *In vivo* potency





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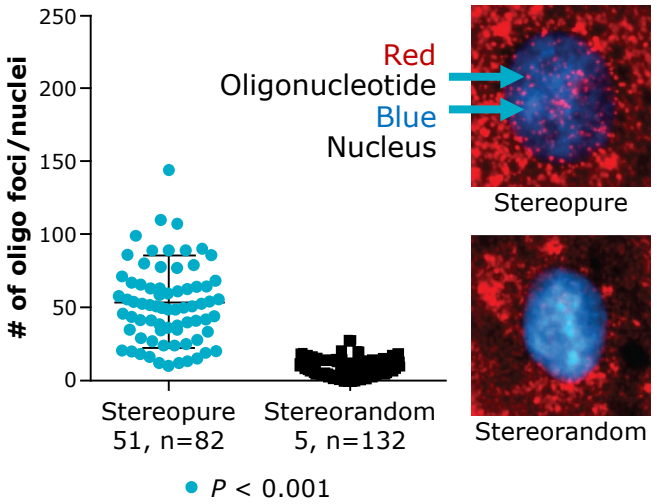
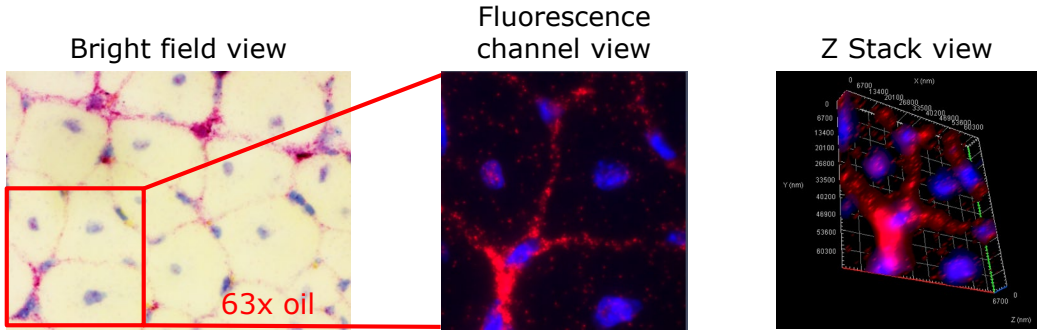
CD1 mice dosed four by 5 mg/kg on days 1, 4, 8, 11; necropsy done day 14

PRISM stereopure oligonucleotides designed to enter the nuclei of cells under free-uptake conditions

Free uptake of stereorandom and stereopure oligonucleotides



Rapid distribution of stereopure oligonucleotide to muscle *in vivo*



Nucleus:
Hematoxylin; Light Blue
Wave oligo:
ViewRNA, Fast Red

Nucleus:
Hoechst33342; Blue
Wave oligo: Fast Red/Cy3; Pink Red

Stereopure oligonucleotides more readily enter the nuclei of cells under free-uptake conditions, which approximates natural delivery in the body

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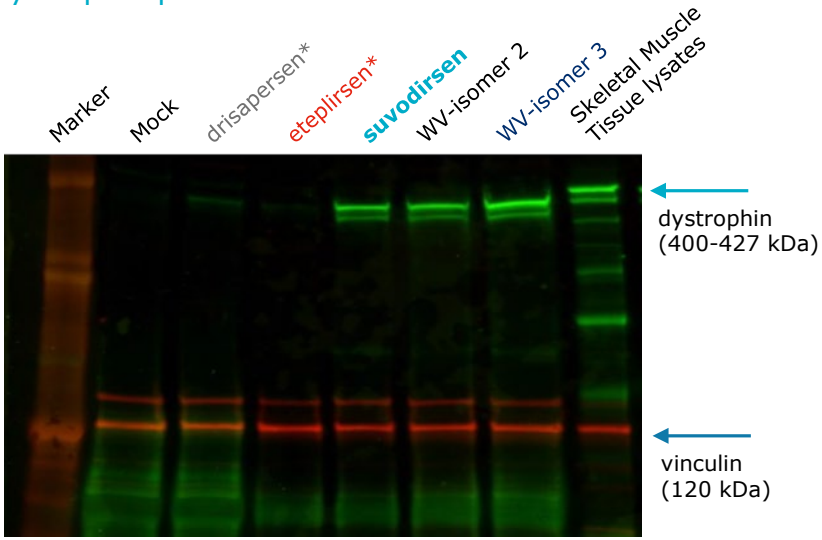
Experimental conditions: Free uptake of ASOs in 18 hour differentiating human DMD myoblasts (Δ48-50). Data derived from *in vivo* preclinical research.
Experimental conditions: A single dose of stereopure oligonucleotide 30 mg/kg IV was administered to mdx 23 mice. Tissues collected 24 hours post dose and ASO was detected in muscles using ViewRNA.

PRISM exon-skipping programs restore significant dystrophin *in vitro*

Suvodirsen (Exon 51)

Dystrophin protein restoration of **~52%** *in vitro*



*Analogs

4Q 2019: Interim clinical dystrophin data readout from OLE expected

WVE-N531 (Exon 53)

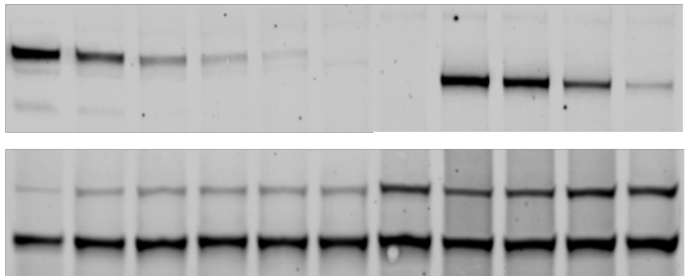
Dystrophin protein restoration of up to **71%** *in vitro*

Western Blot normalized to primary healthy human myoblast lysate

Standard Curve (% WT lysate in D45-52 lysate)						D45-52 Cells				
						Mock	WVE-N531			
						0	10	3.3	1.1	0.3
100%	50%	25%	12%	6%	0%	0%	71%	65%	37%	9.5%

Conc [uM]

% Dystrophin



2H 2020: Topline clinical data expected

Experimental conditions: DMD protein restoration by western blot in patient-derived myotubes with no transfection reagents. Free uptake at 10 μM concentration (left panel) of each compound. Clear dose effect for WVE-N531 (right panel).

PRISM: Wave's proprietary discovery and drug development platform

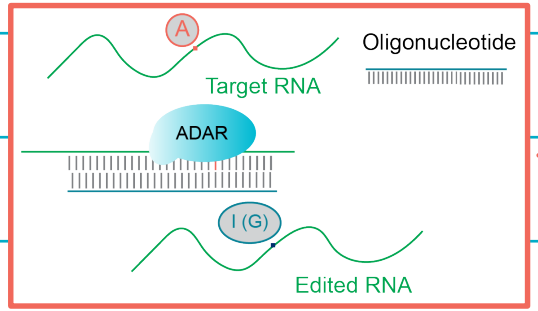
Platform progress

Applied learnings

New modality: ADAR-mediated RNA editing

RNA-editing can be used for several therapeutic applications and supplement Wave's existing modalities

Strategy	Therapeutic Application	Treatment Modality: Silencing	Splicing	RNA Editing
Silence protein expression	Reduce levels of toxic mRNA/protein	✓		✓
Alter mRNA splicing	Exon skipping/inclusion/ restore frame		✓	✓
Fix nonsense mutations that cannot be splice-corrected	Restore protein expression			✓
Fix missense mutations that cannot be splice-corrected	Restore protein function			✓
Modify amino acid codons	Alter protein function			✓
Remove upstream ORF	Increase protein expression			✓



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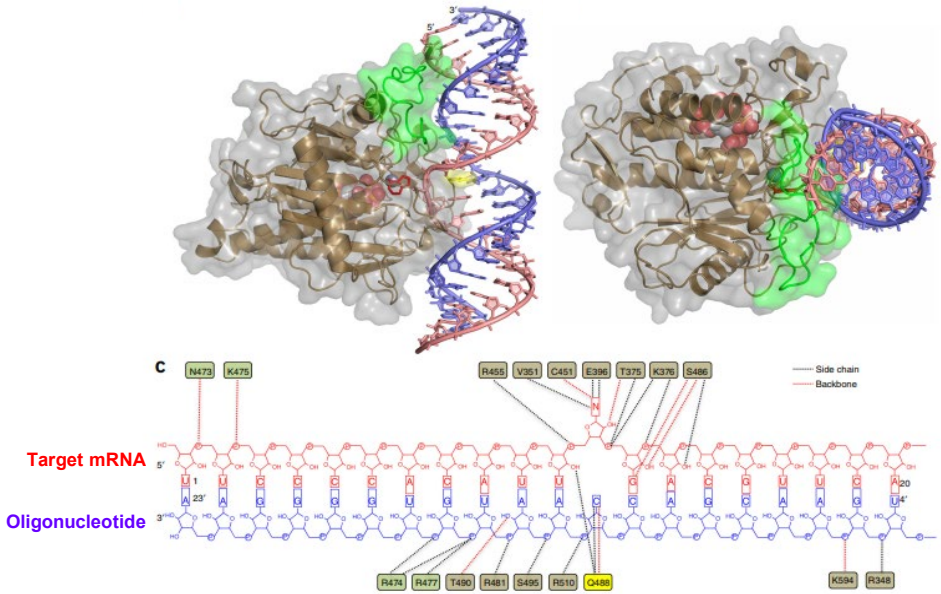
I (G): ADAR converts A>I, I is recognized as G by all cellular machinery; ADAR: Adenosine Deaminase Acting on RNA

Using PRISM to unlock ADAR-mediated RNA editing

Structure of ADAR deaminase domain bound to dsRNA substrate



- ADAR makes multiple contacts with oligonucleotide backbone, sugar and bases
- Using PRISM platform, rationally designed and screened oligonucleotides to optimize:
  - 2' sugar chemistry
  - Backbone chemistry and stereochemistry
  - Size and structure
  - Modified nucleobases

~1,000 RNA editing oligonucleotides tested over the last year to develop SAR for editing format

Structure adapted from Matthews et al., Nat Struct Mol Biol. (2016); SAR = structure-activity relationship; ADAR: Adenosine Deaminase Acting on RNA; dsRNA = double-stranded RNA

Wave's ADAR approach has several advantages over existing technologies

Existing RNA editing technologies		Wave's RNA editing platform
Use unmodified RNA	Stability	Fully chemically-modified stereopure oligonucleotides ✓
Require AAV or lipid nano particle delivery	Delivery	Free uptake into tissues ✓
Require exogenous protein (e.g. CAS13 or chimeric ADAR)	Editing	Uses endogenous ADAR for editing ✓

Single oligonucleotide through free uptake is sufficient for editing

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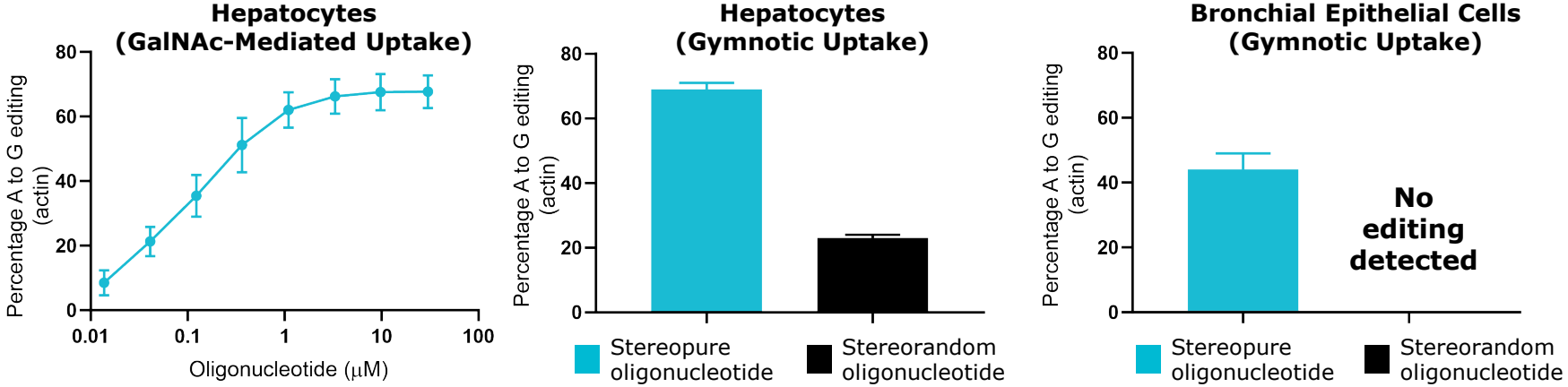
RNA-editing with endogenous ADAR achieved across multiple primary human cell types

Editing UAG Site in Actin mRNA in Primary Human Cell Lines



- Stereochemistry significantly increases editing across all cell lines tested, especially for gymnotic delivery
- GalNAc-conjugated fully-modified stereopure oligonucleotide can be used for targeted editing in hepatocytes; *in vitro* experiments suggest an EC50 of ~100nM in primary hepatocytes
- *In vivo* editing with fully-modified stereopure oligonucleotide studies underway

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***In vivo* editing data expected in 2020**

Portfolio

Paul Bolno, MD, MBA
President and CEO
Wave Life Sciences

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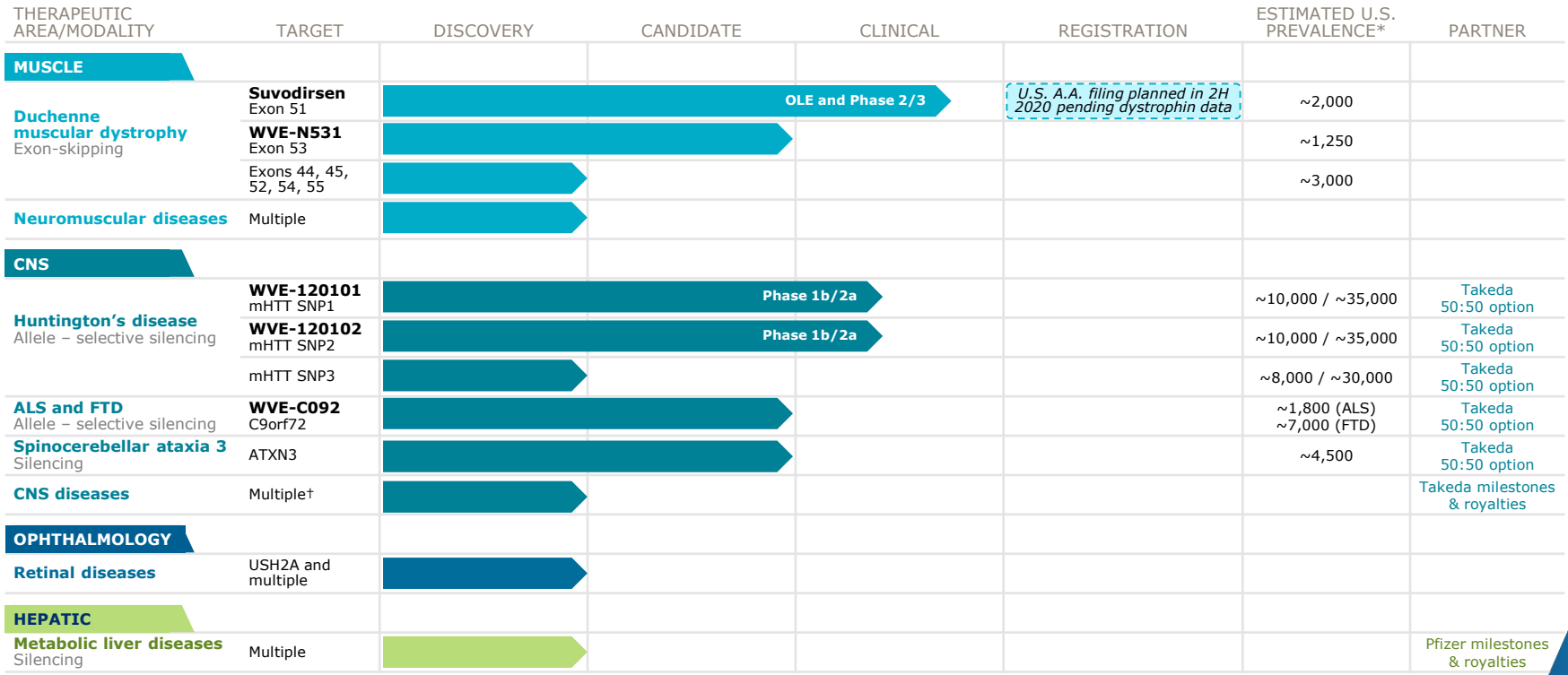
Pipeline spanning multiple modalities, novel targets



*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.
†During a four-year term, Wave and Takeda may collaborate on up to six preclinical targets at any one time.
A.A.: Accelerated approval; ALS: Amyotrophic lateral sclerosis; FTD: Frontotemporal dementia; CNS: Central nervous system

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Biology of Huntingtin (HTT)

Elena Cattaneo, Ph.D.
University of Milano

Frédéric Saudou, M.Sc., Ph.D.
Grenoble Institute of Neurosciences (GIN)

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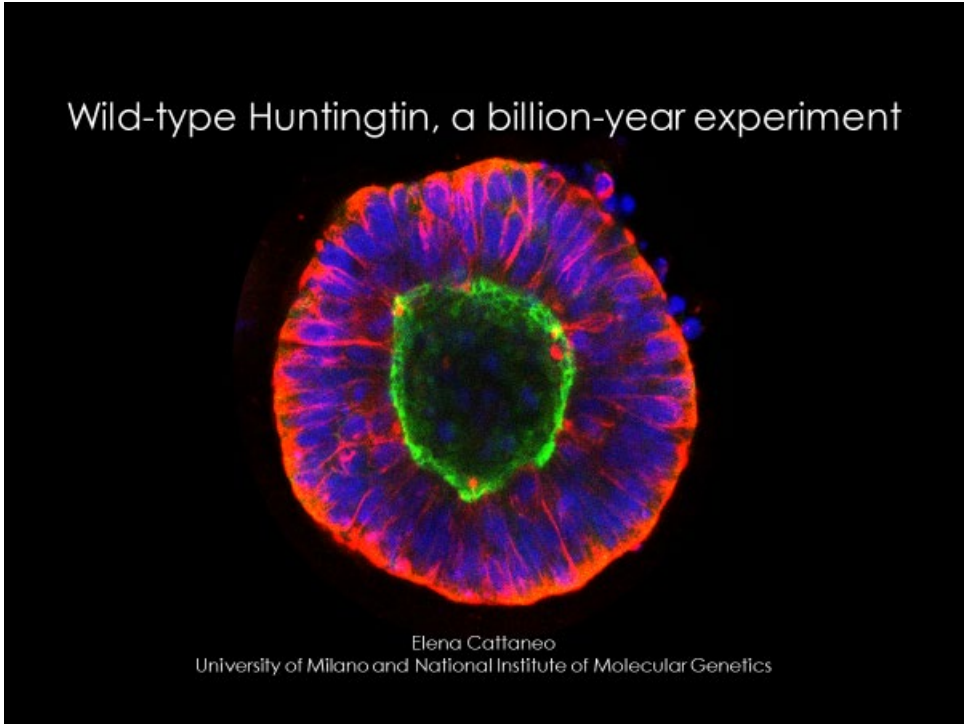
Elena Cattaneo, Ph.D.
University of Milano

- Prof. of pharmacology, director of Laboratory of Stem Cell Biology and Pharmacology of Neurodegenerative Diseases
- Director of UniStem (Centre for Stem Cell Research of the University of Milan)
- Earned PhD in biotechnology applied to pharmacology at University of Milan
- Completed first post-doc at MIT under supervision of Prof. Ronald McKay – studied neural stem cell differentiation associated with neurodegenerative conditions
- Learned strategies for stem cell grafting at Lund University in the lab of Prof. Anders Björklund
- Returned to University of Milan in 1995 as a researcher
- Appointed associate professor in 2001, full professor in 2003
- Today her lab focuses on molecular pathophysiology of HD and mechanisms regulating striatal neurodegeneration
- They are identifying cells, molecules, pathways that are suitable for therapeutic application to slow or prevent the disease
- In 2013, was appointed Senator for life by President Giorgio Napolitano on account of her scientific and social merit

Frédéric Saudou, M.Sc., Ph.D.
Grenoble Institute of Neurosciences (GIN)

- Prof. at University Grenoble Alpes & CHU, director of Grenoble Institute of Neuroscience (GIN)
- Group leader of the team 'Intracellular Dynamics and Neurodegeneration'
- Director of the Grenoble Center of Excellence in Neurodegeneration (COEN-GREEN)
- Undertook his thesis at the University of Strasbourg with Prof. René Hen on serotonin receptors
- Completed first post-doc in Strasbourg with Prof. Jean-Louise Mandel in human genetics
- Completed second post-doc at Harvard Medical School with Prof. Michael Greenberg on neuronal signaling
- In 2000, moved back to France to lead research team at the Institut Curie; became director of department in 2010
- Research team moved to Grenoble in December 2014; major focus is understanding huntingtin function, dysfunction in intracellular trafficking to investigate pathogenic mechanisms
- In 2014, received the Richard Lounsbery prize for medicine and biology from the French and US national academies of Science

[Placeholder] Elena Cattaneo slides



[Placeholder] Frédéric Saudou slides

Understanding the biology of huntingtin for clinical applications

Frédéric Saudou

Grenoble Institut Neuroscience,
Univ. Grenoble Alpes
Inserm Research Center U1216

GIN Grenoble Institut Neurosciences

Université Grenoble Alpes

Instituts thématiques Inserm Institut national de la santé et de la recherche médicale

CHU Grenoble Alpes

Grenoble excellence in neurodegeneration

Advancing HD Portfolio with mHTT SNP3

Chandra Vargeese, Ph.D.
SVP, Head of Drug Discovery
Wave Life Sciences

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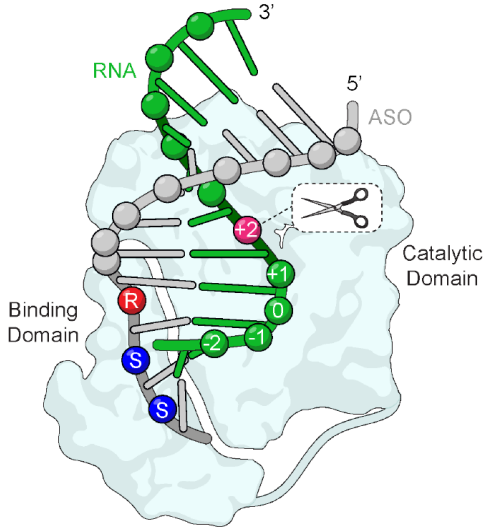
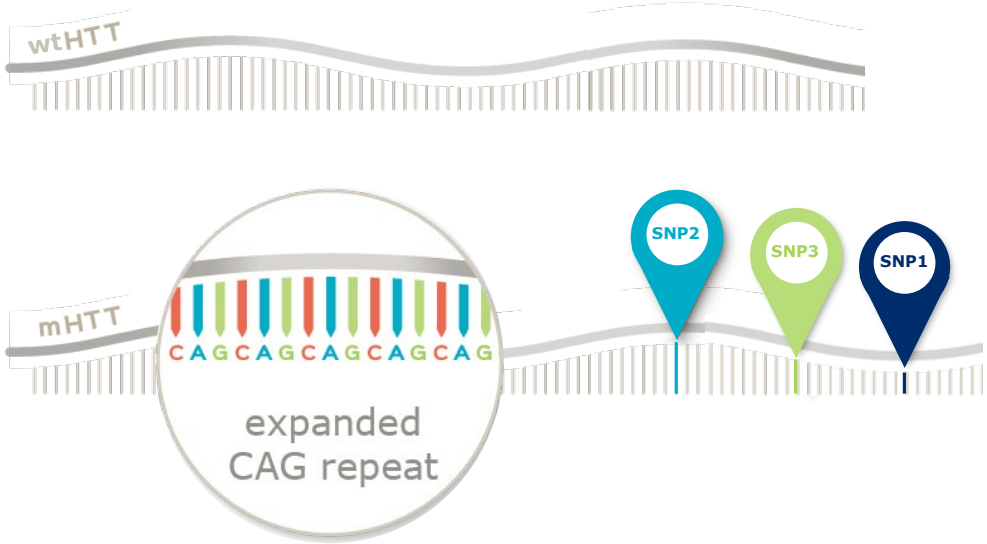
Allele-selective silencing

Aims to lower mHTT transcript while leaving healthy HTT relatively intact



RNase H and ASO:RNA



Allele-selectivity possible by targeting SNPs associated with expanded long CAG repeat in HTT gene

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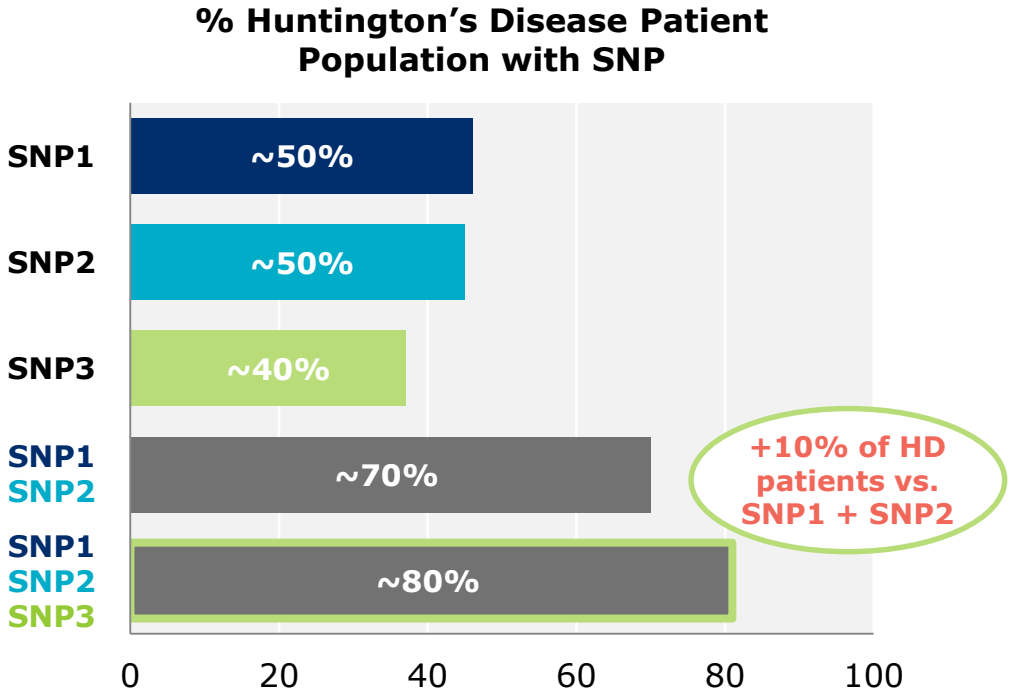
Broadening reach in Huntington's disease with SNP3 development program

SNP3

- Due to overlap, ~80% of the total HD patient population carry SNP1 and/or SNP2 and/or SNP3
- *In vivo* models for SNP3 available for preclinical development



Predicted patient coverage calculated from published phasing data from Canadian HD patients (Carroll et al., 2011)

SNP3 program

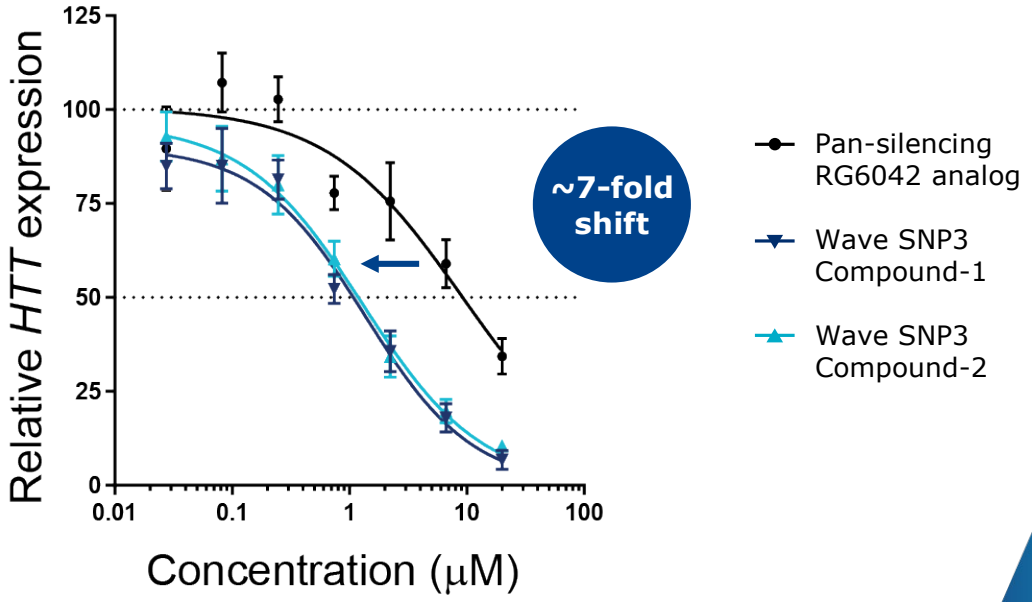
- **Potency** in homozygous iCell neurons as compared to pan-silencing compound
- **Allele-selectivity** *in vitro* as compared to pan-silencing compound
  - Biochemical assay
  - Heterozygous patient neurons
- **Target engagement** and **durability** *in vivo* in BACHD models

Potent mutant HTT knockdown activity

Wave allele-selective compounds are more potent than pan-silencing RG6042 analog in patient-derived neurons

- Greater knockdown of mutant HTT as compared to pan-silencing compound

Homozygous iCell Neurons

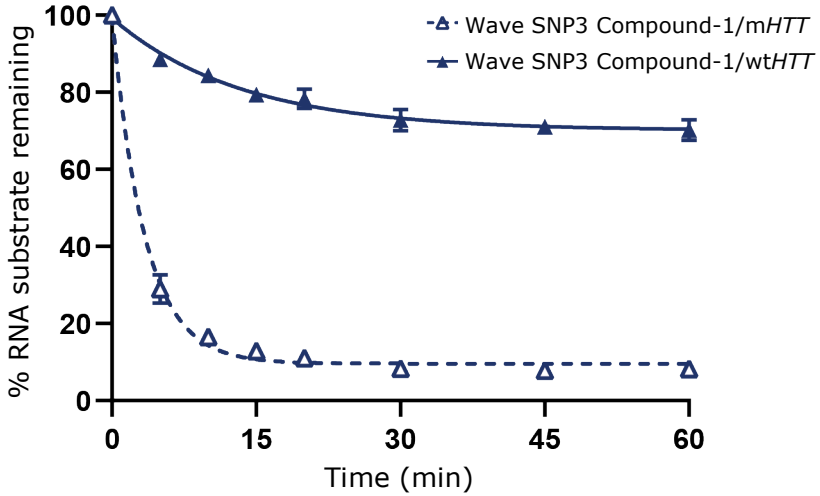


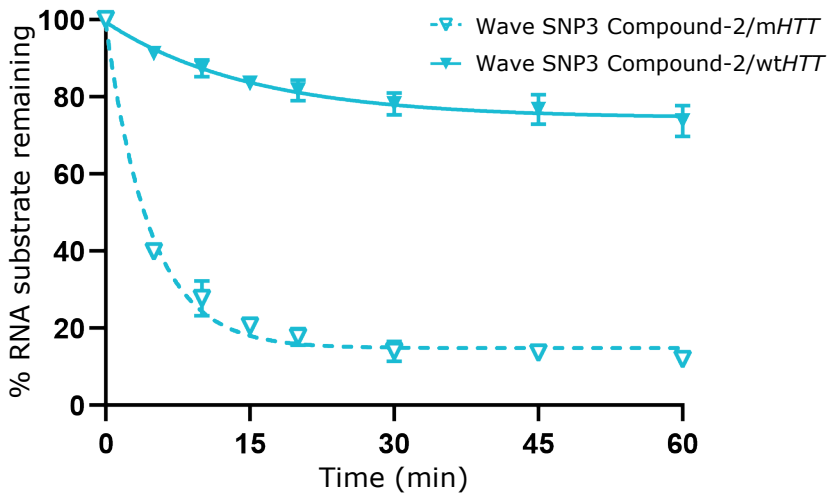
HTT mRNA remaining in iCell neurons (homozygous for SNP) incubated with the indicated ASO under free-uptake conditions. Data show mean ± sem (n=4).

Stereopure oligonucleotides are selective *in vitro*

Stereopure isomers targeting a SNP variant promote RNase H-mediated degradation of mutant *HTT* while sparing wild-type *HTT*

Biochemical RNase H assays



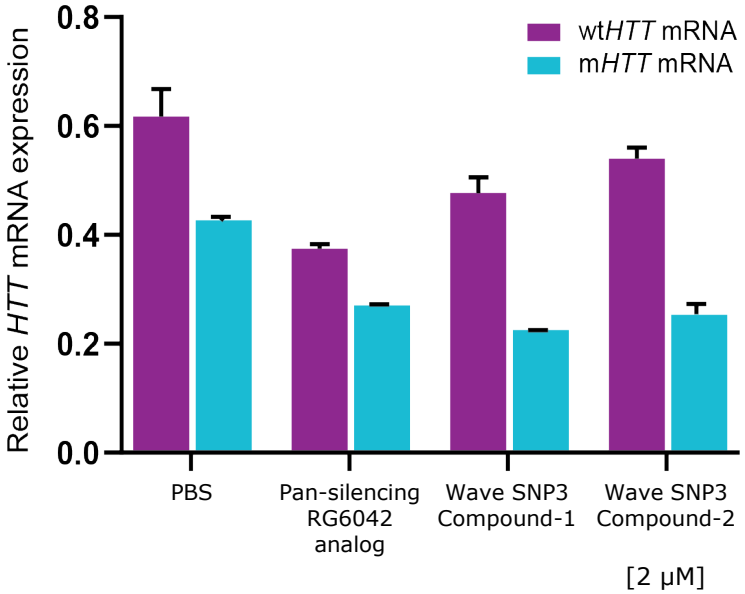


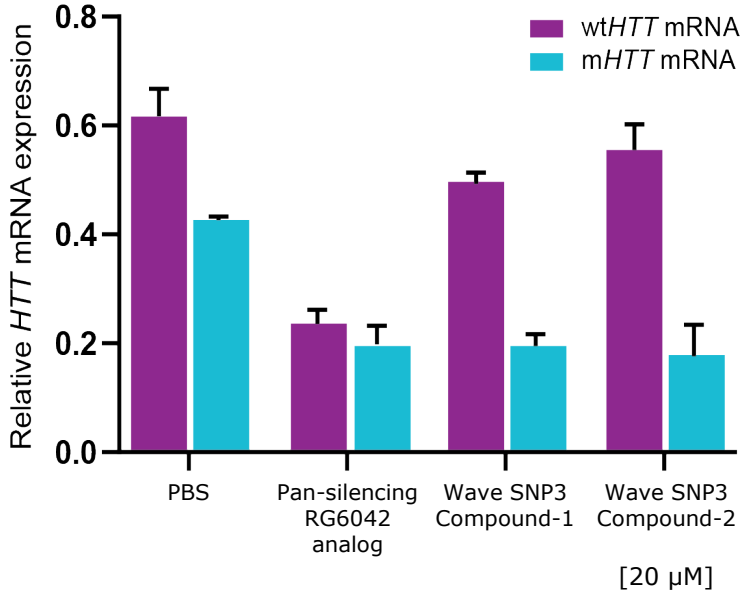
RNase H experiments performed with synthetic RNA substrates corresponding to m*HTT* and wt*HTT* variants (S:E = 100:1; n=2). Percentage of the indicated full-length RNA substrate remaining over time is plotted for the stereopure SNP3 Compound-1 (left) and stereopure SNP3 Compound-2 (right). Abbreviations: S, substrate; E, enzyme.

Demonstration of allele-selective silencing

Stereopure compounds selectively deplete mutant *HTT* mRNA

No loss of selectivity with increasing concentrations





Neurons were derived from GM21756 patient-derived fibroblasts (heterozygous for SNP) and treated with 2.2 μM (left) or 20 μM (right) of the indicated ASO under gymnotic conditions for 7 days. RNA was quantified and normalized to *TUBB3*. Data are mean ± sem (n=3). Percentage of remaining wt*HTT* and m*HTT* mRNA is indicated.

In vivo model to assess target engagement and durability

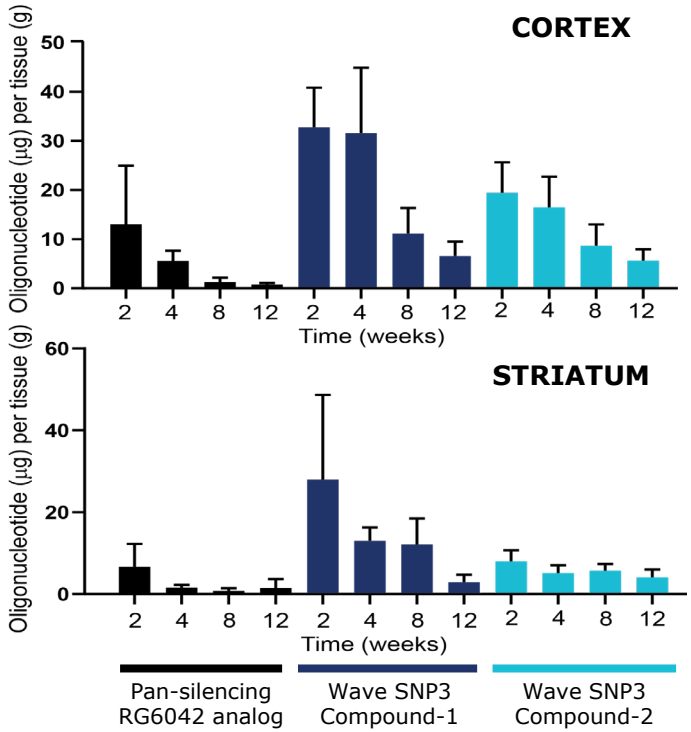
BACHD mouse model

- Expressed transcript includes SNP3 variant that Wave compounds are targeting
- Model is homozygous for mutant *HTT* with SNP3 (only has one type of *HTT*)
- Over-expresses m*HTT* (multiple gene copies)
- No ability to assess allele selectivity

Oligonucleotide concentration in tissues

- Achieved good tissue exposure over 12-weeks in BACHD cortex and striatum

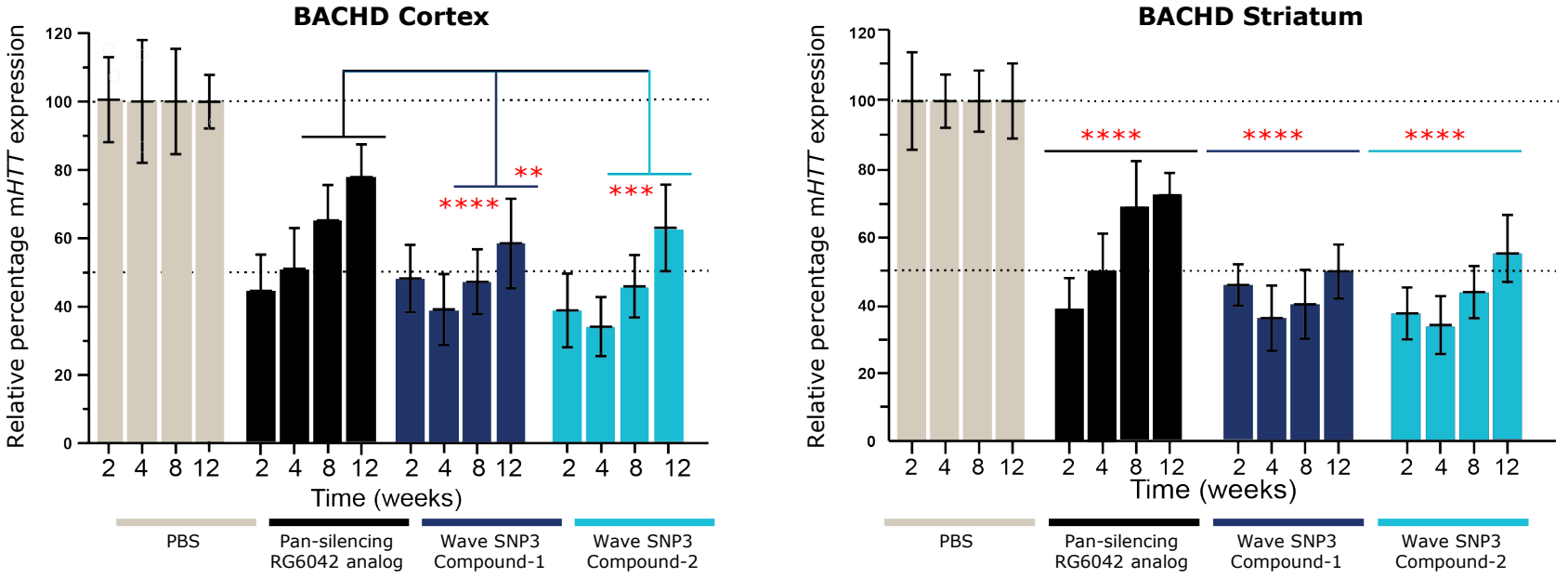
Tissue exposure over time



Oligonucleotide or PBS (3 x 100 µg ICV) was delivered to BACHD mice. Oligonucleotides were quantified by ELISA.

Durable *in vivo* mutant *HTT* knockdown with stereopure SNP3 compounds

Knockdown persists for 12 weeks



BACHD model only has mutant HTT (no wildtype HTT)

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Oligonucleotide or PBS (3 x 100 mg ICV) was delivered to BACHD mice. Relative percentage of HTT/TUBB3 mRNA in cortex with respect to levels in PBS-treated mice is shown at 2-12 weeks post-injection. Statistics: All oligo treatment groups are statistically significantly different from PBS; One-way ANOVA ****, P≤0.0001. Wave SNP3 Compound-1 and Compound-2 are also significantly different from RG6042 analog at 8 and 12 weeks ***, P<0.005; **P=0.001.

Lead Inherited Retinal Disease Program: USH2A

Michael Byrne, Ph.D.
Director In Vivo Biology and Ophthalmology
Wave Life Sciences

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Stereopure oligonucleotides for inherited retinal diseases (IRDs)

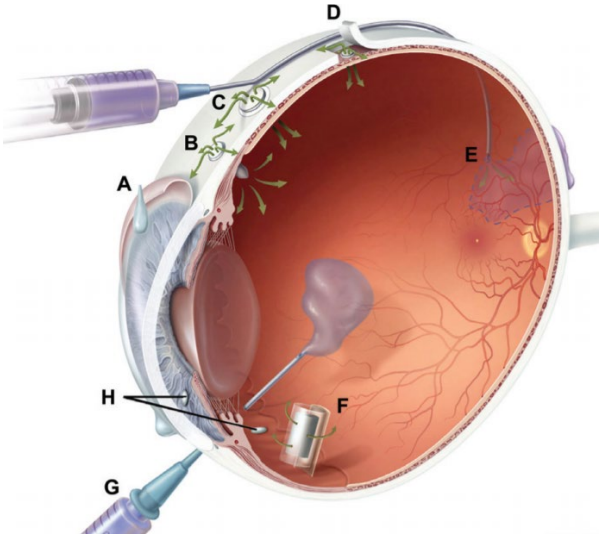
Wave ophthalmology opportunity

- Oligonucleotides can be administered by intravitreal (IVT) injection; targeting twice per year dosing
- Stereopure oligonucleotides open novel strategies in both dominant and recessive IRDs; potential for potent and durable effect with low immune response

Successful targeting of *MALAT1* is a surrogate for an ASO mechanism of action

- Widely expressed in many different cell types
- Only expressed in the nucleus

Lead program USH2A

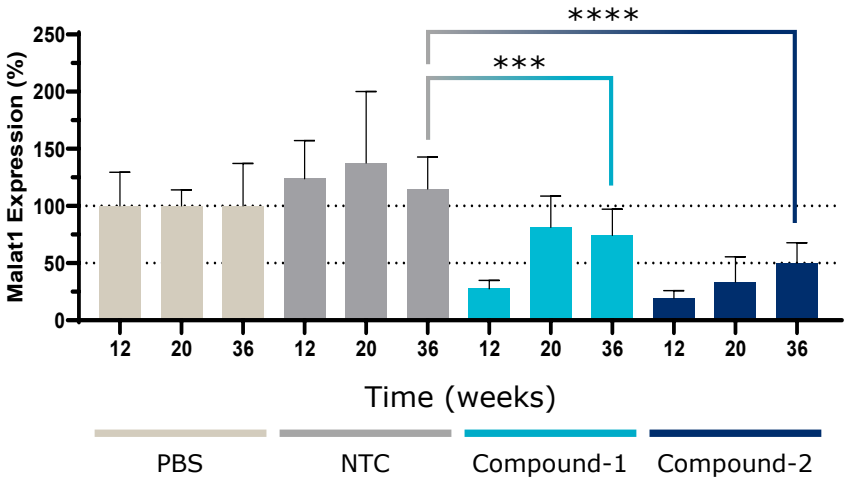


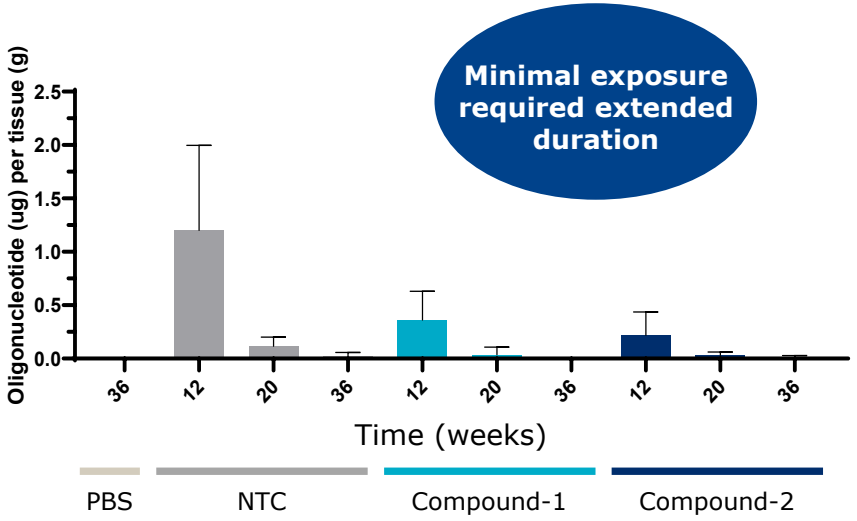
Intravitreal injection

Sources: Daiger S, et al. *Clin Genet*. 2013;84:132-141. Wong CH, et al. *Biostatistics*. 2018; DOI: 10.1093/biostatistics/kxx069. Athanasiou D, et al. *Prog Retin Eye Res*. 2018;62:1–23. Daiger S, et al. *Cold Spring Harb Perspect Med*. 2015;5:a017129. Verbakel S, et al. *Prog Retin Eye Res*. 2018:66:157-186.; Short, B.G.; *Toxicology Pathology*, Jan 2008.

Stereopure compounds durably deplete *MALAT1* for 9 months *in vivo*

~50% *MALAT1* knockdown at 9 months in the posterior of the eye



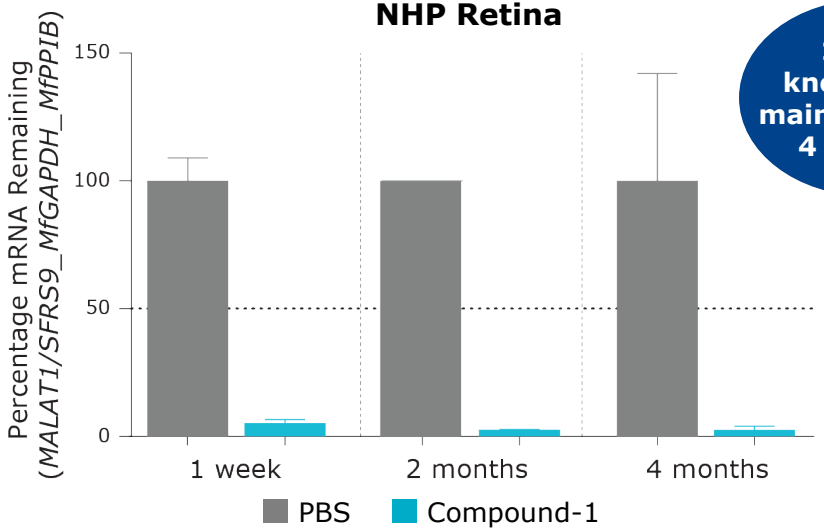


Compound or PBS (1 x 50 mg IVT) was delivered to C57BL6 mice. Relative percentage of Malat1 RNA in the posterior of the eye (retina, choroid, sclera) to PBS-treated mice is shown at 12, 20 and 36 weeks post-single injection. Statistics: Compound-2 Malat1 levels are significantly different from NTC at 36 weeks ***, P<0.001; **** P<0.0001, respectively. PBS = phosphate buffered saline; NTC= chemistry matched non-targeting control; Compound-1 and Compound-2 are stereopure MALAT1-targeting antisense oligonucleotide.

Stereopure compound induces potent and durable *MALAT1* knockdown in the eye

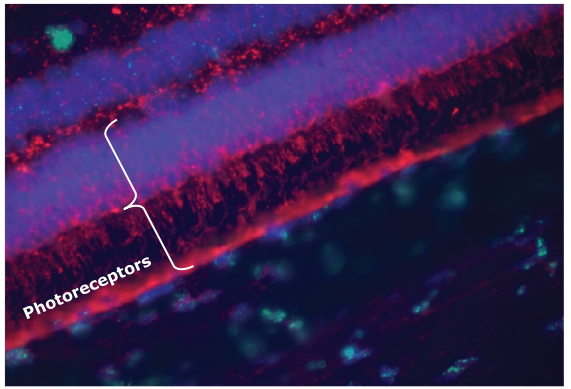
90% knockdown of *MALAT1* in NHP Retina

In vivo duration of effect in the NHP Retina



>90% knockdown maintained for 4 months

Compound-1 detected in NHP Retina 4-months post-dose

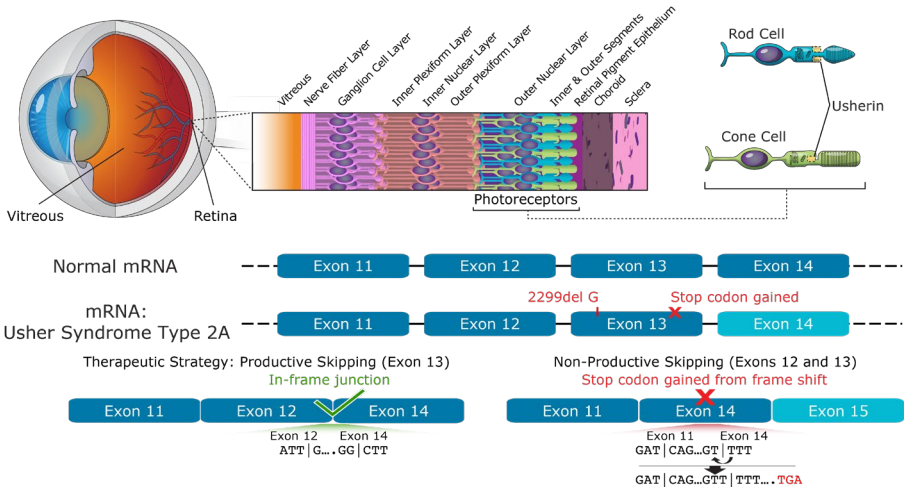


Cell Nuclei Compound-1 *MALAT1* RNA

Oligonucleotide or PBS (1 x 450 μg IVT) was delivered to NHP. Relative percentage of *MALAT1* RNA in the retina to PBS-treated is shown at 1 week, 2 and 4 months, post-single injection. Compound-1 is a stereopure *MALAT1*-RNA-targeting antisense oligonucleotide.

Usher Syndrome Type 2A: a progressive vision loss disorder

- Autosomal recessive disease characterized by hearing loss at birth and progressive vision loss beginning in adolescence or adulthood
- Caused by mutations in USH2A gene (72 exons) that disrupt production of usherin protein in retina, leading to degeneration of the photoreceptors
- No approved disease-modifying therapies
- **~5,000 addressable patients in US**



Oligonucleotides that promote USH2A exon 13 skipping may restore production of functional usherin protein

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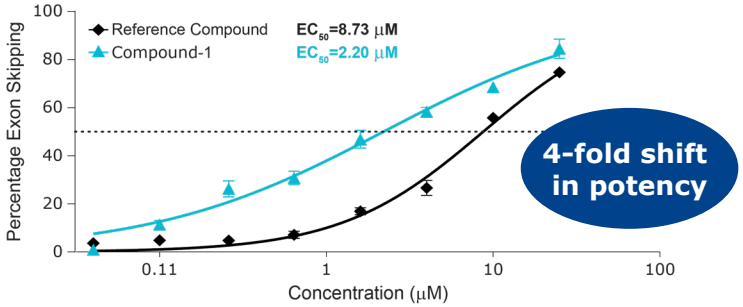
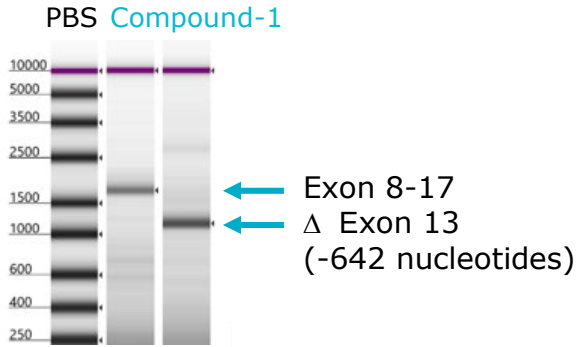
Sources: Boughman et al., 1983. *J Chron Dis*. 36:595-603; Seyedahmadi et al., 2004. *Exp Eye Res.* 79:167-173; Liu et al., 2007. *Proc Natl Acad Sci USA* 104:4413-4418.

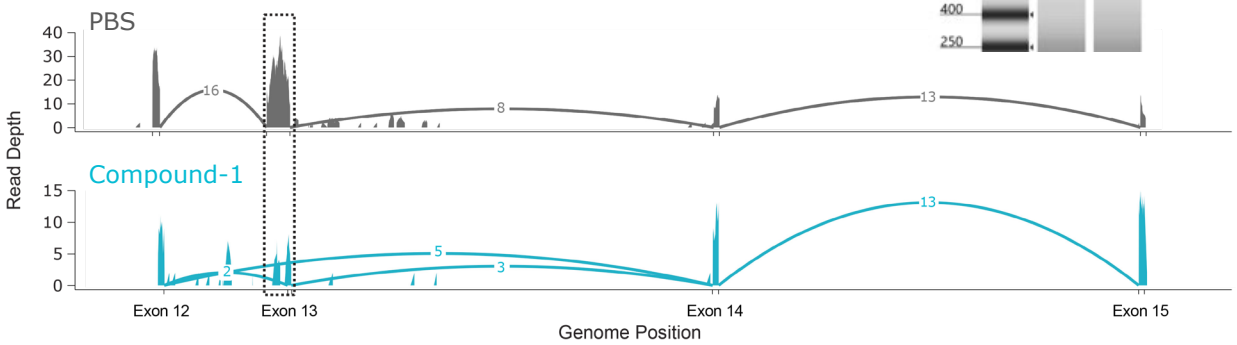
Productive USH2A exon 13 skipping with stereopure compound

Exon skipping in Y79 cells



Gel shift & RNA-seq confirm productive exon skipping





Compounds were added to Y79 cells under free-uptake conditions. Exon skipping was evaluated by Taqman assays. *USH2A* transcripts were normalized to *SRSF9*. Data are mean±s.d., n=2. Primers mapping to exons 8 and 17 were used to amplify region containing skipped exon. RNA-Seq was performed on the miSEQ platform. Reference Compound: van Diepen *et al.* 2018. Antisense oligonucleotides for the treatment of eye disease. W02018055134A1. Compound-1 is a stereopure antisense oligonucleotide.

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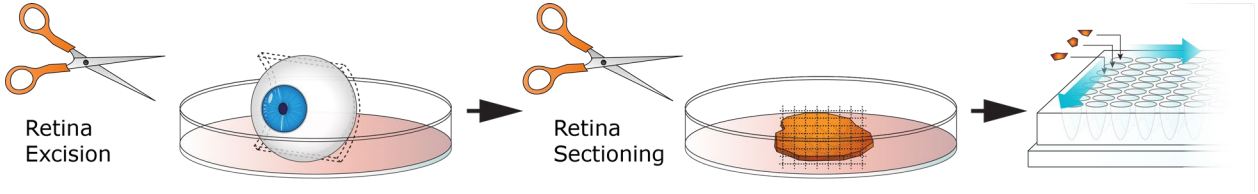
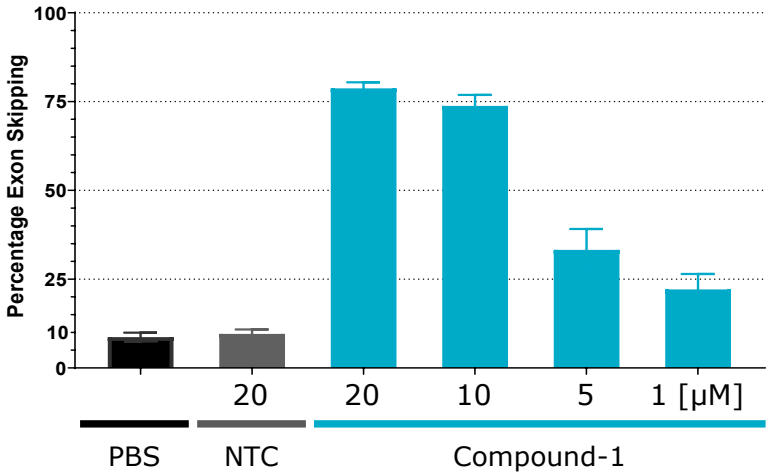
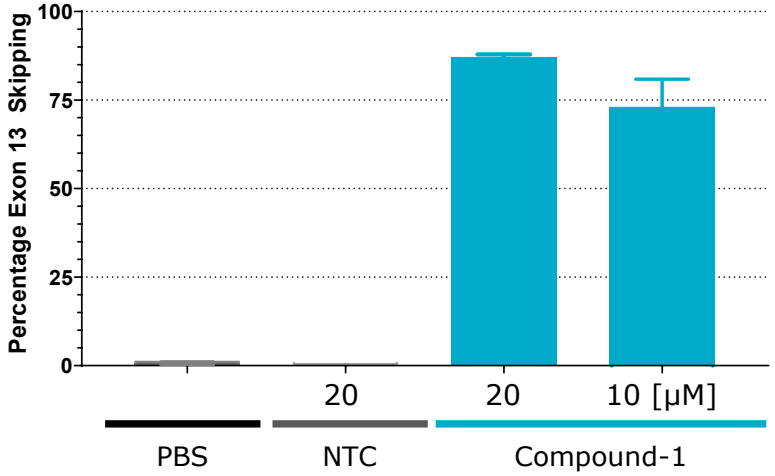
Potent USH2A exon skipping *ex vivo* in NHP and human retinas



Target engagement in NHP (left) and human (right) retinas

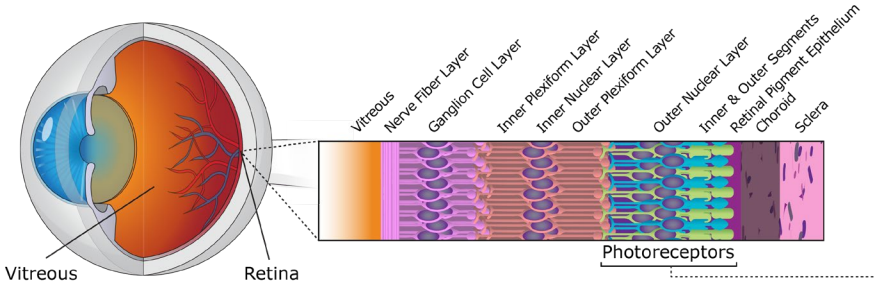




Whole NHP and human eyes were enucleated (n=4 and n=2, respectively) and compounds (1–20 μM) were added to extracted retinas under free-uptake conditions. Exon skipping was evaluated by Taqman assays on RNA. USH2A transcript levels were normalized to SRSF9. Data presented are mean± s.e.m. Compound-1 is a stereopure antisense oligonucleotide.

Autosomal dominant retinitis pigmentosa (adRP) associated with Rhodopsin P23H mutation

- Retinitis pigmentosa (RP) is a group of rare, genetic disorders of the eye resulting in progressive photoreceptor cell death and gradual functional loss
- Currently no cure for RP
- ~10% of US autosomal dominant RP cases are caused by the P23H mutation in the rhodopsin gene (RHO)
- Mutant P23H rhodopsin protein is thought to misfold and co-aggregate with wild-type rhodopsin, resulting in a gain-of-function or dominant negative effect in rod photoreceptor cells
- **~1,800 addressable patients in US**



Allele-selective reduction of the mutant P23H allele while maintaining the wild type rhodopsin allele may prevent further cell loss

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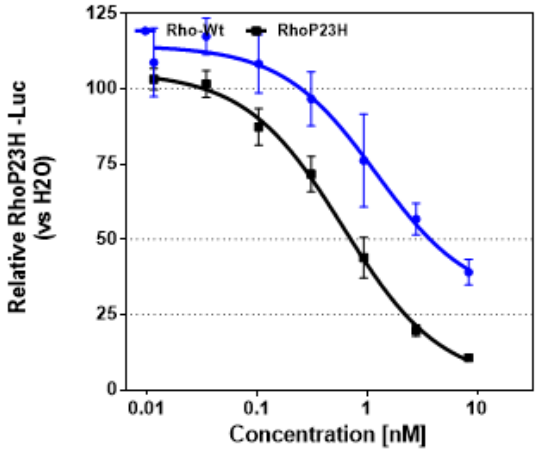
Ferrari et al., *Current Genomics.* 2011;12:238-249.

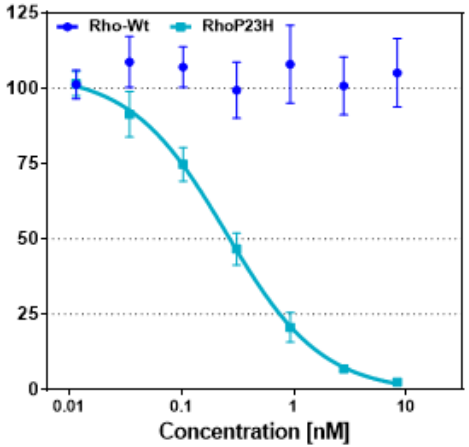
adRP associated with Rhodopsin P23H mutation

Stereopure oligonucleotides achieve allele-selective reduction of SNP-containing allele

Stereorandom



Stereopure



In vivo

Collaborations in place for evaluation in transgenic human Rho P23H pig model

Stereopure compound is allele selective compared with stereorandom

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Reporter assays on a Wave stereopure sequence as well as a sequence described in WO2016138353A1: ASO and luciferase reporter plasmids (wild-type and mutant rhodopsin) are transfected into Cos7 cells. 48-hours later, cells are harvested, and relative luminescence is measured.

Summary

- Wave stereopure compounds induce potent and durable *MALAT1* knockdown in the eye
- USH2A is Wave's lead ophthalmology program
  - Productive USH2A exon 13 skipping in cellular models
  - Confirmed skipping at the sequence level
  - Potent exon skipping demonstrated *ex vivo* in NHP and human retinas
  - USH2A *in vivo* studies ongoing
- Discovery work underway for second ophthalmology program (RHO P23H)

IND-enabling studies for USH2A candidate expected to begin in 2020

Conclusion

Paul Bolno, MD, MBA
President and CEO
Wave Life Sciences

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Analyst and Investor Research Day

OCTOBER 7, 2019
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