PTC R&D Day

December 2, 2025

R&D Day 2025 Agenda

Welcome and Introduction
Matthew Klein, MD

Oral Small Molecule Splicing Platform: Overview & Programs
Christopher Trotta, PhD
Anu Bhattacharyya, PhD

Splicing Q&A

Inflammation & Ferroptosis Platform: Overview & Programs
Jeff Trimmer, PhD
Mayzie Johnston, PharmD

Inflammation & Ferroptosis Q&A

Closing Remarks
Matthew Klein, MD

Forward Looking Statements

This presentation contains forward-looking statements within the meaning of The Private Securities Litigation Reform Act of 1995. All statements contained in this presentation, other than statements of historic fact, are forward-looking statements, including statements regarding: the future expectations, plans and prospects for PTC, including with respect to the expected timing of clinical trials and studies, availability of data, regulatory submissions and responses and other matters with respect to its products and product candidates; PTC's strategy, future operations, future financial position, future revenues, projected costs; and the objectives of management. Other forward-looking statements may be identified by the words, "guidance," "plan," "anticipate," "believe," "estimate," "expect," "intend," "may," "target," "potential," "will," "would," "could," "should," "continue," "aim," and similar expressions.

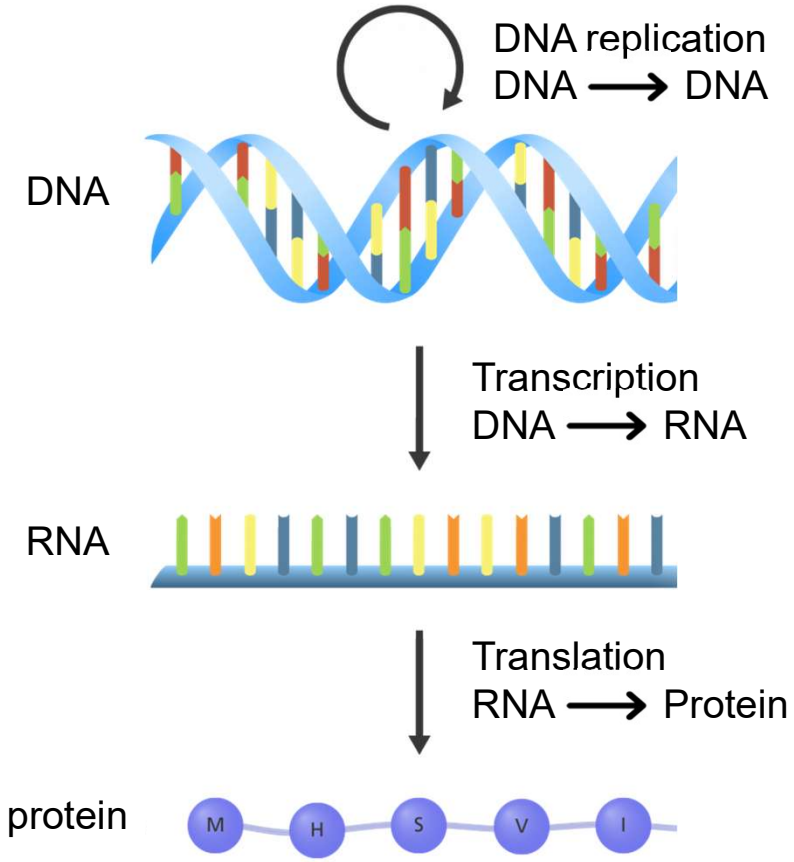
PTC's actual results, performance or achievements could differ materially from those expressed or implied by forward-looking statements it makes as a result of a variety of risks and uncertainties, including those related to: the outcome of pricing, coverage and reimbursement negotiations with third party payors for PTC's products or product candidates that PTC commercializes or may commercialize in the future; significant business effects, including the effects of industry, market, economic, political or regulatory conditions; changes in tax and other laws, regulations, rates and policies; the eligible patient base and commercial potential of PTC's products and product candidates; PTC's scientific approach and general development progress; and the factors discussed in the "Risk Factors" section of PTC's most recent Quarterly Report on Form 10-Q and Annual Report on Form 10-K, as well as any updates to these risk factors filed from time to time in PTC's other filings with the SEC. You are urged to carefully consider all such factors.

As with any pharmaceutical under development, there are significant risks in the development, regulatory approval and commercialization of new products. There are no guarantees that any product will receive or maintain regulatory approval in any territory, or prove to be commercially successful.

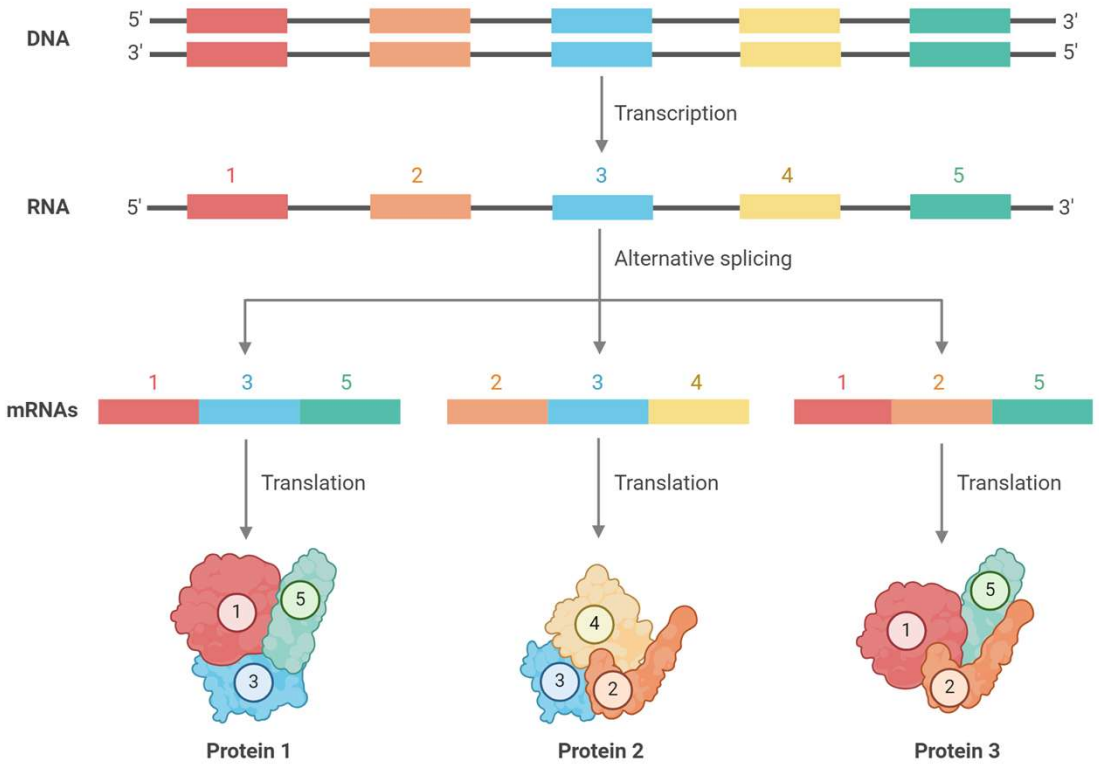
The forward-looking statements contained herein represent PTC's views only as of the date of this presentation and PTC does not undertake or plan to update or revise any such forward-looking statements to reflect actual results or changes in plans, prospects, assumptions, estimates or projections, or other circumstances occurring after the date of this presentation except as required by law.

Oral Small Molecule Splicing Program Overview

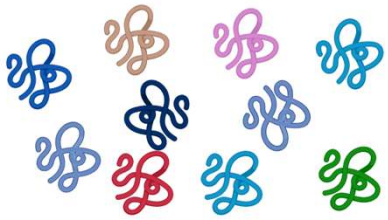
Central Dogma of Life: DNA to RNA to Protein



Splicing Enables Diversity of Protein Production from Limited Number of Genes



20,000 genes



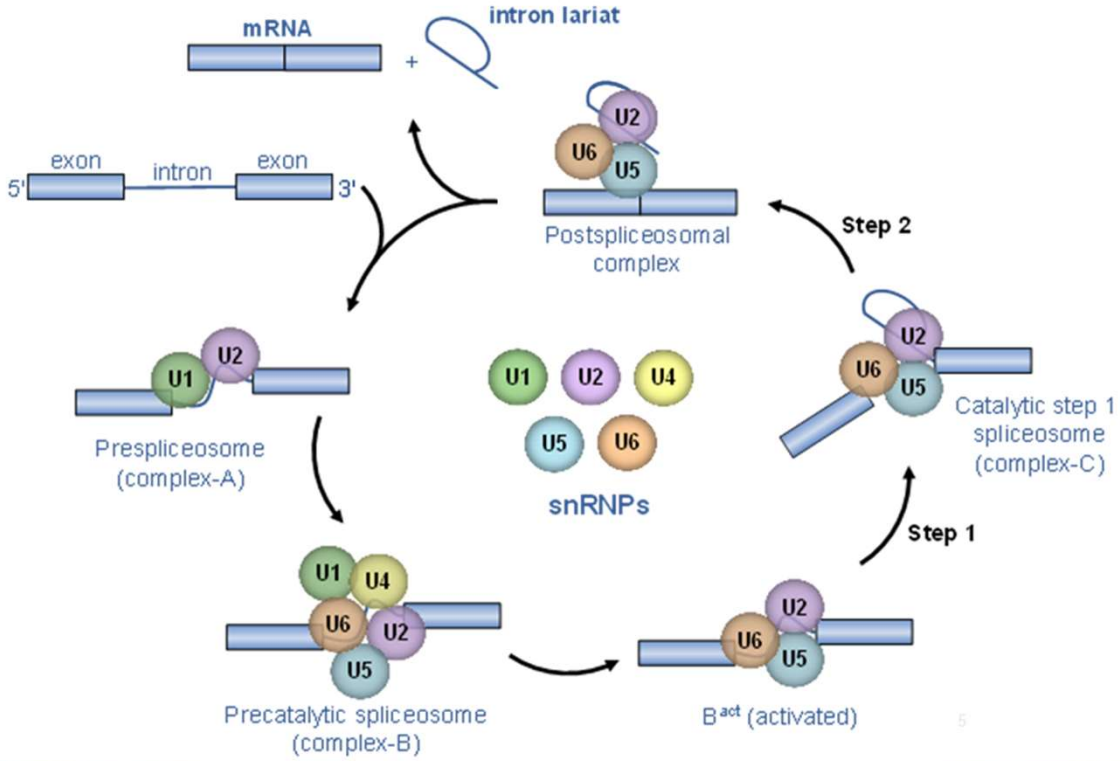
1,000,000 proteins

Richard Roberts **Phillip Sharp**

1993

Pre-mRNA Splicing is a Complex Process Rich in Potential Targets

Splicing is a multi-step process using many RNA-enzyme interactions



Why Small Molecule (Oral) Splicing Molecules?

- Antisense oligonucleotides have historically been used to correct splicing abnormalities
  - Lack of oral bioavailability
  - Do not cross the blood-brain barrier
  - Require repeat intrathecal or intraparenchymal delivery yet incomplete brain distribution
- Small molecules hold great appeal
  - Broadly biodistributed—ideal for CNS and whole-body diseases
  - Simpler scale up and manufacturing
  - More amenable to dose titration

PTC Pioneered Small Molecule Splicing Therapies

Global leading spinal muscular atrophy (SMA) therapy approved in > 100 countries

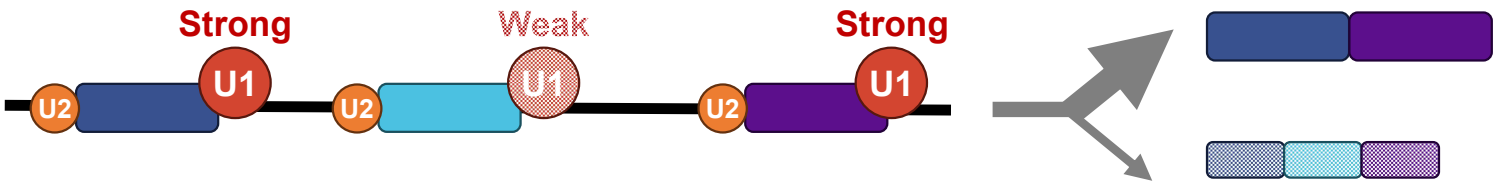
votoplam (PTC518)

Leading oral disease-modifying therapy in development for Huntington's disease

Our two flagship splicing programs remain at the **forefront of innovation** for small molecule oral therapies

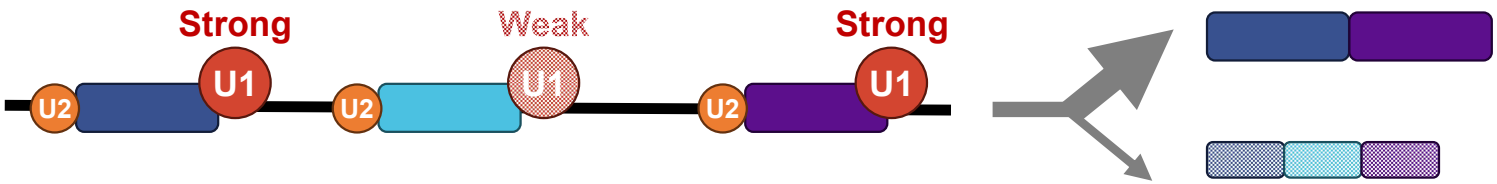
Evrysdi commercialized by Roche and votoplam licensed to Novartis

Small Molecules Target U1-RNA Interaction to Affect mRNA Composition and Protein Expression



U1 U2 **Spliceosome subunits that define splice sites in pre-mRNA**

Small Molecule Enhancement of U1 Interaction Leads to Increased Inclusion of Exons

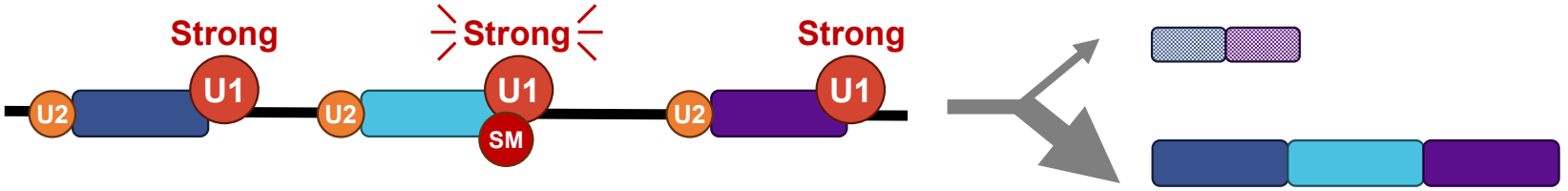


SM

Targeting must be highly specific for RNA sequence and binding site morphology

U1 U2 **Spliceosome subunits that define splice sites in pre-mRNA**

Small Molecule Enhancement of U1 Interaction Leads to Increased Inclusion of Exons



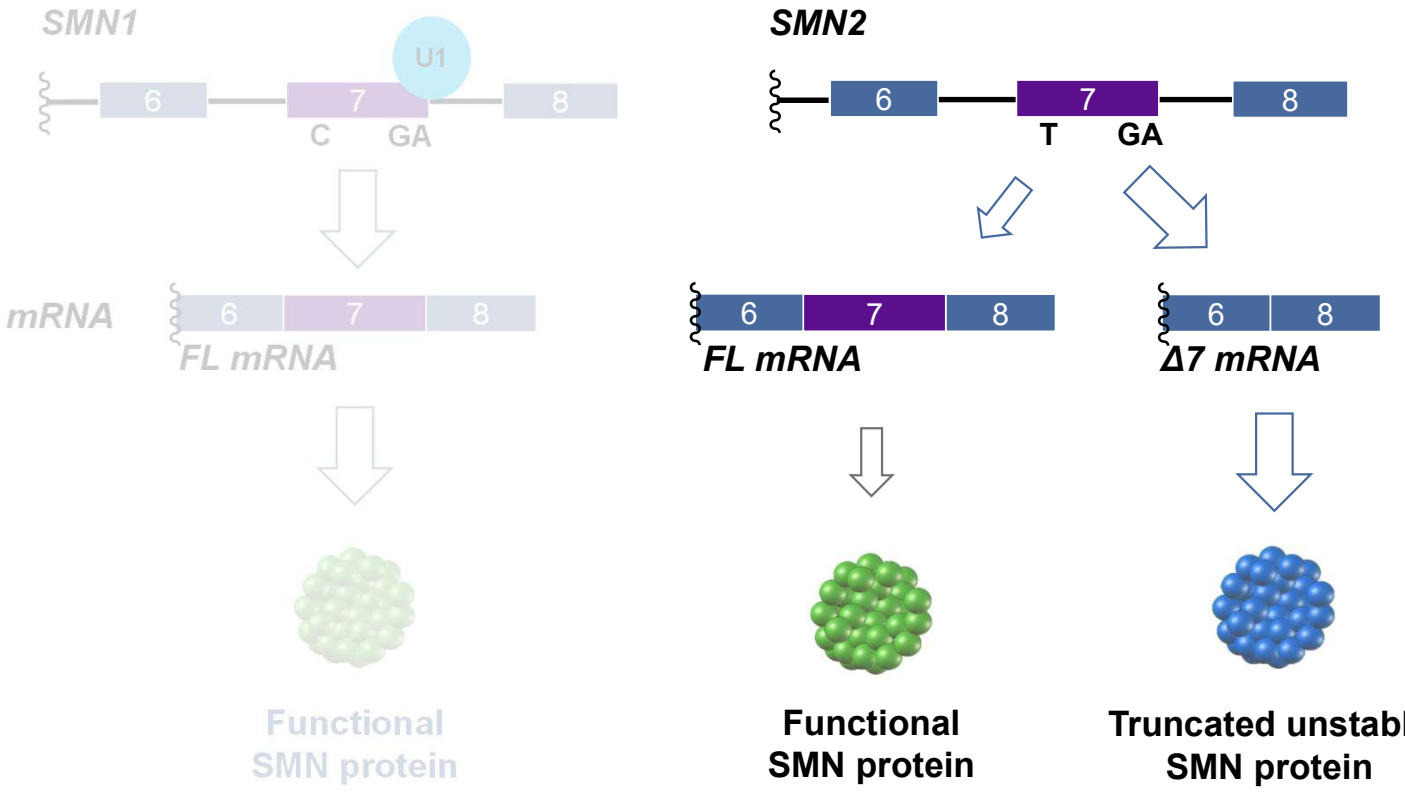
Distinct mRNA transcripts are generated

Evrysdi® risdiplam — Exon inclusion leading to increase of functional SMN protein deficient in SMA

votoplam (PTC518) — Exon inclusion leading to decrease of mutant HTT protein—the disease causing protein

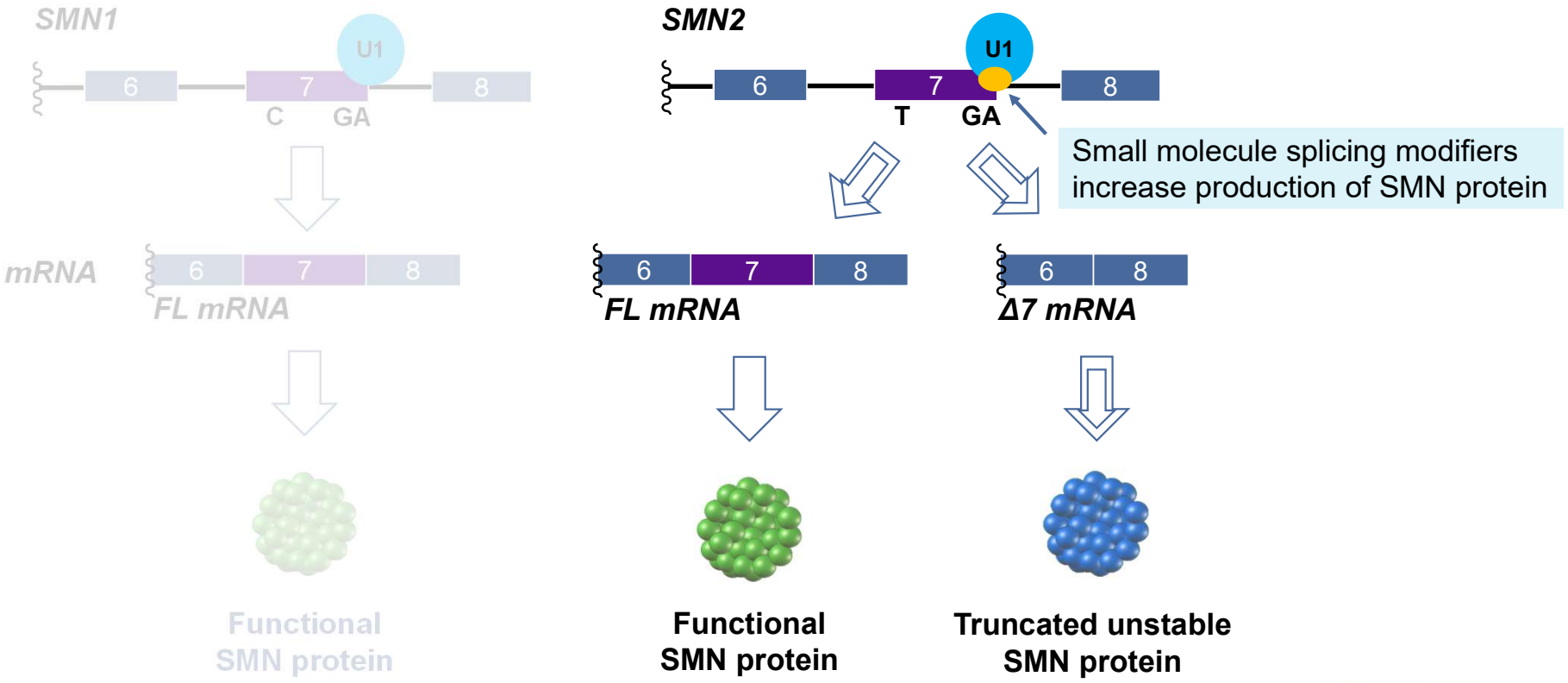
U1 U2 **Spliceosome subunits that define splice sites in pre-mRNA**

Targeting Alternative Splicing of SMN2 Gene to Address SMA Pathology



Singh et al. Crit rev euk gene expr (2004)
Cho and Dreyfuss. Genes Dev. (2010)

Targeting Alternative Splicing of SMN2 Gene to Address SMA Pathology

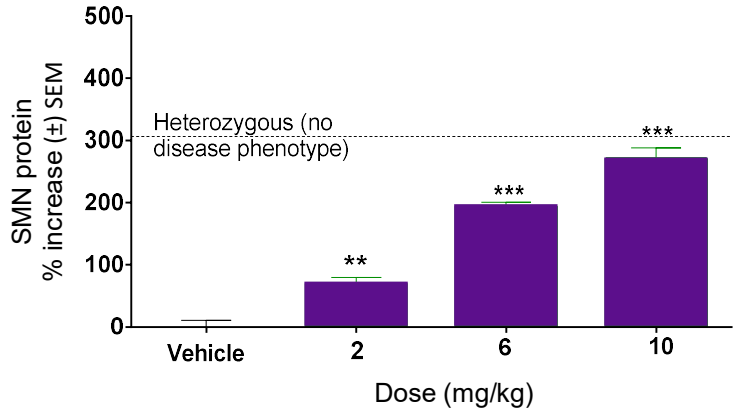


Singh et al. Crit rev euk gene expr (2004)
Cho and Dreyfuss. Genes Dev. (2010)

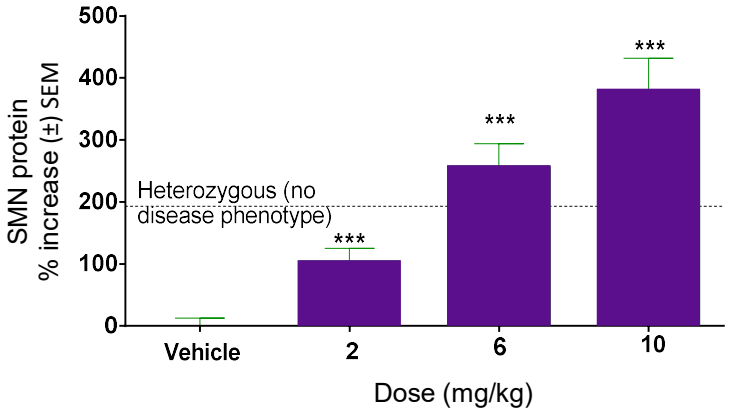
Splicing Modulator Increases SMN Protein in Multiple Tissues to Near or Above Heterozygous Levels

Oral dosing for 10 days in mild SMA mouse model

Brain



Peripheral Blood Mononuclear Cells



SMN protein levels in peripheral blood cells correlate to those in brain

Similar increases in SMN observed in spinal cord, muscle, heart, liver, skin

Naryshkin et al. Science 2014

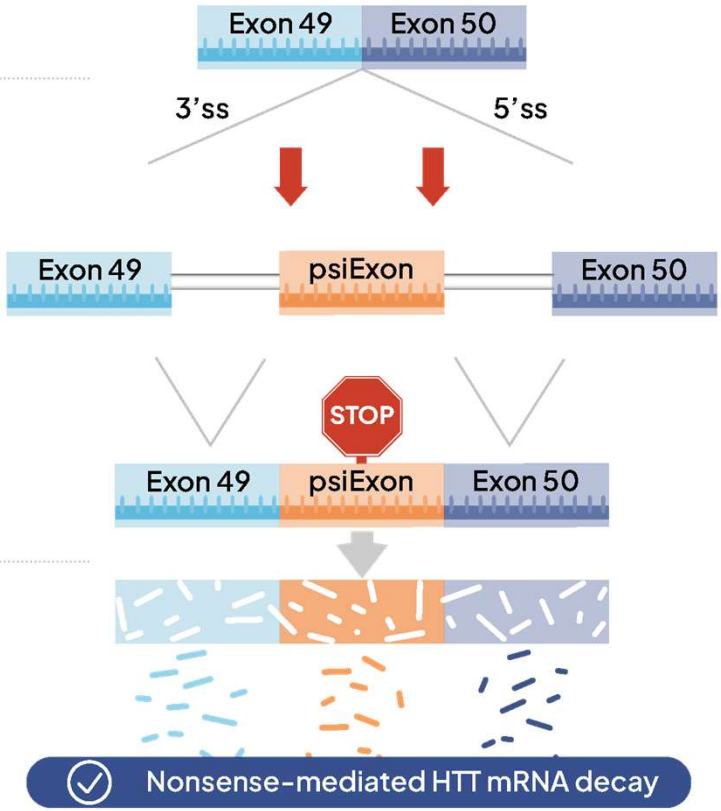
Novel Splicing Mechanism Leading to Degradation of Mutant HTT mRNA to Decrease Toxic Protein Levels

No compound

Pseudoexon is not spliced in;
full length HTT protein is produced

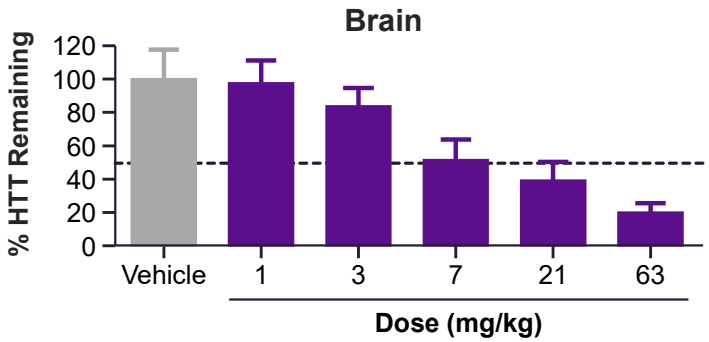
With votoplam

Pseudoexon is spliced in;
Nonsense mutation leads
to mRNA degradation

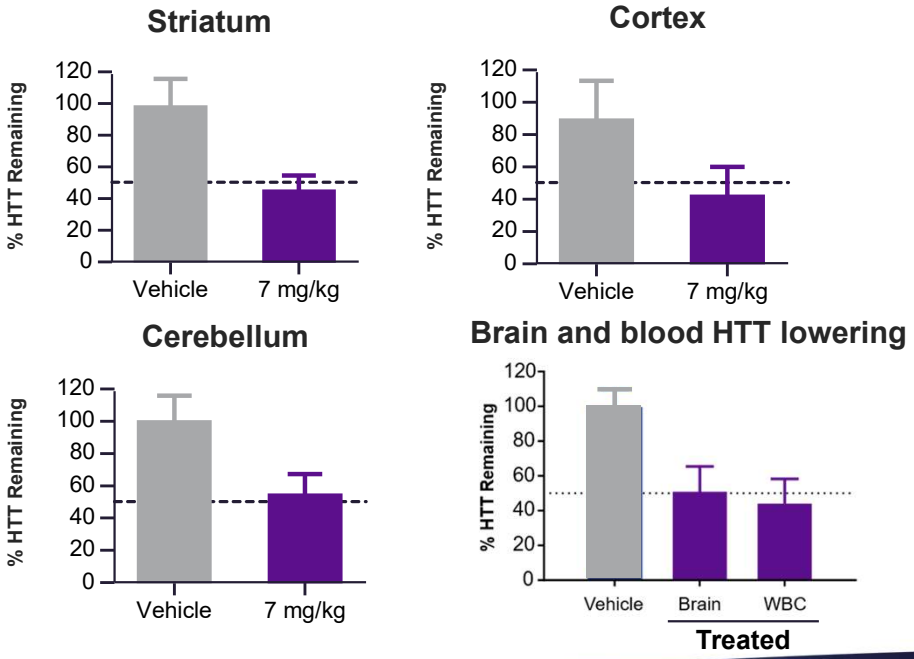


HD Splicing Small Molecules Demonstrate Broad Tissue Distribution in BACHD Mice

Dose dependent HTT lowering in the brain in BACHD mice

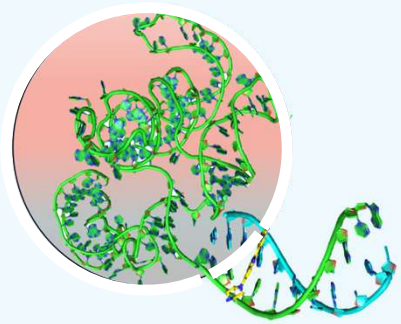


Measurements demonstrate uniform HTT lowering across brain regions with ~1:1 brain and blood concentrations



PTC has Leveraged the Learnings from SMA and HD Programs to Build a Robust Discovery Platform Including PTSeek™ Screening Technology

Splicing Foundation



2005 — 2020

- SMA
- Huntington's disease

Splicing Platform

- Database
- Screening tools
- Library

Splicing Future

PTSeek™

2025 and beyond

- Neurodegenerative Diseases
- Oncology
- Metabolic Disorders

Oral Small Molecule Splicing Platform

Christopher Trotta, PhD
Anu Bhattacharyya, PhD

Targeting RNA Significantly Increases Druggable Target Space

DNA

Pre-mRNA

PROTEIN

Traditional small molecule targets

- GPCRs
- Enzymes
- Ion Channels
- Nuclear Receptors

Targeting RNA Splicing with small molecules has significantly expanded the pool of therapeutic targets

PTSeek™

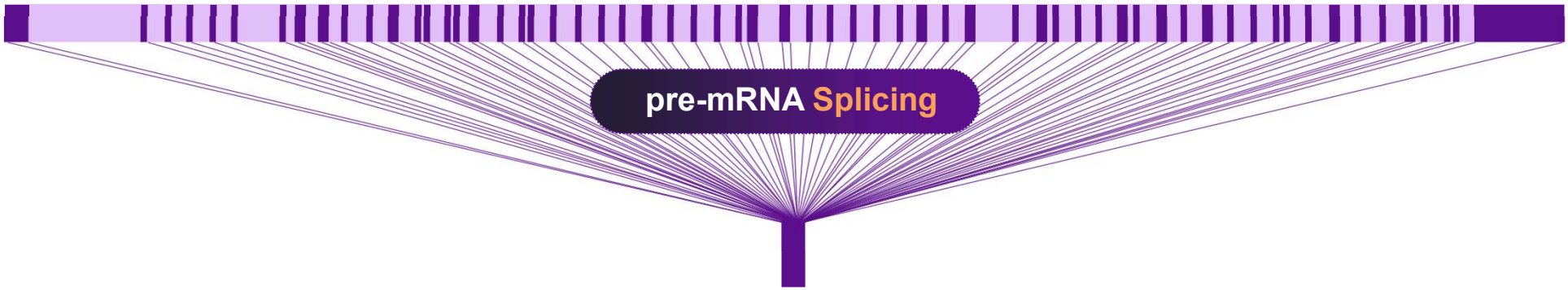
Small molecule splicing modulator discovery engine

10 - 15% are druggable with small molecules

PTC Has Pioneered Targeting RNA Splicing

Huntingtin pre-mRNA

180,000 nucleotides, 67 exons, 66 introns

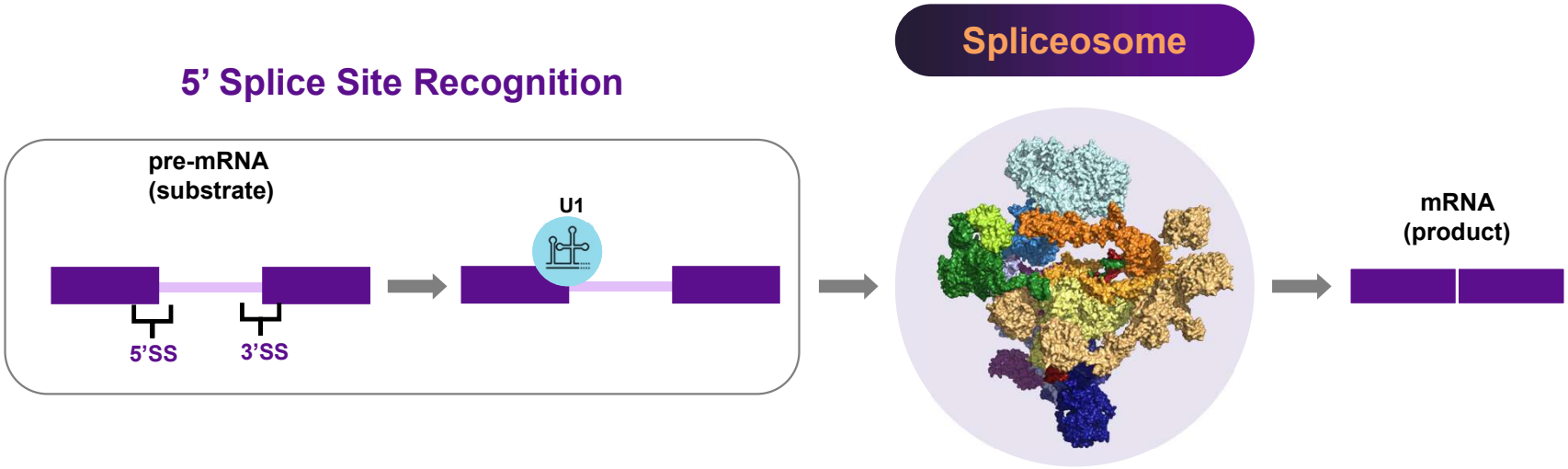


Huntingtin mRNA

13,000 nucleotides, 67 exons

intron exon

Deep Understanding of Splicing has Enabled Identification of the Key Targetable Step in Pre-mRNA Splicing



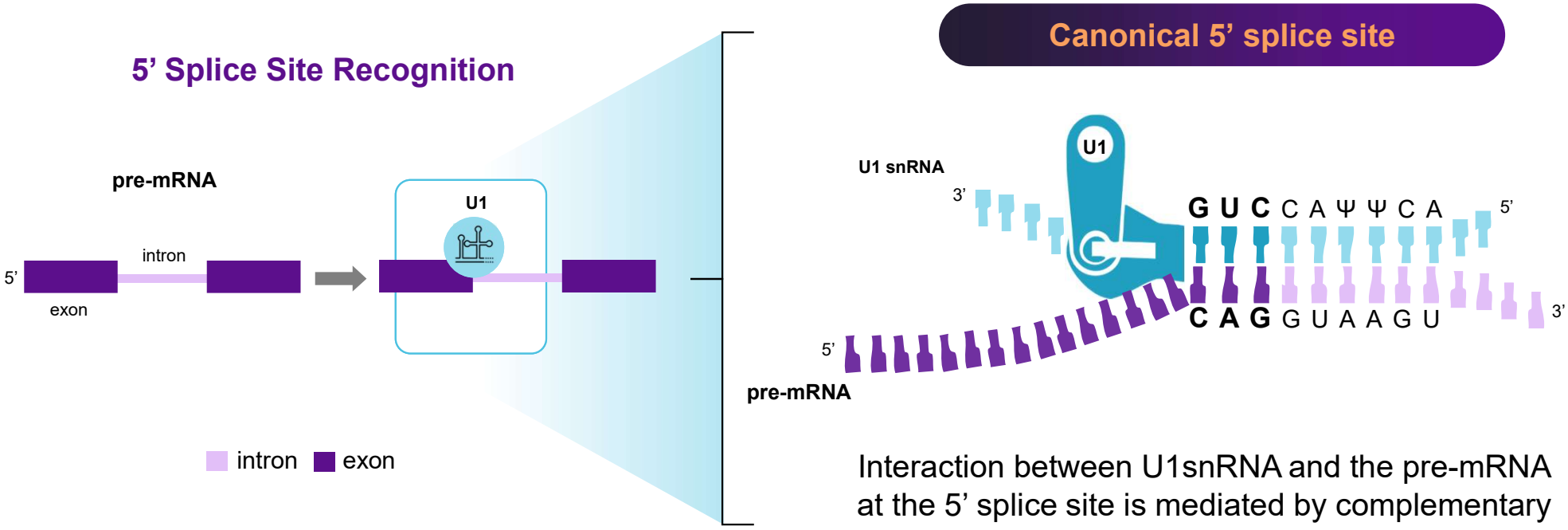
Recognition of a 5’ splice site by U1 snRNP is key step in pre-mRNA engagement

The Spliceosome is a complex and dynamic single turnover enzyme

intron exon

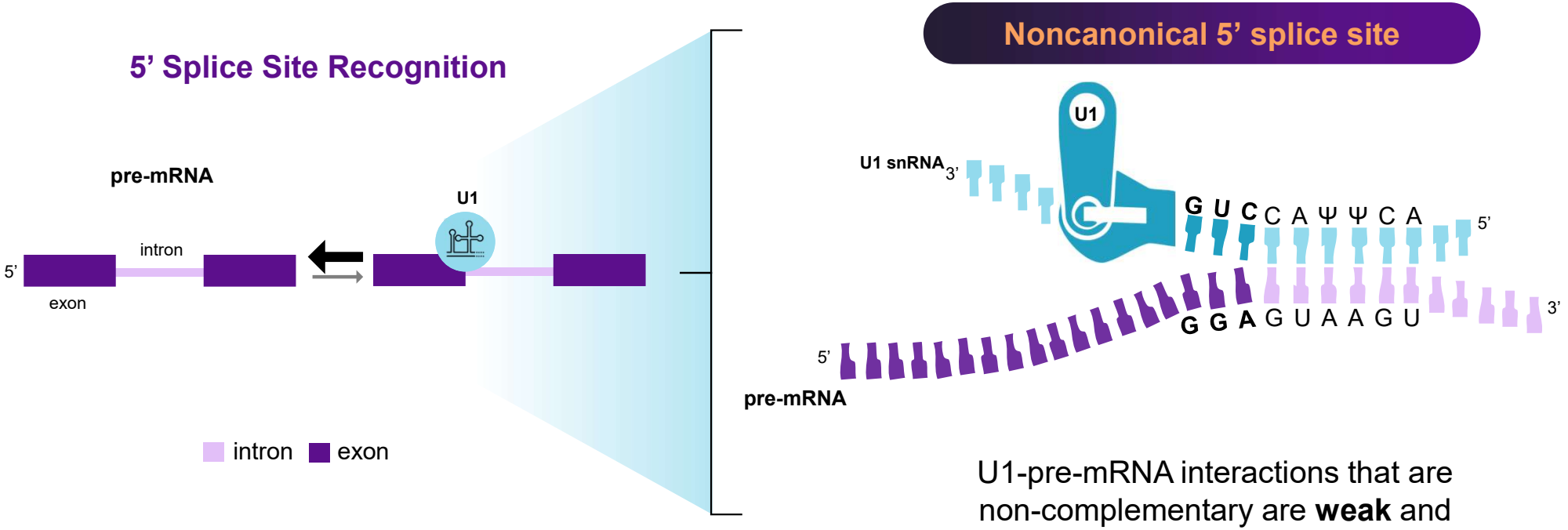
Kosmyna and Query Nature (2016)

U1 Binding to the 5’ Splice Site is Mediated by Formation of a Stable RNA duplex



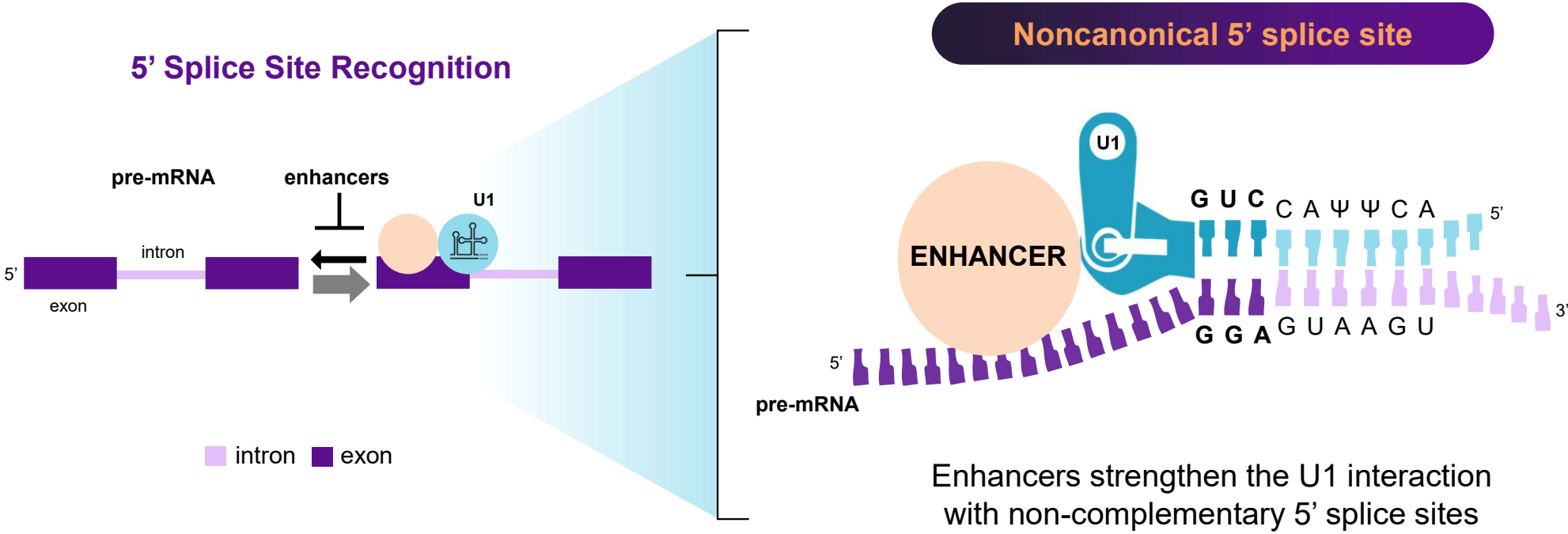
Interaction between U1snRNA and the pre-mRNA at the 5’ splice site is mediated by complementary base-pairing and base-stacking interactions

U1 Binding to the 5’ Splice Site of a Noncanonical 5’ Splice Site Forms an Unstable RNA Duplex



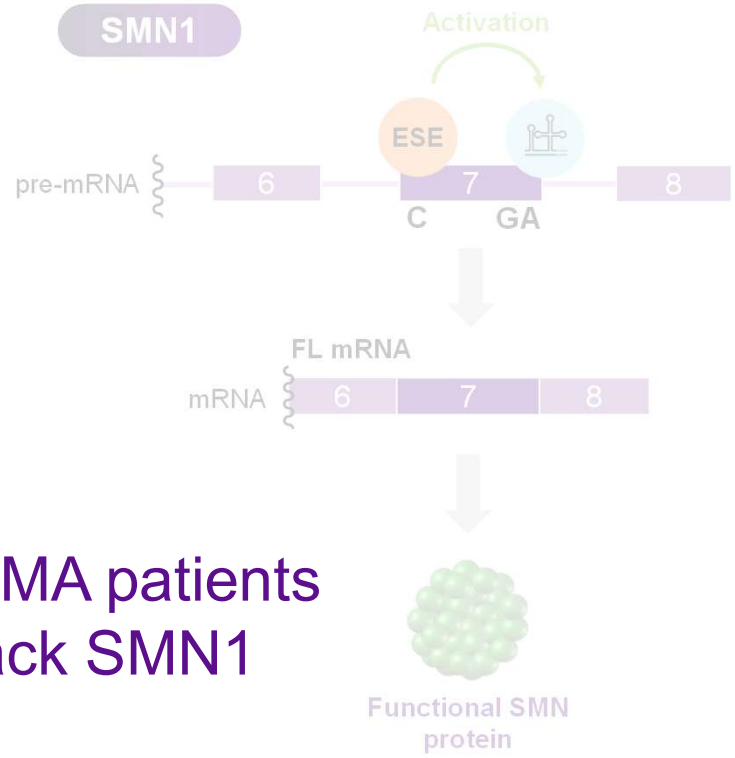
U1-pre-mRNA interactions that are non-complementary are **weak** and destabilize binding at the 5’ splice site

Protein Enhancers Stabilize the Structures Found at Noncanonical 5’ Splice Sites

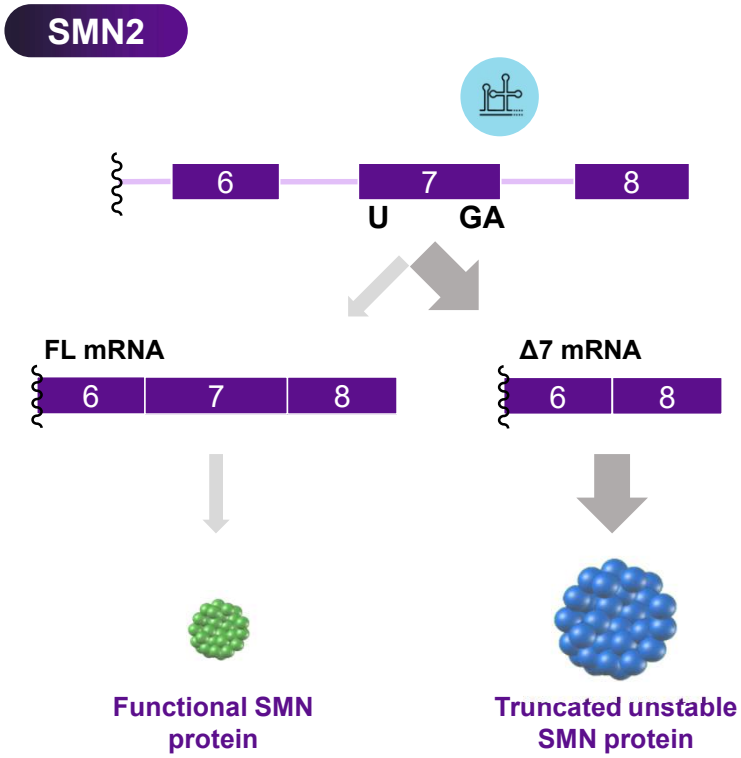


Enhancers strengthen the U1 interaction with non-complementary 5’ splice sites

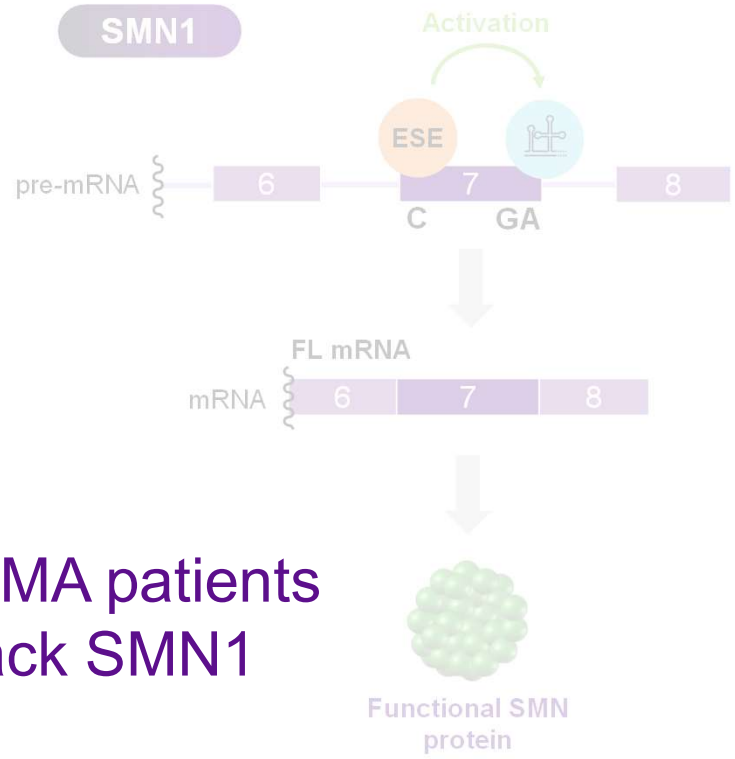
Spinal Muscular Atrophy is Caused by a Noncanonical 5' Splice Site in the SMN2 Pre-mRNA



SMA patients lack SMN1



PTC's Discovery of a Small Molecule 5' Splice Site Enhancer Established a New Small Molecule Therapeutic Modality



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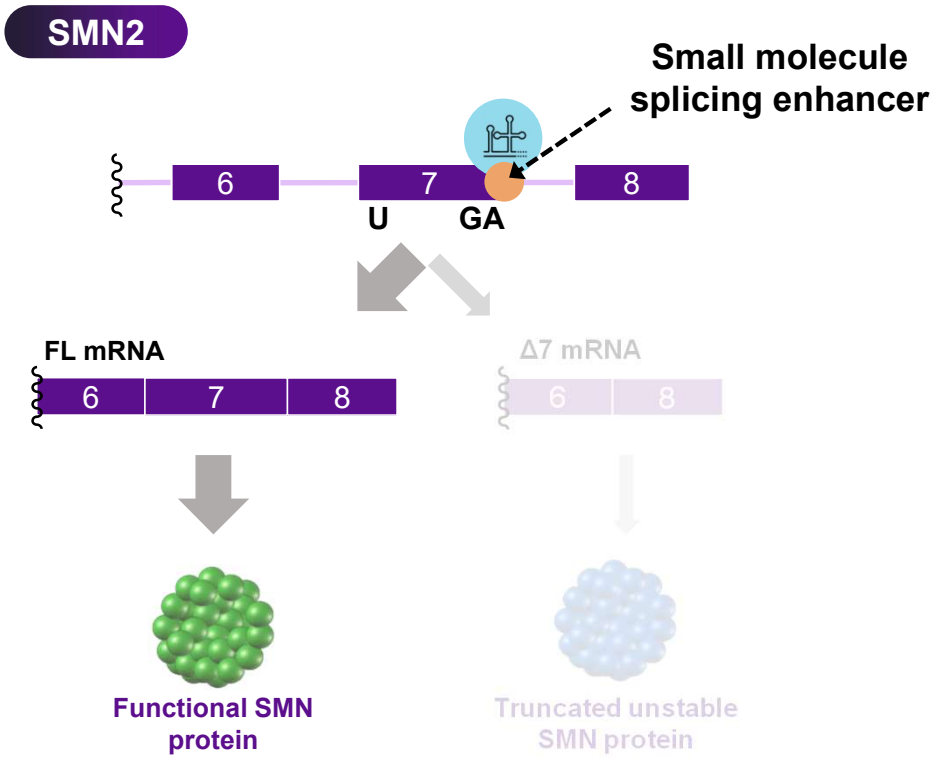
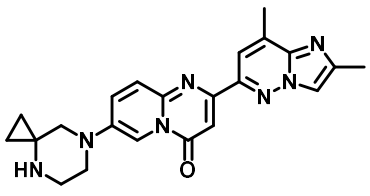
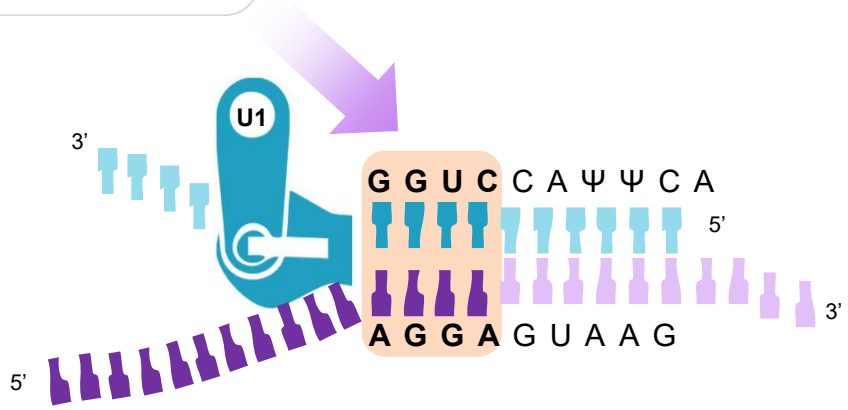


Evrysdi is the First Small Molecule Splicing Modulator for the Treatment of SMA

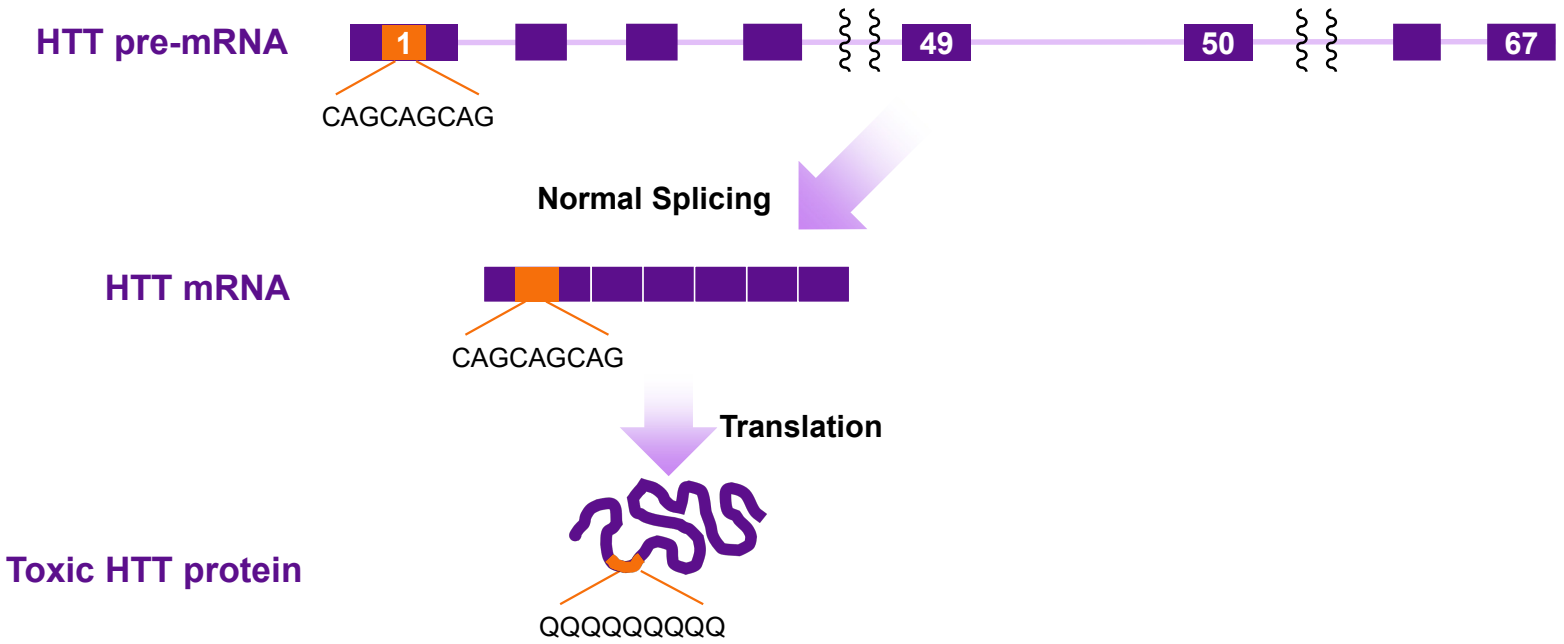


Evrysdi® risdiplam

Evrysdi functions as a sequence specific splicing enhancer



PTC's Discovery of Votoplam, the Second Small Molecule Splicing Modulator, which is Being Advanced to Treat Huntington's Disease



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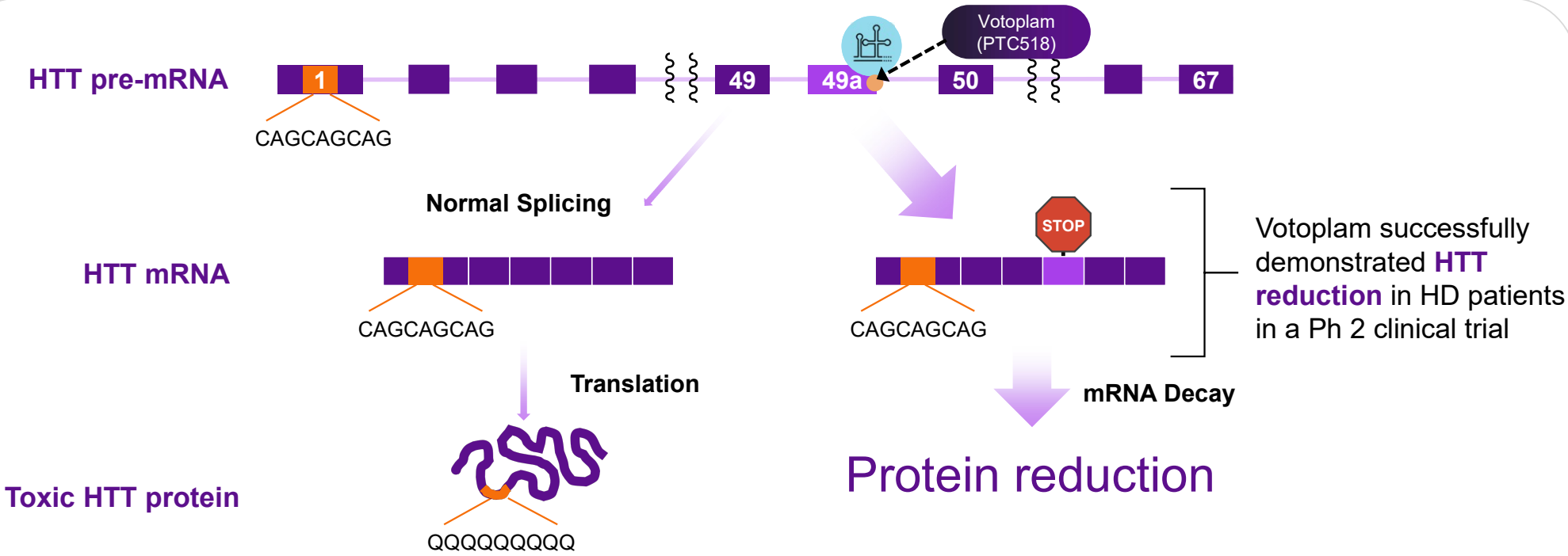
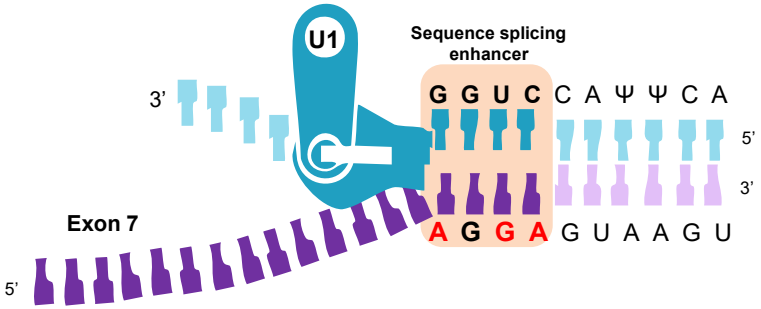


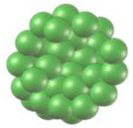
Foundational discovery: Small molecule splicing modulators can significantly reduce gene expression by enhancing the inclusion of an mRNA decay-inducing exon

Bhattacharyya A., et al., Nature Commun. 2021

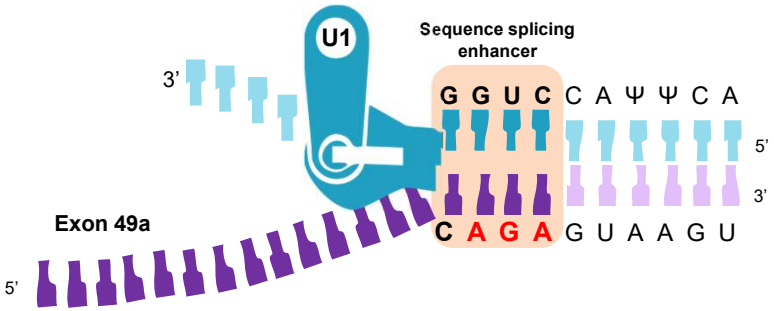
PTC's Small Molecule Splicing Enhancers are Sequence Specific and Target Selective



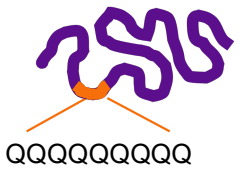
Evrysdi® risdiplam



Functional SMN protein



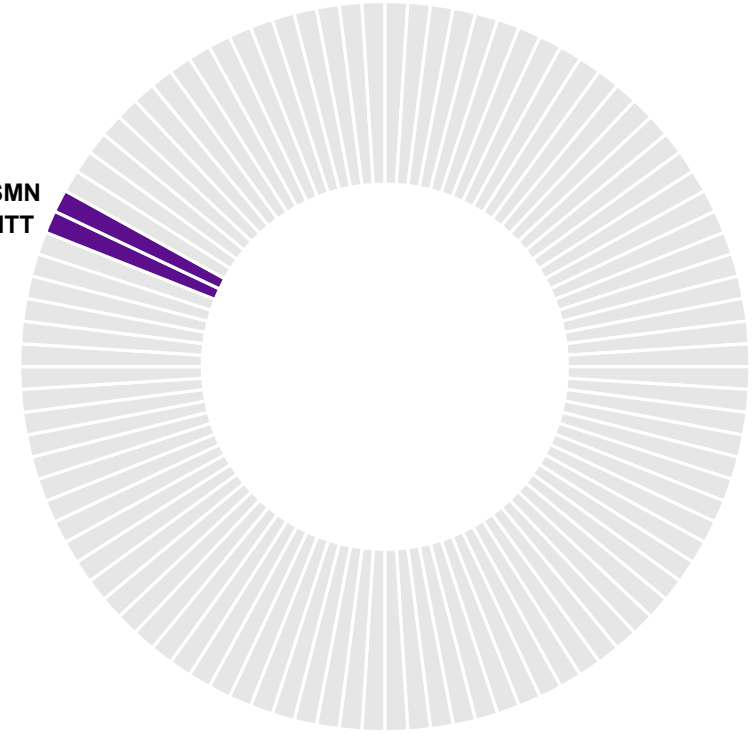
Votoplam (PTC518)



Lead optimization efforts led to **highly selective** activity for the targeted 5' splice site sequence within compound-induced exons (**iExons**)

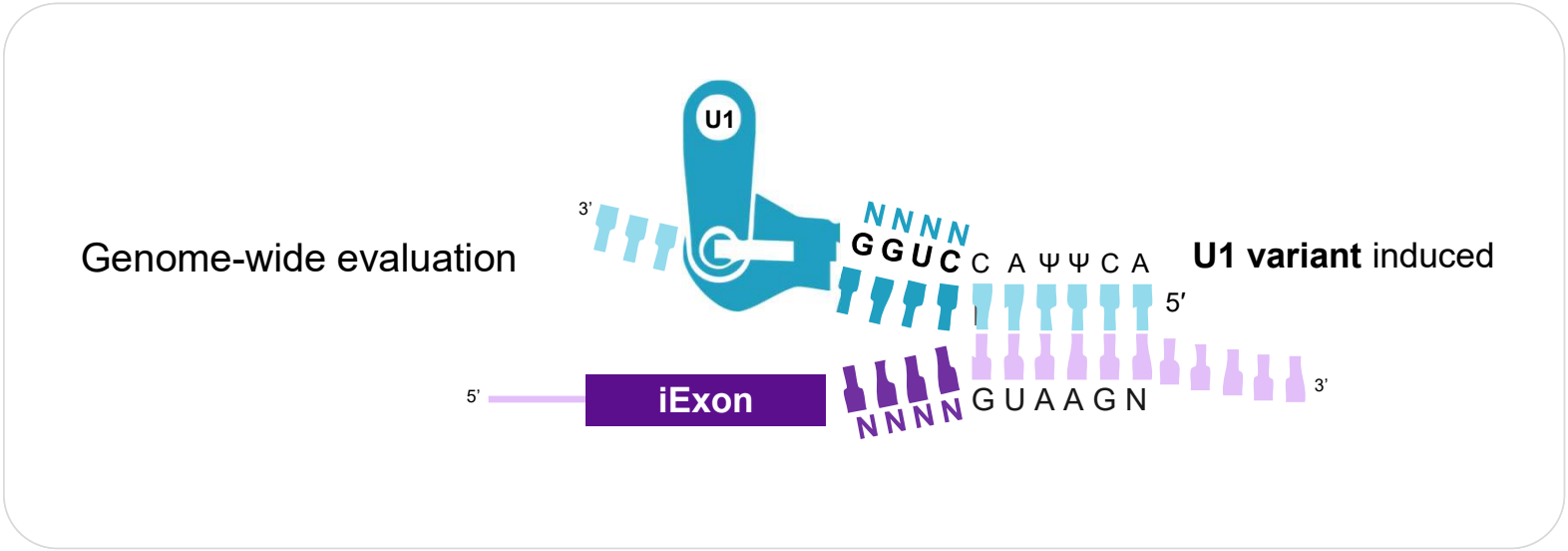
PTC has Discovered the Next Generation of Novel Splicing Therapies

256 potential targetable sequences



- How many and in what genes do iExons exist?
- Can we systematically discover distinct small molecule splicing enhancers for each of the sequence found at the 5’ splice site?

PTC Discovered iExons Throughout the Entire Transcriptome

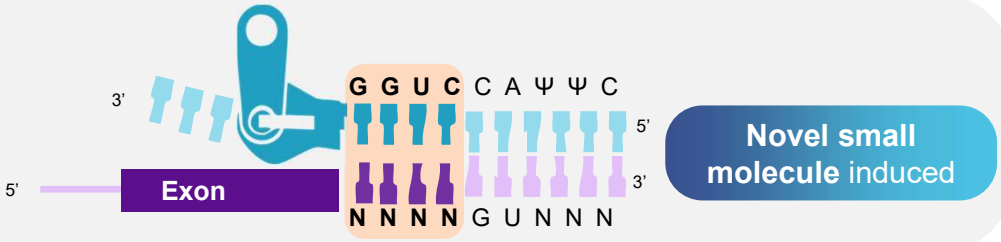


iExons exist for all 256 sequences
covering **a majority** of genes

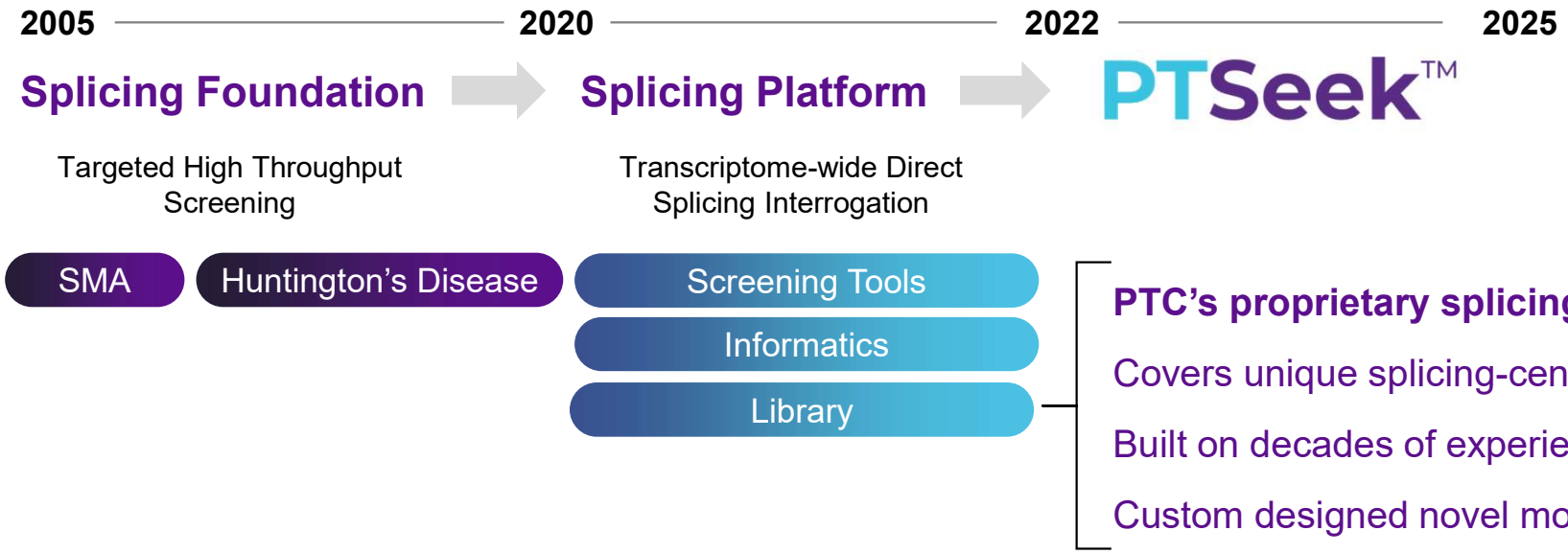
Targeting the Splicing of iExons to Identify Novel Small Molecule Enhancers

Can we leverage our knowledge of small molecule splicing modulation of risdiplam and votoplam to systematically target iExons to regulate therapeutic targets?

Small molecule screening to identify small molecule splicing enhancers for all iExons



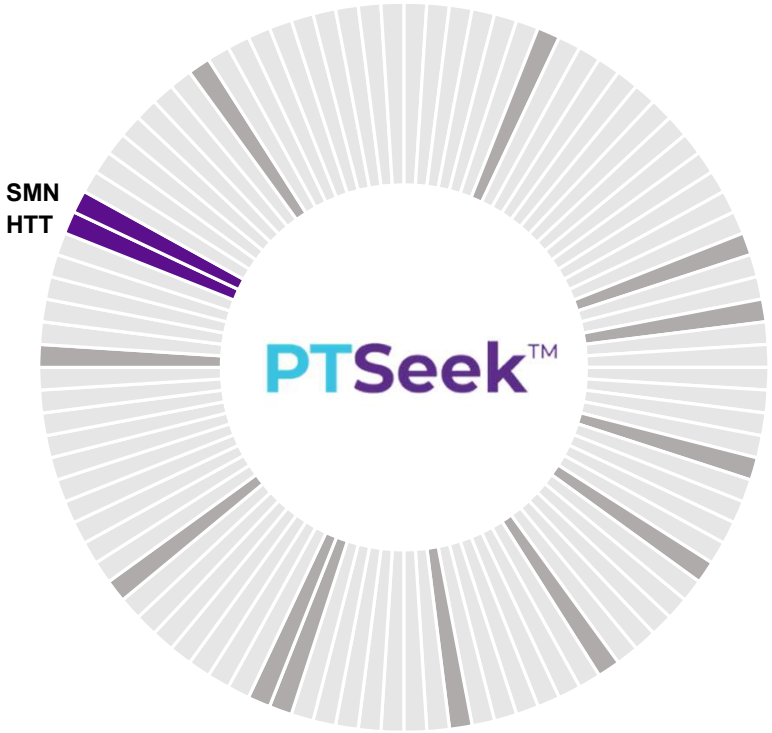
PTC has Leveraged Insights from the SMA and HD Programs to Develop PTSeek™



PTSeek™ has Led to Discovery of Novel Sequence Selective 5' Splice Site Enhancers for iExons Distinct from the SMA and HD Space

PTSeek™ platform has identified:

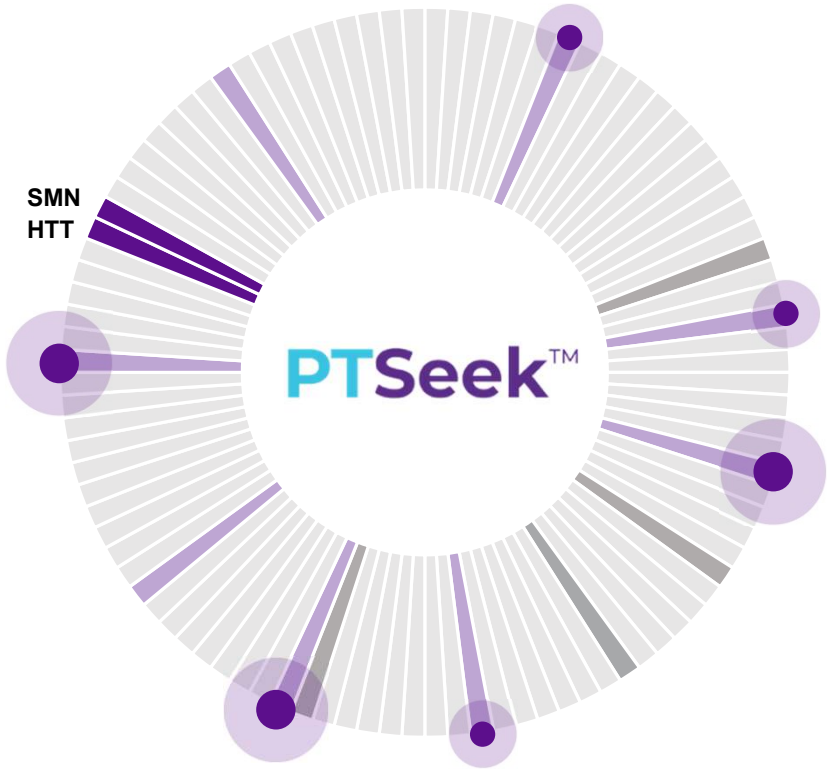
- Numerous novel chemical scaffolds with distinct Structure-Sequence-Relationship (SSR)



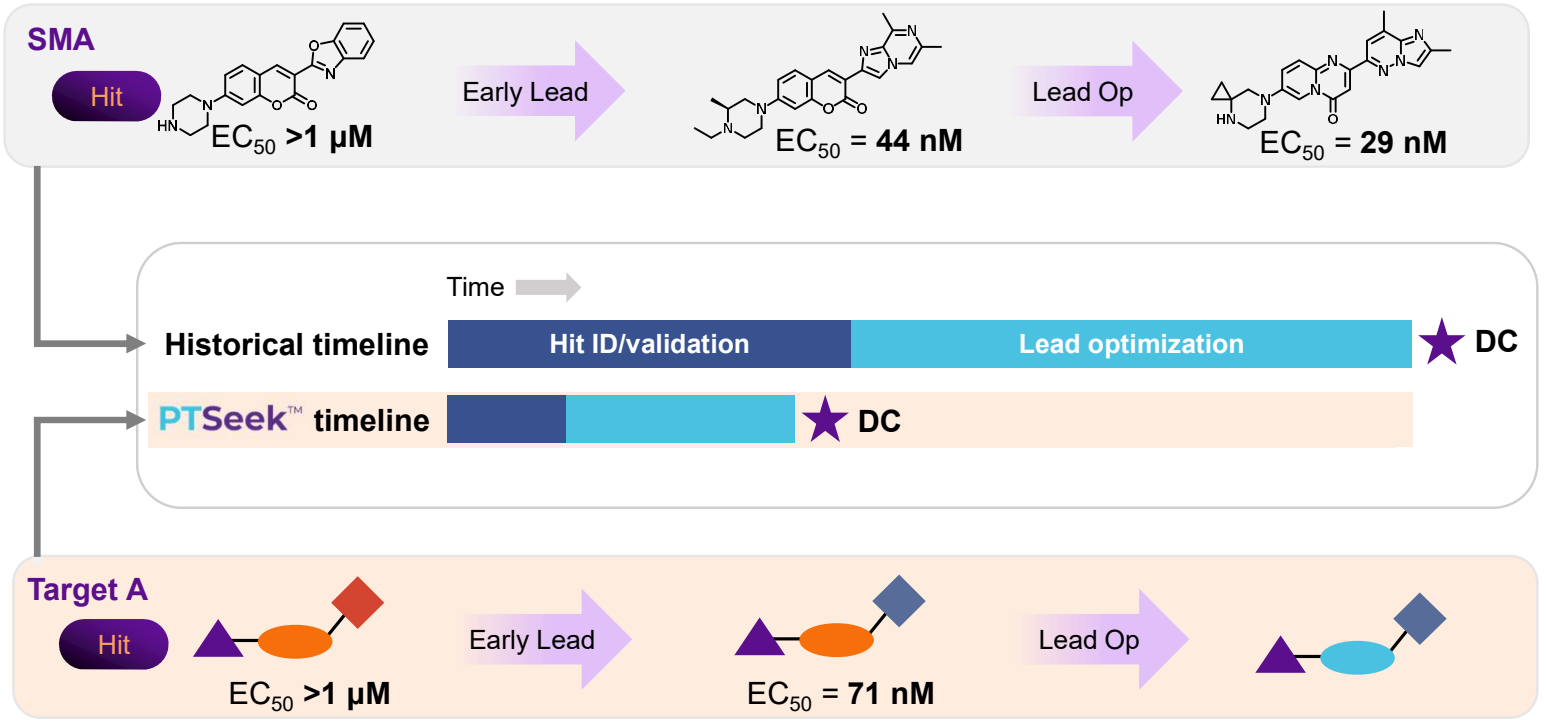
PTSeek™ Discovered Molecules that Induce iExon Inclusion in Targets Associated with a Broad Range of Therapeutic Indications

PTSeek™ platform has identified:

- Numerous novel chemical scaffolds with distinct Structure-Sequence-Relationship (SSR)
- Numerous targetable iExons within therapeutically relevant targets

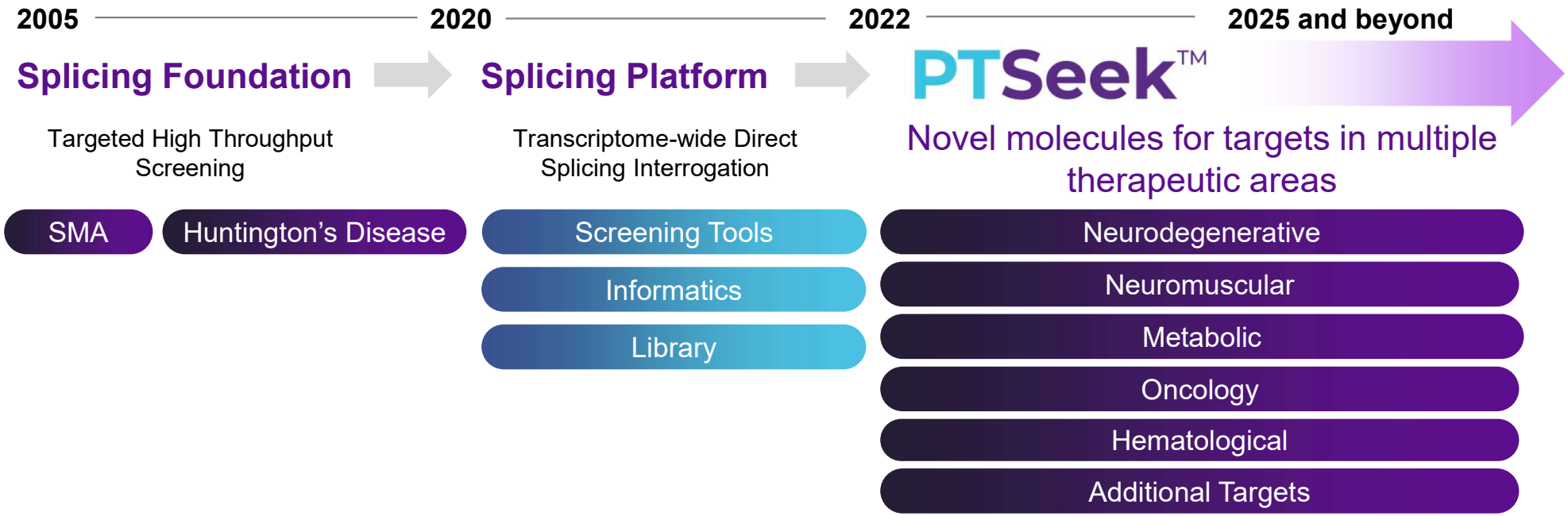


PTSeek™ Enables Rapid Identification of High-Quality Hits Leading to Accelerated Preclinical Development Timelines



DC = Development Candidate

PTC's Innovative Advantage in Splicing Modulation is Delivering on the Promise of Targeting Splicing to Develop Novel Therapeutics



Oral Small Molecule Splicing Programs

Anu Bhattacharyya, PhD

Select Splicing Platform Programs

	TARGET	INDICATION(S)
Late Stage	MSH3	Huntington's Disease, Myotonic Dystrophy I
	ATXN3	Spinocerebellar Ataxia 3
	Undisclosed	Brain Tumors & Metastases
Early Stage	Undisclosed	Sickle Cell Disease, β-Thalassemia
	Undisclosed	Neurodegenerative Diseases

MSH3 Program: Targeting Nucleotide Repeat Disorders

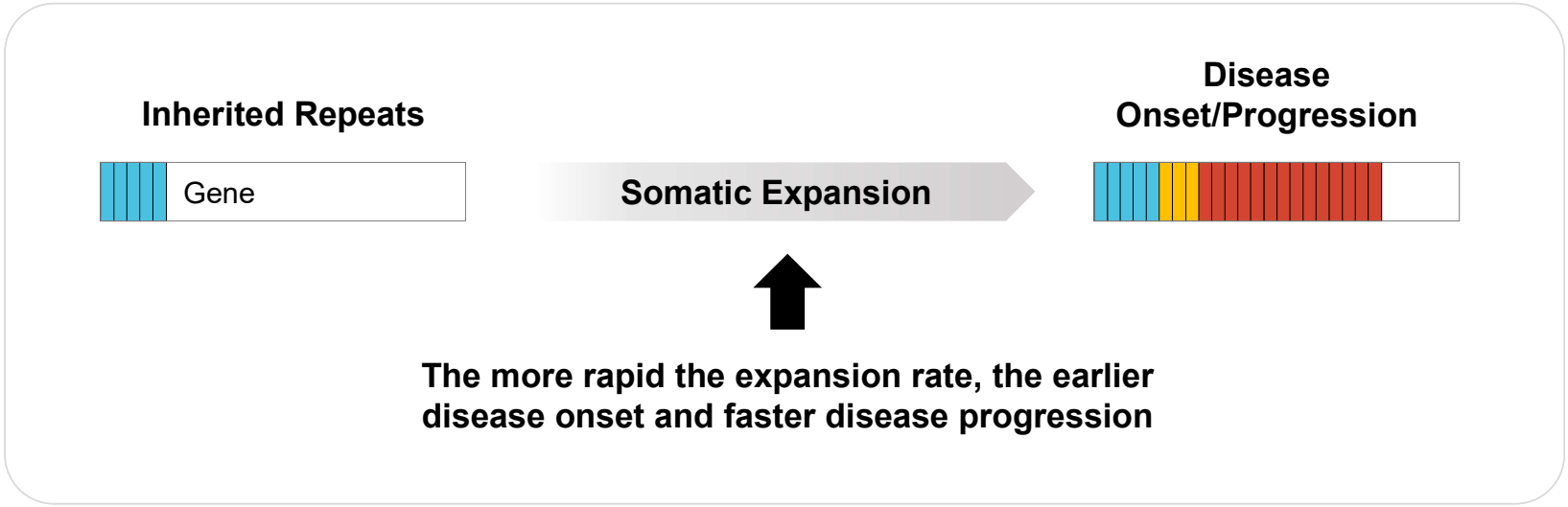
Patient living with HD

Nucleotide Repeat Disorders (NRDs) – Disease Onset and Progression Associated with Rate of Somatic Expansion

Huntington's Disease

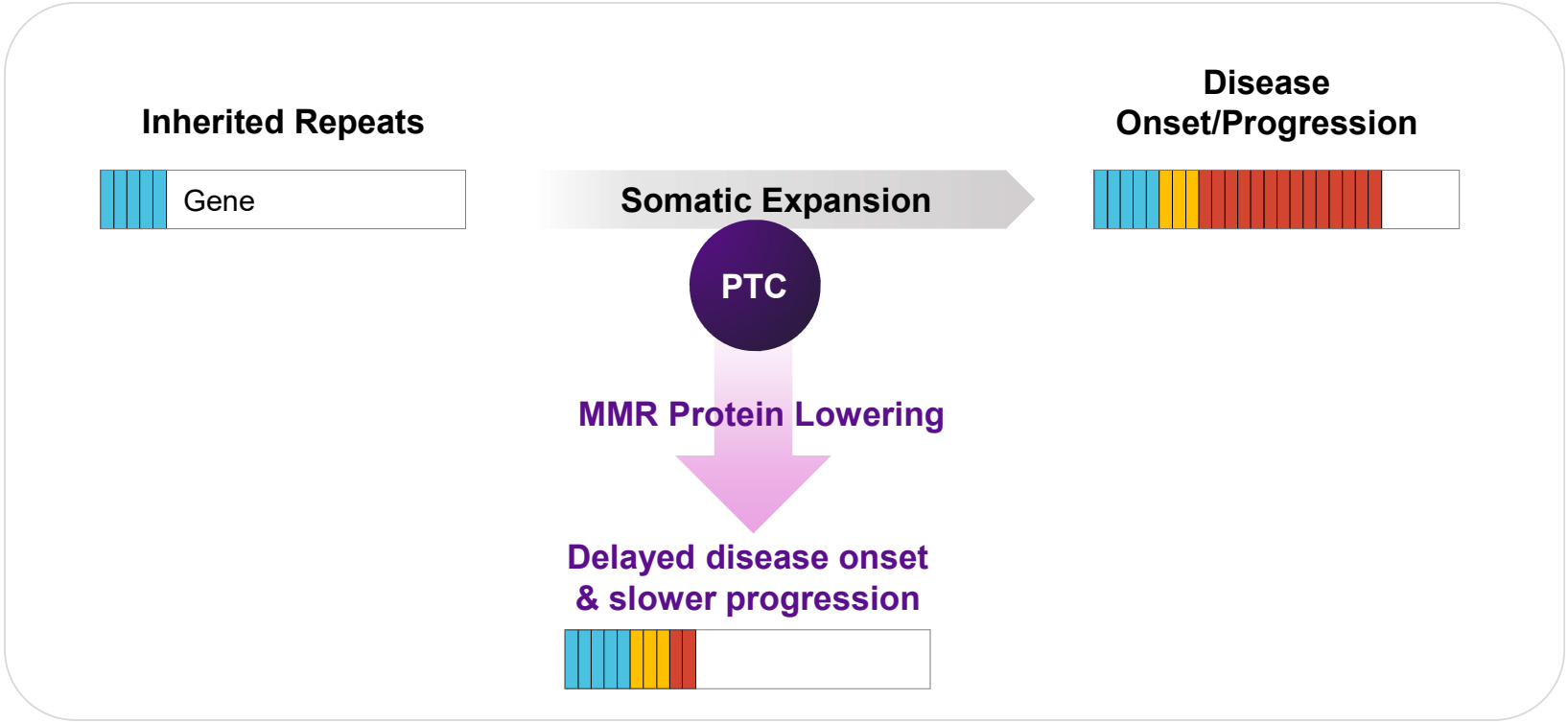
Myotonic Dystrophy 1

PTC's Splicing Technology Targets Key Proteins Driving Somatic Expansion



The rate of somatic expansion is primarily driven by a family of proteins called mismatch repair (MMR) proteins

PTC's Splicing Technology Targets Key Proteins Driving Somatic Expansion



MSH3 has Emerged as a Promising Therapeutic Target

Molecular Therapy
Commentary

Can MSH3 lowering stop HTT repeat expansion in its CAG tract?

Ross Ferguson[1,2] and Sarah J. Tabrizi[1,2]

Cell
Article

Distinct mismatch-repair complex genes set neuronal CAG-repeat expansion rate to drive selective pathogenesis in HD mice

Graphical abstract

Authors
Nan Wang, Shasha Zhang, Peter Langfelder, ..., Jeffrey S. Aaronson, Jim Rosinski, X. William Yang

Correspondence
xwyang@mednet.ucla.edu

In brief
Genes encoding distinct mismatch-repair complexes (i.e., Msh3 and Pms1) set a fast CAG-repeat expansion rate in vulnerable neurons to drive selective and progressive striatal and cortical pathogenesis in a mouse model of Huntington's disease (HD).

SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

NEURODEGENERATIVE DISEASE

Antisense oligonucleotide–mediated MSH3 suppression reduces somatic CAG repeat expansion in Huntington's disease iPSC–derived striatal neurons

Emma L. Bunting[1†], Jasmine Donaldson[1†], Sarah A. Cumming[2], Jessica Olive[1], Elizabeth Broom[1], Mihai Micläus[3,4], Joseph Hamilton[1], Matthew Tegtmeyer[5], Hien T. Zhao[6], Jonathan Brenton[3,7], Won-Seok Lee[3,8], Robert E. Handsaker[3,8], Susan Li[6], Brittany Ford[6], Mina Ryten[3,7], Steven A. McCarroll[3,8], Holly B. Kordasiewicz[6], Darren G. Monckton[2], Gabriel Balmus[3,4], Michael Flower[1], Sarah J. Tabrizi[1*]

Expanded CAG alleles in the huntingtin (*HTT*) gene that cause the neurodegenerative disorder Huntington's disease (HD) are genetically unstable and continue to expand somatically throughout life, driving HD onset and progression. MSH3, a DNA mismatch repair protein, modifies HD onset and progression by driving this somatic CAG repeat expansion process. *MSH3* is relatively tolerant of loss-of-function variation in humans, making it a potential therapeutic target. Here, we show that an *MSH3*-targeting antisense oligonucleotide (ASO) effectively engaged with its RNA target in induced pluripotent stem cell (iPSC)–derived striatal neurons obtained from a patient with HD carrying *125 HTT* CAG repeats (the 125 CAG iPSC line). ASO treatment led to a dose-dependent reduction of MSH3 and subsequent stalling of CAG repeat expansion in these striatal neurons. Bulk RNA sequencing revealed a safe profile for *MSH3* reduction, even when reduced by >95%. Maximal knockdown of MSH3 also effectively slowed CAG repeat expansion in striatal neurons with an otherwise accelerated expansion rate, derived from the 125 CAG iPSC line where *FAN1* was knocked out by CRISPR-Cas9 editing. Last, we created a knockin mouse model expressing the human *MSH3* gene and demonstrated effective in vivo reduction in human MSH3 after ASO treatment. Our study shows that ASO-mediated MSH3 reduction can prevent *HTT* CAG repeat expansion in HD 125 CAG iPSC–derived striatal neurons, highlighting the therapeutic potential of this approach.

Brain Sciences
Study Research About the Faculty Institutes and Divisions News and Events Contact

Reducing DNA repair protein levels targets root cause of Huntington's disease

A new study co-led by UCL researchers has made significant strides in advancing genetic therapies for Huntington's disease.

13 February 2025

GWAS Stories

MSH3, a promising drug target for Huntington's disease

A new study reports that knocking down MSH3 halts the CAG repeat expansion in Huntington's disease

VEERA M. RAJAGOPAL
JAN 24, 2024

Share

Today, I stumbled upon an interesting *Scientific Reports* article that reports that knocking down the DNA mismatch repair gene MSH3 in Huntington's mice model dose-dependently reduced the somatic expansion HTT CAG repeats.

nature genetics

Letter

https://doi.org/10.1038/s41588-024-02054-5

In vivo CRISPR–Cas9 genome editing in mice identifies genetic modifiers of somatic CAG repeat instability in Huntington's disease

Received: 24 May 2024
Accepted: 6 December 2024
Published online: 22 January 2025
Check for updates

Ricardo Mouro Pinto[1,2,3], Ryan Murtha[1], António Azevedo[1], Cameron Douglas[1], Marina Kovalenko[1], Jessica Ulloa[1], Steven Crescenti[1], Zoe Burch[1], Esaria Oliver[1], Maheswaran Kesavan[1,4], Shota Shibata[1,2,3], Antonia Vitalo[1,2], Eduarda Mota-Silva[1], Marion J. Riggs[1,2], Kevin Correia[1], Emanuela Elezi[1], Brigitte Demelo[1], Jeffrey B. Carroll[5], Tammy Gillis[1], James F. Gusella[1,2,3,6], Marcy E. MacDonald[1,2,3] & Vanessa C. Wheeler[1,2,3]

Huntington's disease, one of more than 50 inherited repeat expansion disorders[1], is a dominantly inherited neurodegenerative disease caused by a CAG expansion in *HTT*[2]. Inherited CAG repeat length is the primary determinant of age of onset, with human genetic studies underscoring that

doi:10.1093/brain/awz115 BRAIN 2019: 142; 1876–1886 | 1876

BRAIN
A JOURNAL OF NEUROLOGY

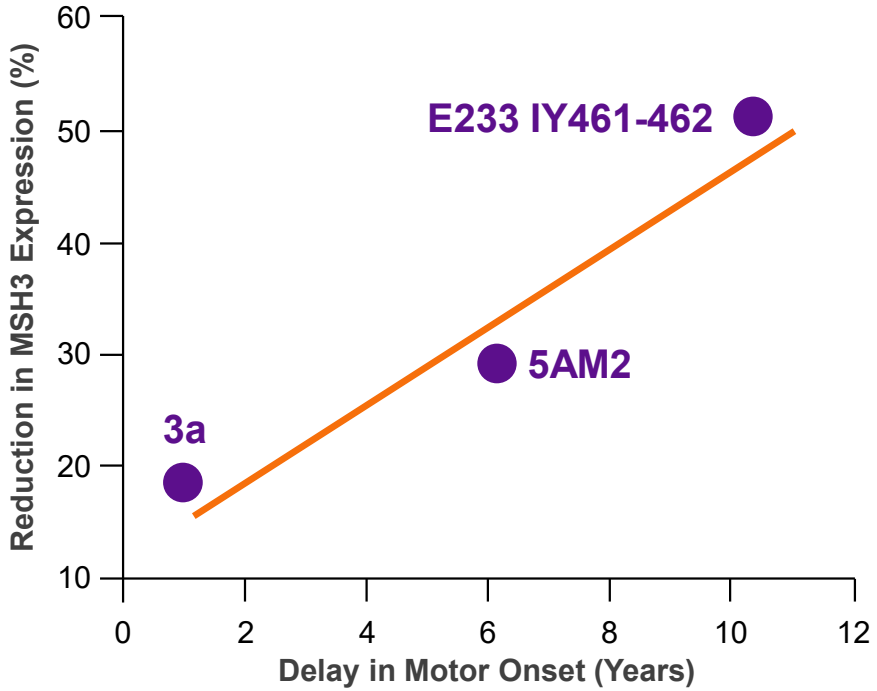
REPORT

MSH3 modifies somatic instability and disease severity in Huntington's and myotonic dystrophy type 1

Michael Flower,[1,†] Vilija Lomeikaite,[2,†] Marc Ciosi,[2] Sarah Cumming,[2] Fernando Morales,[2,3] Kitty Lo,[4] Davina Hensman Moss,[1] Lesley Jones,[5] Peter Holmans,[5] the TRACK-HD Investigators,[§] the OPTIMISTIC Consortium,[§] Darren G. Monckton[2,*] and Sarah J. Tabrizi[1,*]

Clear Linear Correlation Between Magnitude of MSH3 Reduction and HD Progression in Patients

VARIATION IN MSH3 GENE (HD PATIENTS)*	MSH3 PROTEIN	DELAY IN AGE AT MOTOR ONSET (YEARS)
3a	-17%	1.05
5AM2	-30%	6.1
E233 IY461-462	-50%	10.6

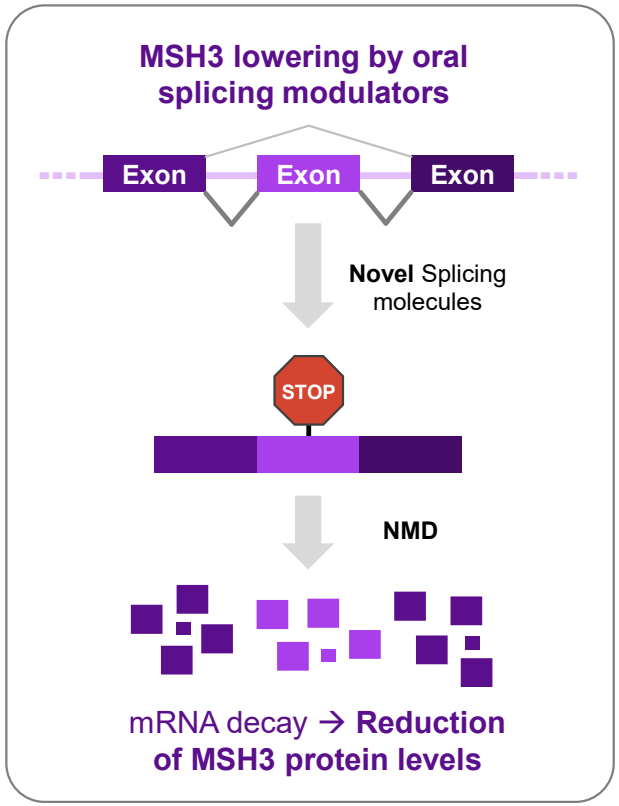


A similar trend has been observed for DM1

*Flower. M et al. Brain. 2019 Jun 19;142(7):1876–1886
Branduff McAllister et al. Nature Neuroscience 2022 April Vol 25: 446–457
Genetic Modifiers of Huntington's Disease (GeM-HD) Consortium Cell 2019 August 8;178, 887–900

PTC Identified a Novel Class of Splicing Modulators that Lower MSH3 mRNA and Protein Levels

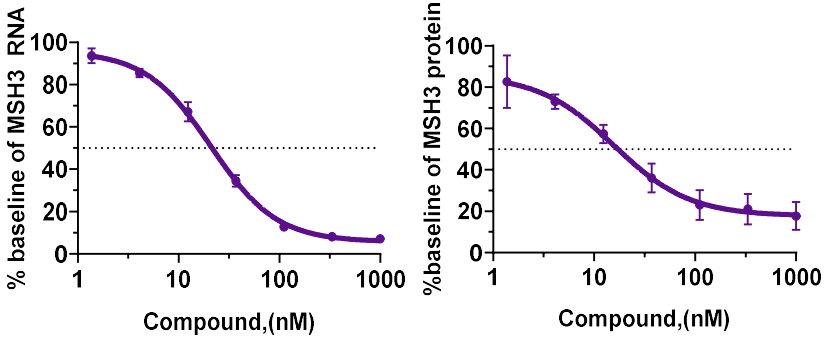
PTSeek™



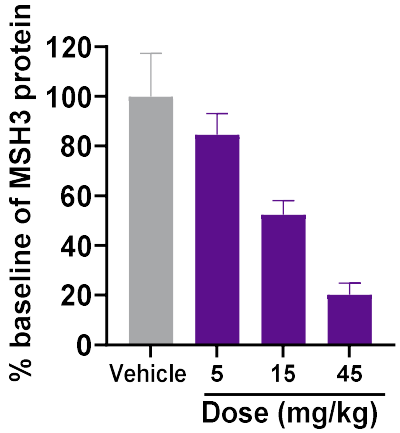
Novel splicing modulators **selectively induce MSH3 mRNA decay**

PTC Compounds Optimized for Activity, Selectivity, and Drug-like Properties

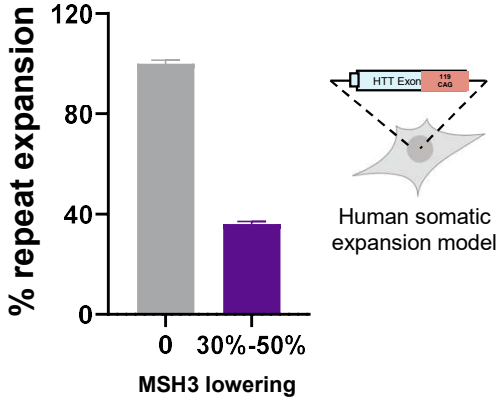
In vitro



In vivo



Expansion model



- Highly potent and selective
- Dose-dependent lowering of MSH3 mRNA and protein levels
- Uniform distribution in both the central nervous system and peripheral organs
- Validated in human expansion model – 30-50% MSH3 lowering stalls expansion*

*in line with human genetic and pre-clinical data

MSH3 Program Status

- Novel class of small molecule splicing modulators identified and optimized
- In vitro and in vivo proof of concept MSH3 lowering validated
- Plan to select clinical candidate in early 2026
- Phase 1 ready expected late 2026

Spinocerebellar Ataxia 3 (SCA3) Program

Spinocerebellar Ataxia 3 – a Progressive and Devastating Neurodegenerative Disease

- **Spinocerebellar Ataxia 3 (SCA3)** is an inherited monogenic disorder
- Neurodegenerative disease – cerebellum, brainstem, and spinal cord are primarily affected
- No disease modifying therapies

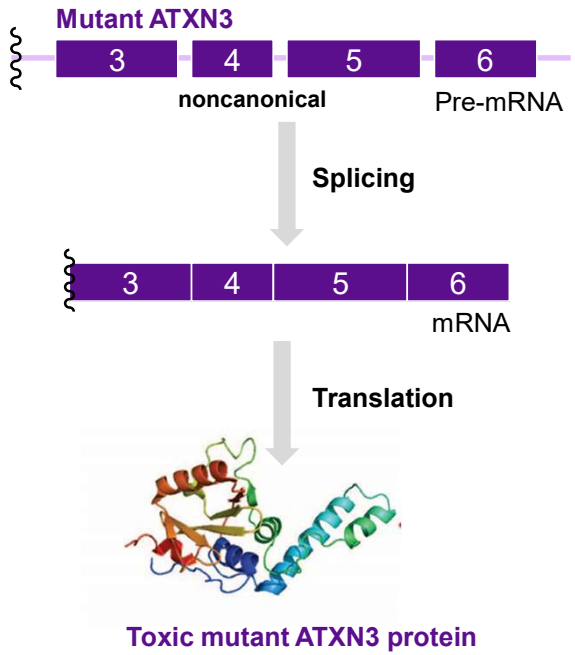
Most common autosomal dominant ataxia

~3.5K
Patients (US)

~2K
Patients (Japan)

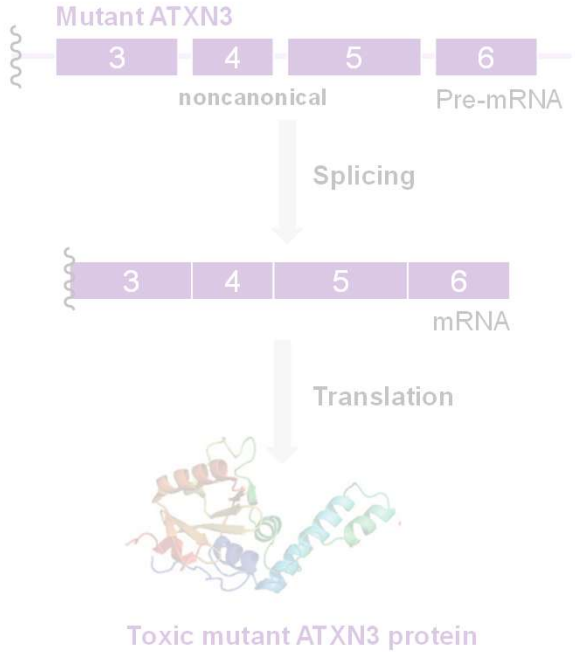
Therapeutic Strategy Directed Towards Lowering Production of Disease-Causing Protein

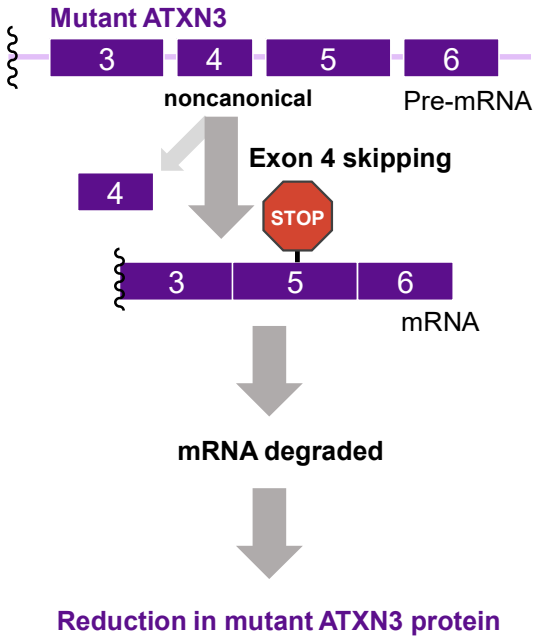
- Mutant ATXN3 is the primary toxicity driver of SCA3



Therapeutic Strategy Directed Towards Lowering Production of Disease-Causing Protein

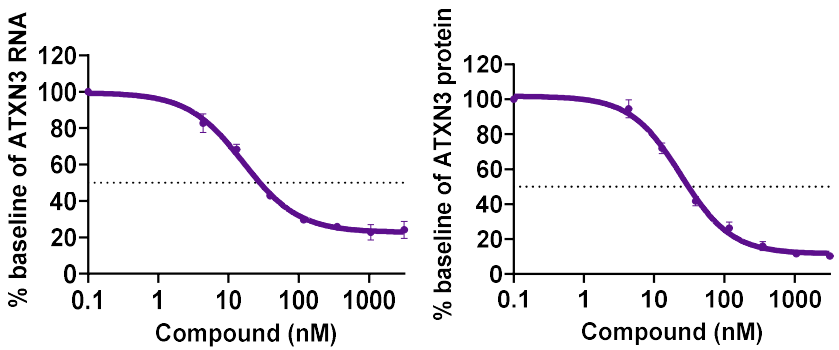
- Mutant ATXN3 is the primary toxicity driver of SCA3
- Splicing modulators lower mutant ATXN3 protein by inducing a skipping event



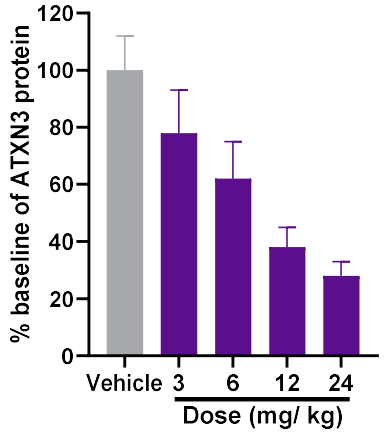


Lead Compound Optimized for Activity, Selectivity, and Drug-like Properties

In vitro



In vivo



- Highly potent and dose-dependent lowering of ATXN3 levels
- Uniform distribution in both the central nervous system and peripheral organs

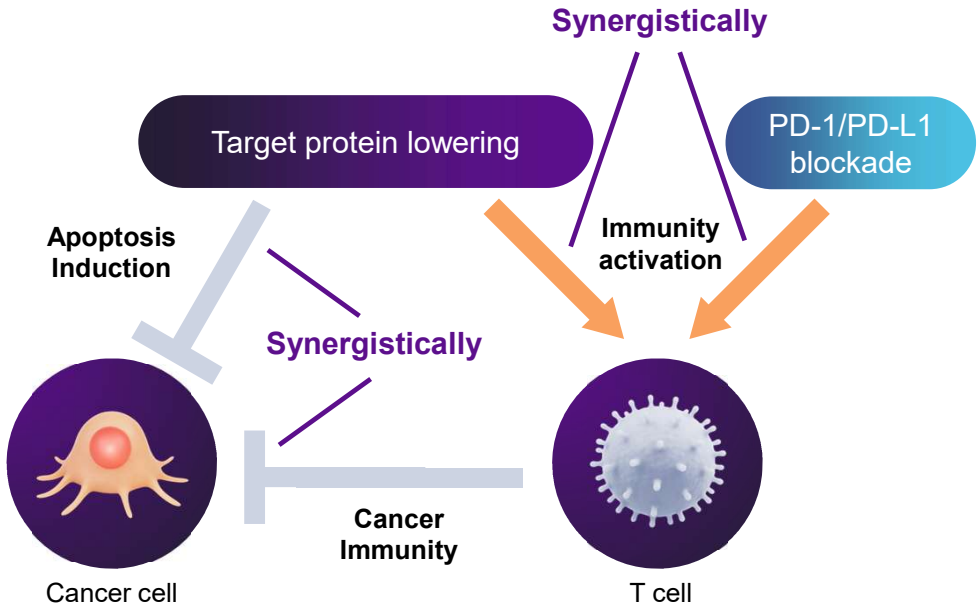
SCA3 Program Status

- Lead selected from a novel class of small molecule splicing modulators
- Demonstrated lowering of ATXN3 mRNA and protein levels in vitro and in vivo
- Plan to select clinical candidate in early 2026
- Phase 1 ready expected late 2026

Brain Tumors and Metastases

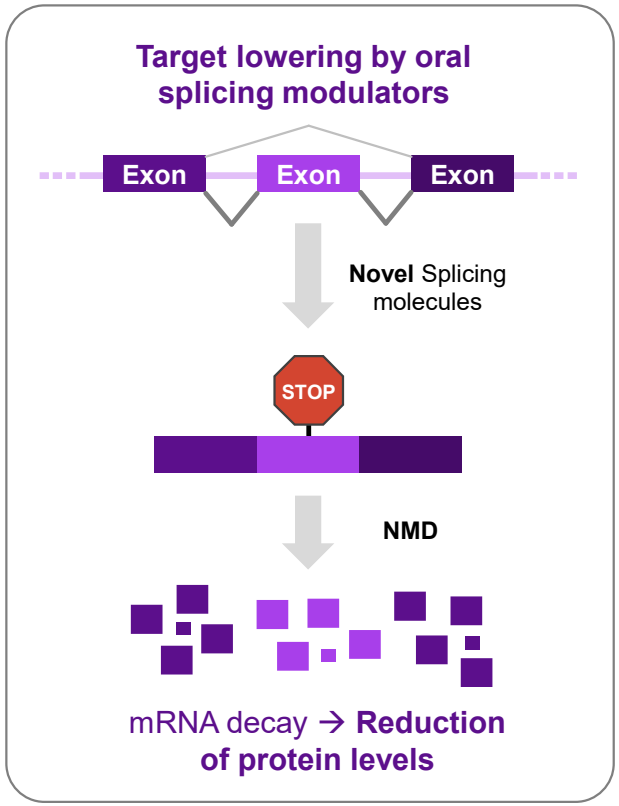
Targeted Enhancing of T-cell Function and Anti-tumor Immunity in Solid Tumors

- Target for cancer immunotherapy
- Works synergistically with immune checkpoint inhibitors to target solid tumors and addresses T-cell exhaustion
- Brain penetrant molecules identified to target brain metastases

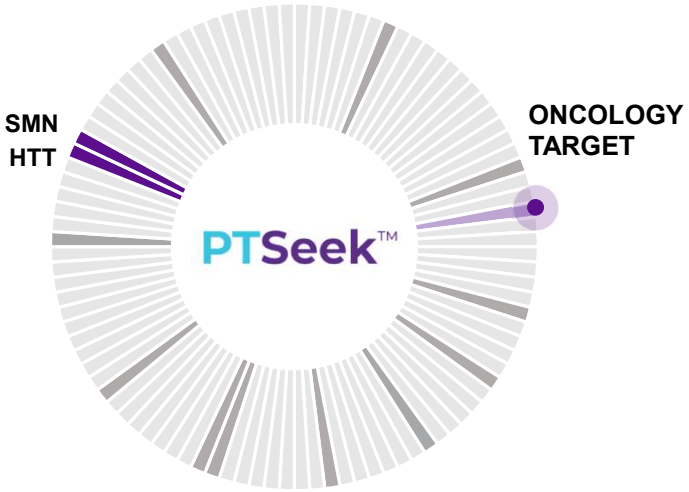


Therapeutic Strategy Targets Production of Key Protein in Cancer Biology

PTSeek™

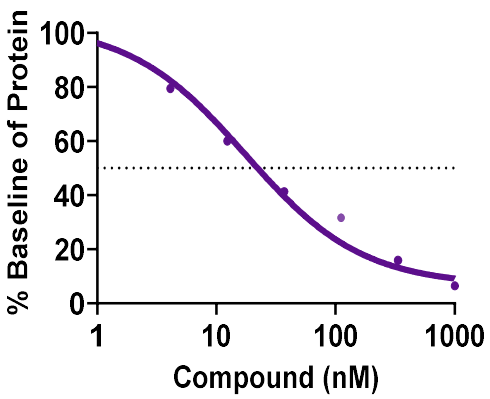


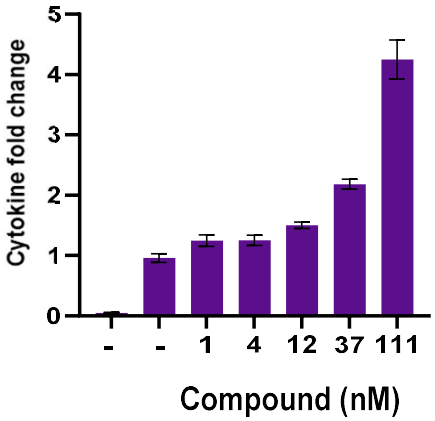
Novel splicing modulators **selectively induce mRNA decay**



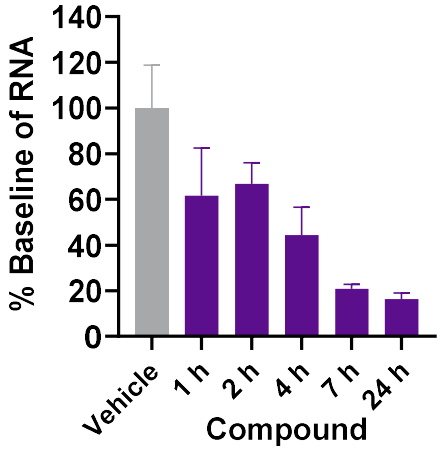
PTC Compounds Lower mRNA and Protein Levels and Activate T-Cell Function

In vitro





In vivo



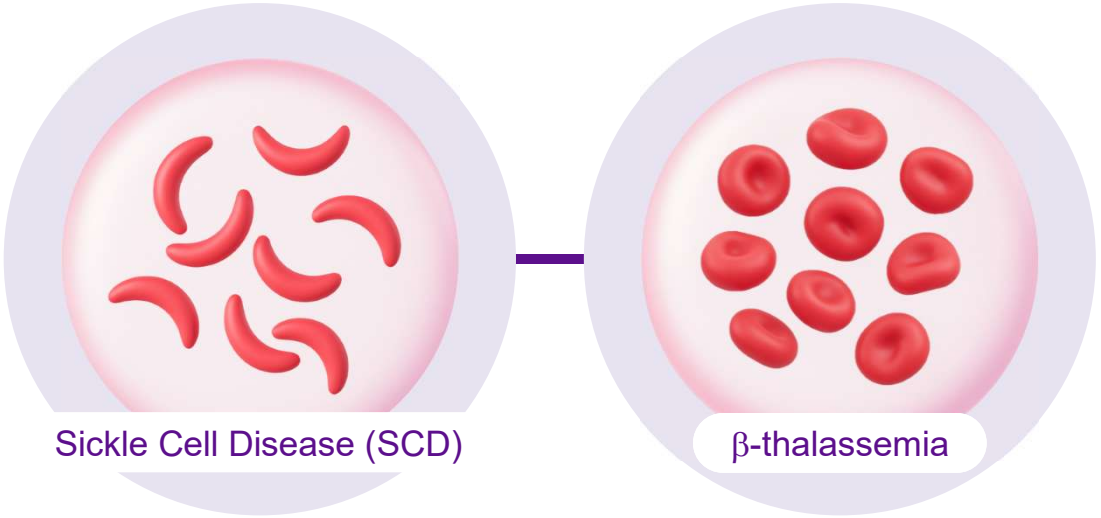
- Highly potent and dose-dependent lowering of target levels
- Robust functional validation – activates T-cells
- Molecules optimized for brain penetration

Oncology Program Status

- Novel class of small molecule splicing modulators identified
- Lead molecules reduce levels of targeted protein and activate T-cell function
- Assessment of synergy with anti-checkpoint inhibitors in progress
- Clinical candidate selection planned for early 2026

β–Hemoglobinopathies Program

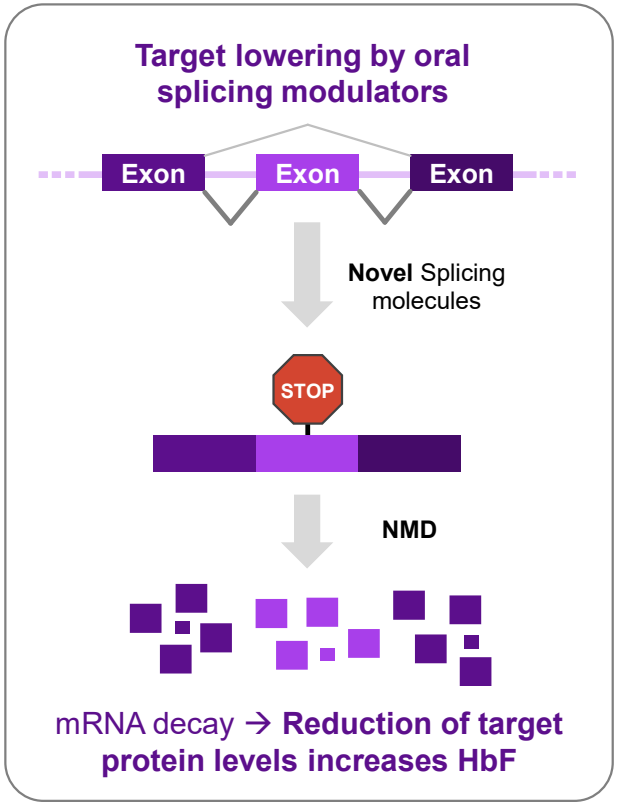
Therapeutic Strategy to Target β-Hemoglobinopathies – Induction of Fetal Hemoglobin (HbF)



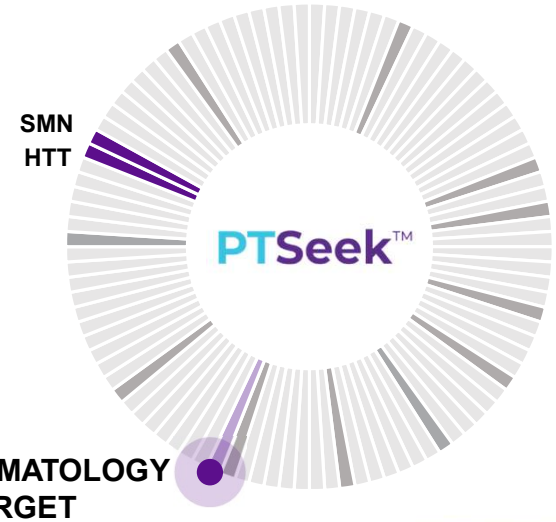
- Well-validated therapeutic strategy
- Severity is ameliorated by increase in fetal hemoglobin (HbF) levels
- Leverage PTSeek to find molecules that target regulators of HbF levels

Therapeutic Strategy Directed Towards Lowering Key Inhibitor of HbF Protein Production

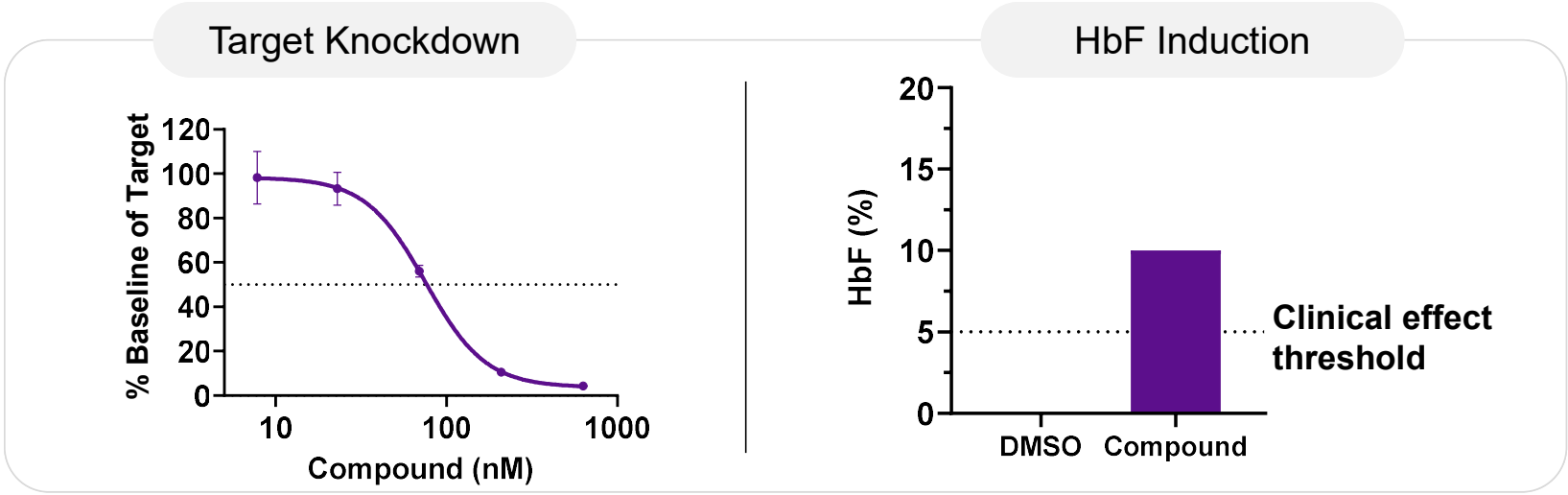
PTSeek™



Novel splicing modulators **selectively induce mRNA decay**



Therapeutic Strategy Directed Towards Lowering Key Inhibitor of HbF Protein Production



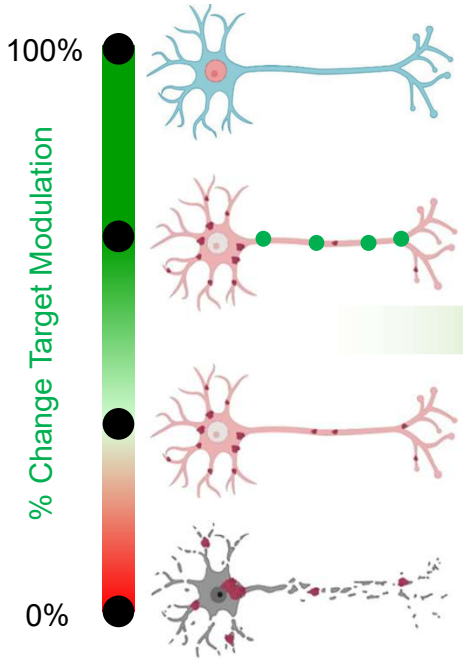
- Novel splicing modulators lowered a validated target of HbF induction
- Lowering of target resulted in HbF induction in the therapeutic range
- Next steps – Identify lead molecules with improved potency, efficacy, and drug-like properties

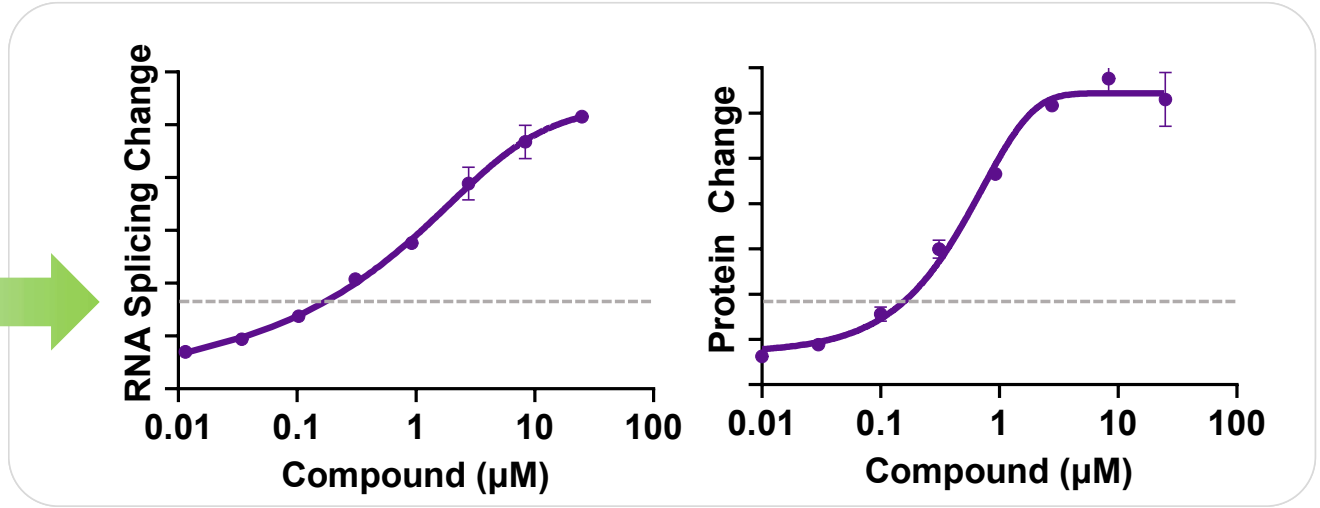
Undisclosed Target: Targeting a Key and Common Aspect of Neurodegenerative Disease Pathology

Therapeutic Strategy Directed Towards Targeting a Common Pathway in Neurodegenerative Diseases

- **Accumulation of protein aggregates** is a common feature of many neurodegenerative diseases including PD, AD, and ALS
- Leveraging **PTSeek™** to identify novel splicing modulators that can mitigate the neuronal dysfunction resulting from protein aggregation
- Program objective is to have a single therapy with broad utility across multiple disorders

PTC Compounds Target a Key Protein in Neurodegenerative Diseases





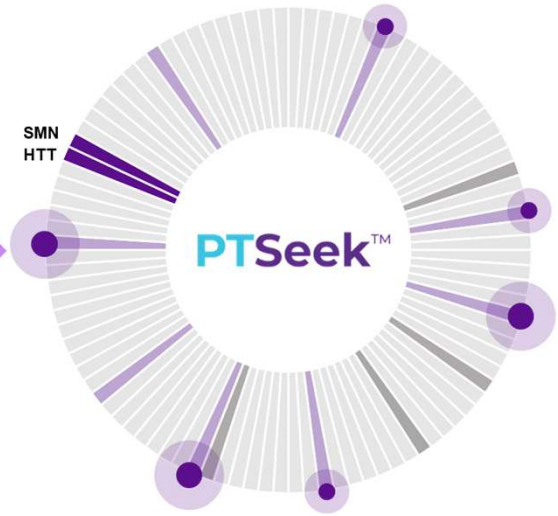
- Novel splicing modulators with good activity and selectivity identified
- Target modulation observed in the therapeutic range
- Next steps – Identify lead molecules with improved potency, efficacy and drug-like properties

Summary: PTC Well Positioned to Continue to Lead the Field of Small Molecule Splicing

Evrysdi® risdiplam

Votoplam (PTC518)

Groundbreaking work to develop Evrysdi and votoplam informed and evolved our approach



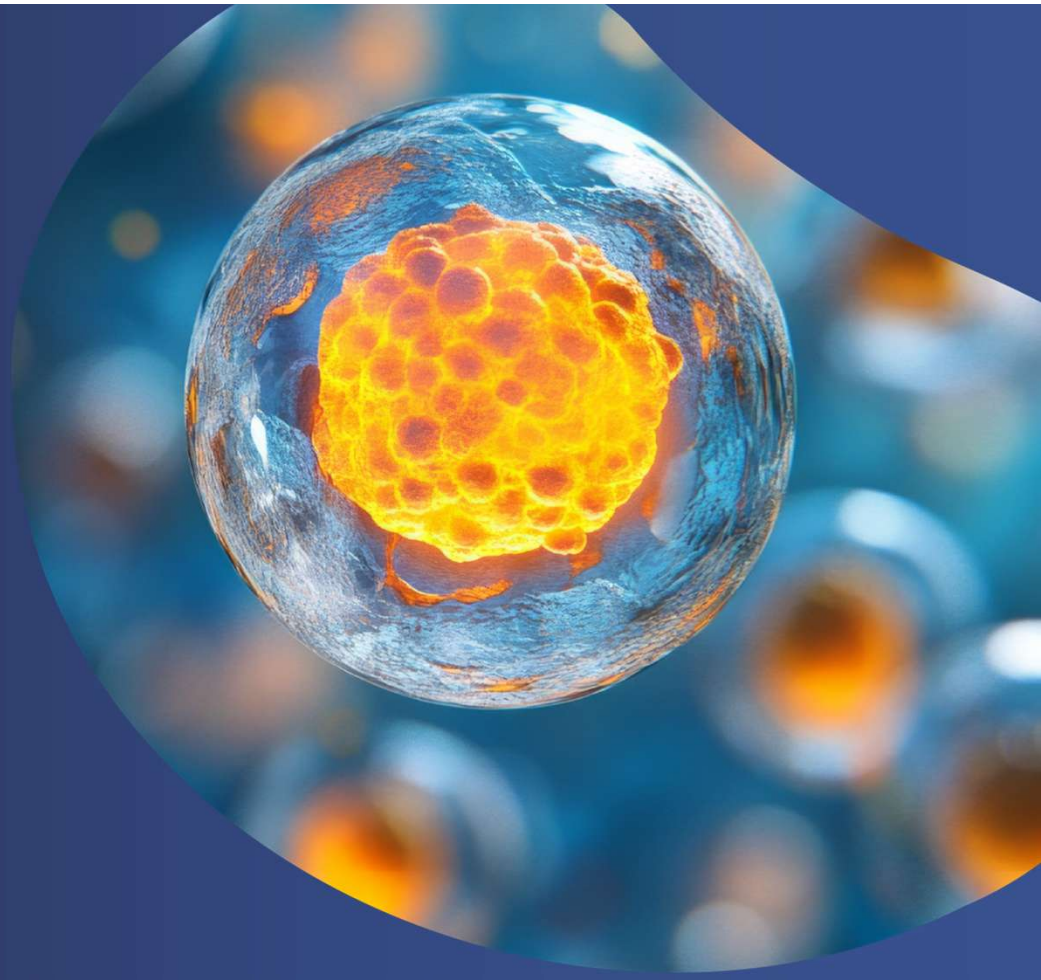
PTSeek™ is the result of decades of experience, splicing know how, enriched chemical libraries and advanced bioinformatics

Our innovative splicing platform is **unlocking a previously unknown RNA target space** cementing PTC as the industry leader in delivering novel RNA small molecule therapies

Splicing Q&A

Inflammation and Ferroptosis

Jeff Trimmer, PhD
Mayzie Johnston, PharmD



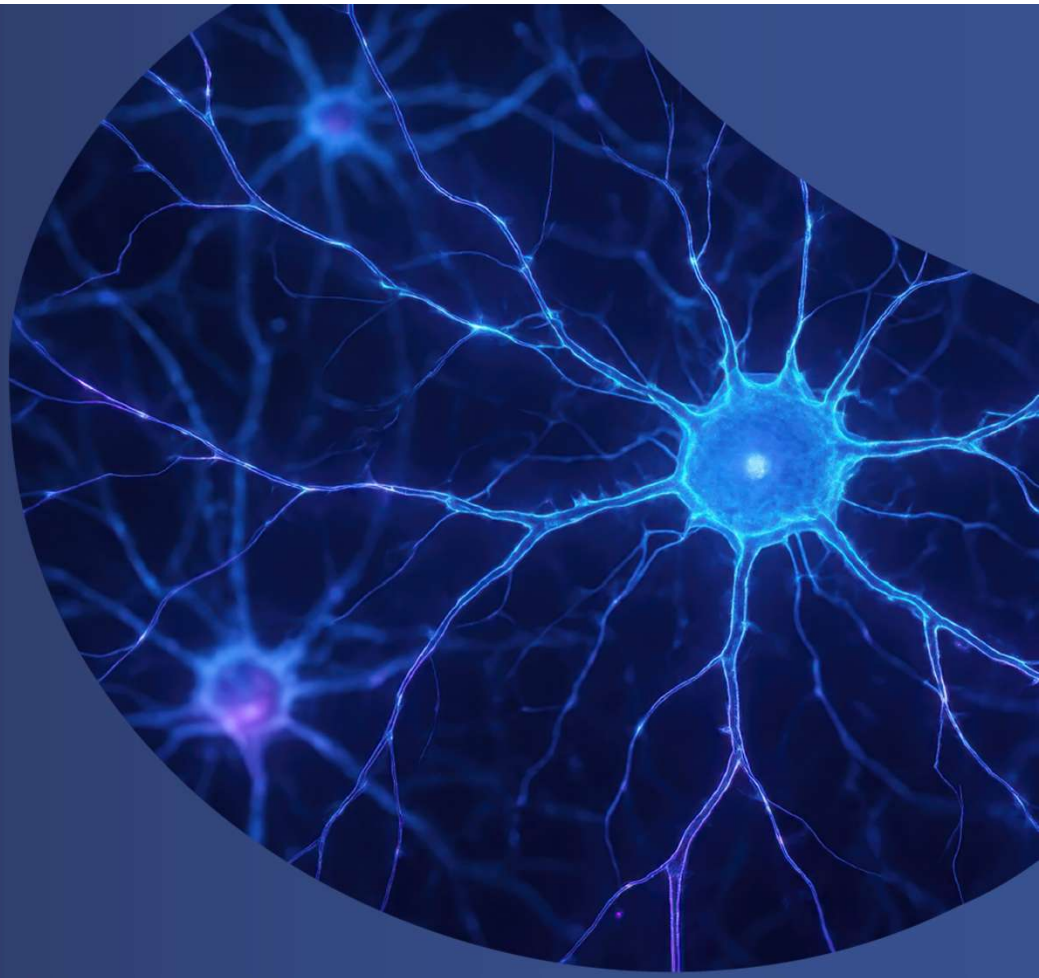
Inflammation & Ferroptosis Platform Overview

- Targeting specialized enzyme hubs that act as essential regulators of biological functions, such as inflammation, energy production and oxidative stress
- Leverage PTC's unique small molecule library to deliver differentiated or first-in-class therapies
- Advancing multiple pre-clinical and clinical programs for both CNS and non-CNS indications

Summary of Inflammation Platform Programs

	TARGET	INDICATION(S)
Pre-Clinical	15-LO	Parkinson's Disease
	NRF2	CNS, non-CNS
IND Enabling/Clinical	NLRP3	Inflammatory Lung Diseases
	DHODH	T-Cell Mediated Autoimmune Diseases

Parkinson's Disease Program



Ferroptosis is Key Pathway in Parkinson's Disease

- Ferroptosis is a newly identified form of programmed cell death characterized by oxidative stress, iron accumulation, and formation of highly reactive lipid peroxides
- Together these processes elicit oxidative damage, cell membrane disruption, activation of inflammatory pathways and neuronal cell death
- 15-LO is a key regulatory governor of ferroptosis, and 15-LO inhibition can prevent cell injury and death
- Our compound library includes redox active scaffolds that can uniquely inhibit 15-LO to decrease ferroptosis

Growing Body of Evidence Linking Ferroptosis and Parkinson's Disease

Research Article

Glutathione as a Biomarker in Parkinson's Disease: Associations with Aging and Disease Severity

Laurie K. Mischley,[1,2,3] Leanna J. Standish,[1] Noel S. Weiss,[4] Jeannie M. Padowski,[5] Terrance J. Kavanagh,[6] Collin C. White,[6] and Michael E. Rosenfeld[6]

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[5]*Elson S. Floyd College of Medicine and College of Pharmacy, Washington State University, P.O. Box 1495, Spokane, WA 99210-1495, USA*
[6]*Department of Environmental & Occupational Health Sciences, University of Washington, P.O. Box 357234, Seattle, WA 98195, USA*

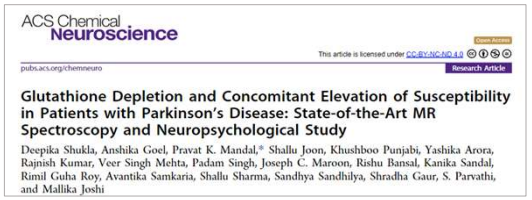
Pradhan et al. *Cell Death and Disease* (2020)11:739
https://doi.org/10.1038/s41419-020-02942-8

Cell Death & Disease

ARTICLE Open Access

Enhanced accumulation of reduced glutathione by Scopoletin improves survivability of dopaminergic neurons in Parkinson's model

Priyadarshika Pradhan[1], Olivia Majhi[1], Abhijit Biswas[1], Vinod Kumar Joshi[2] and Devanjan Sinha[1]



ACS Chemical Neuroscience

pubs.acs.org/chemneuro

Research Article

Glutathione Depletion and Concomitant Elevation of Susceptibility in Patients with Parkinson's Disease: State-of-the-Art MR Spectroscopy and Neuropsychological Study

Deepika Shukla, Anshika Goel, Pravat K. Mandal,* Shallu Joon, Khushboo Punjabi, Yashika Arora, Rajnish Kumar, Veer Singh Mehta, Padam Singh, Joseph C. Maroon, Rishu Bansal, Kanika Sandal, Rimil Guha Roy, Avantika Samkaria, Shallu Sharma, Sandhya Sandhilya, Shradha Gaur, S. Parvathi, and Mallika Joshi

ELSEVIER

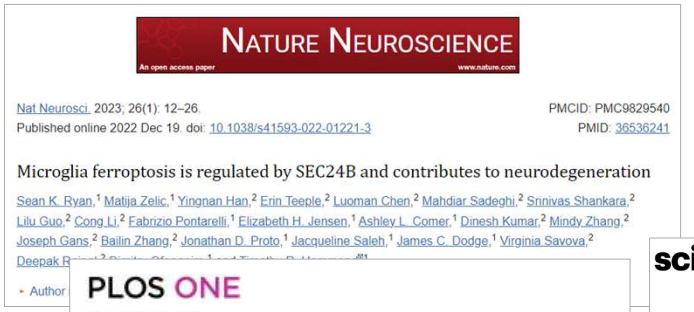
Progress in Neurobiology

Volume 196, January 2021, 101890

Review article

Ferroptosis and its potential role in the physiopathology of Parkinson's Disease

Laura Mahoney-Sánchez[a 1], Hind Bouchaoui[a 1], Scott Ayton[b], David Devos[a 1], James A. Duce[b c 1], Jean-Christophe Devedjian[a d 1]



NATURE NEUROSCIENCE

An open access paper www.nature.com

Nat Neurosci. 2023; 26(1): 12–26.
Published online 2022 Dec 19. doi: 10.1038/s41593-022-01221-3

PMCID: PMC9829540
PMID: 36536241

Microglia ferroptosis is regulated by SEC24B and contributes to neurodegeneration

Sean K. Ryan,[1] Matija Zelic,[1] Yingnan Han,[2] Erin Teeple,[2] Luoman Chen,[2] Mahdiar Sadeghi,[2] Srinivas Shankara,[2] Lilu Guo,[2] Cong Li,[2] Fabrizio Pontarelli,[1] Elizabeth H. Jensen,[1] Ashley L. Comer,[1] Dinesh Kumar,[2] Mindy Zhang,[2] Joseph Gans,[2] Bailin Zhang,[2] Jonathan D. Proto,[1] Jacqueline Saleh,[1] James C. Dodge,[1] Virginia Savova,[2] Deepak R...

Author

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Iron Pathophysiology in Parkinson Diseases

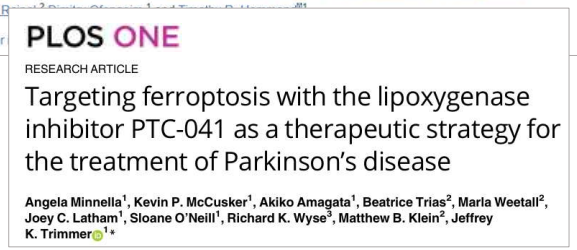
Hong Jiang, Ning Song, Qian Jiao, Limin Shi & Xixun Du

Chapter | First Online: 28 August 2019

Invited Review Article

Iron(ing) out parkinsonisms: The interplay of proteinopathy and ferroptosis in Parkinson's disease and tau-related parkinsonisms

Maria João da Costa Caiado[a,b,c,*], Amalia M. Dolga[b,c], Wilfred F.A. den Dunnen[b]



PLOS ONE

RESEARCH ARTICLE

Targeting ferroptosis with the lipoxygenase inhibitor PTC-041 as a therapeutic strategy for the treatment of Parkinson's disease

Angela Minnella[1], Kevin P. McCusker[1], Akiko Amagata[1], Beatrice Trias[2], Marla Weetall[2], Joey C. Latham[1], Sloane O'Neill[1], Richard K. Wyse[3], Matthew B. Klein[2], Jeffrey K. Trimmer[1]*

scientific reports

Check for updates

OPEN

Ferroptosis-related factors in the substantia nigra are associated with Parkinson's disease

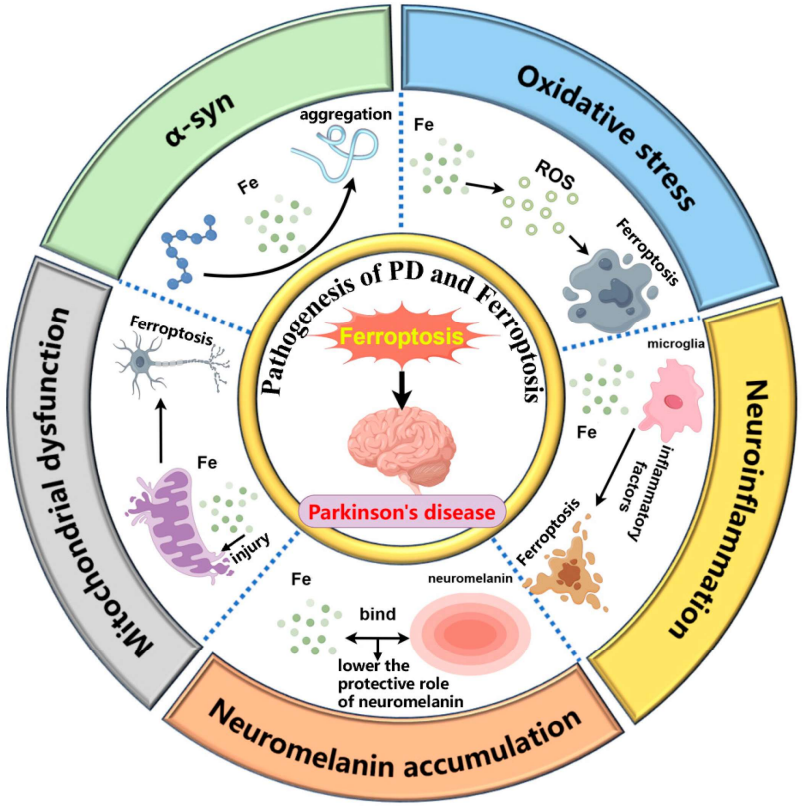
Lei Liu, Yange Cui, Yan-Zhong Chang & Peng Yu

RESEARCH ARTICLE

Study of molecular patterns associated with ferroptosis in Parkinson's disease and its immune signature

Lixia Chen[1‡], Guanghao Xin[1‡], Yijie He[1‡], Qinghua Tian[2], Xiaotong Kong[1], Yanchi Fu[1], Jianjian Wang[1], Huixue Zhang[1]*, Lihua Wang[1]*

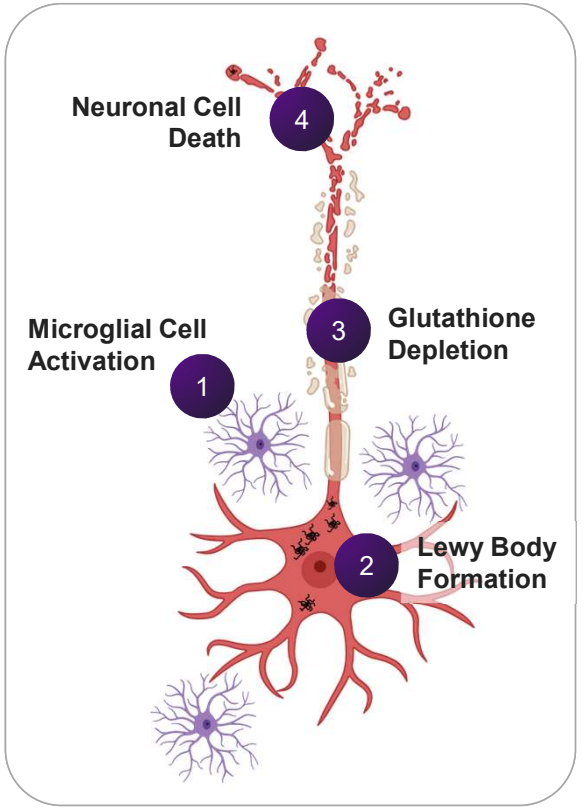
Ferroptosis Linked to Several Key Aspects of Parkinson's Disease



Zhou et al., Int J Mol Sci. 2024 Dec 4;25(23):13042. PMID: 39684753, PMCID: PMC11641825

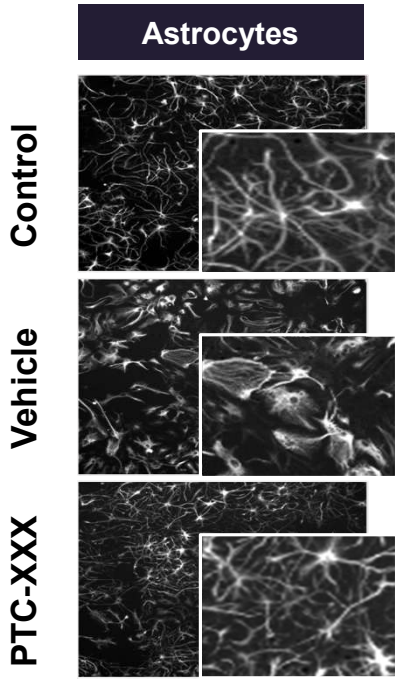
Targeting 15-LO & Ferroptosis Addresses Four Fundamental Parkinson's Disease Processes

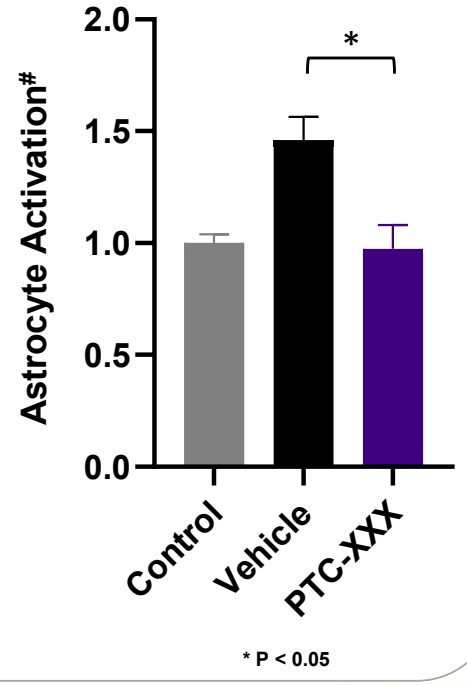
1. **Microglial Cell Activation**: Prevent activation of proinflammatory astrocytes and glial cells to mitigate neuroinflammation
2. **Lewy Body Formation**: Block α-synuclein phosphorylation and aggregation
3. **Glutathione Depletion**: Restore endogenous glutathione antioxidant defense system
4. **Neuronal Cell Death**: Prevent lipid peroxidation-mediated loss of cell membrane integrity



PTC Compounds Prevent Activation of Proinflammatory Cells to Mitigate Neuroinflammation (*in vitro*)

- Astrocytes and glial cells activated by introducing a ferroptosis challenge
- Addition of PTC compound inhibits ferroptosis-induced activation of inflammatory pathways
  - Restores astrocyte morphology & reduces cytokine production



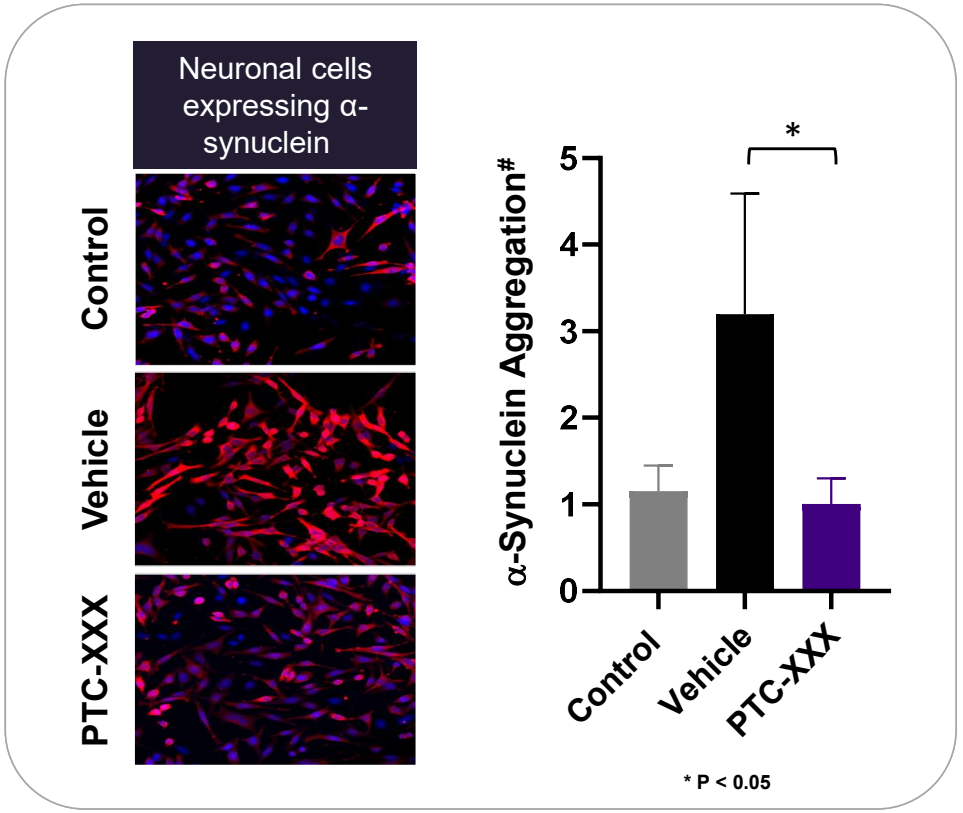


* P < 0.05

Normalized to unchallenged conditions

PTC Compounds Block α-Synuclein Phosphorylation and Aggregation (*in vitro*)

- α-Synuclein phosphorylation and aggregation occurs following ferroptosis challenge and activation of astrocytes and glial cells
- Addition of PTC compound prevents protein aggregation

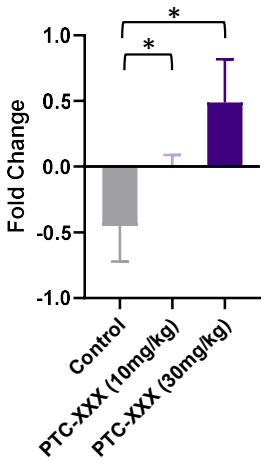


Normalized to unchallenged conditions. Minnella A, et al. (2024). PLoS ONE 19(9): pone.0309893

PTC Compounds Prevent Protein Degradation in Critical Neuronal Pathways (*in vivo*)

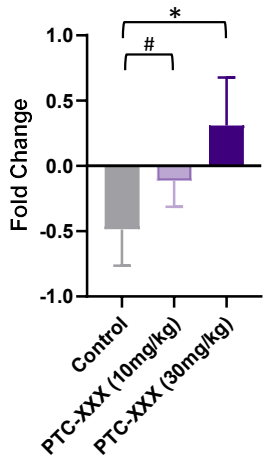
- Human α-synuclein expressing Parkinson's Disease mouse model (Line 61 mouse)
- PTC compounds dose-dependently restore structural and functional brain proteins in critical pathways

Neuronal Structure (14 proteins)



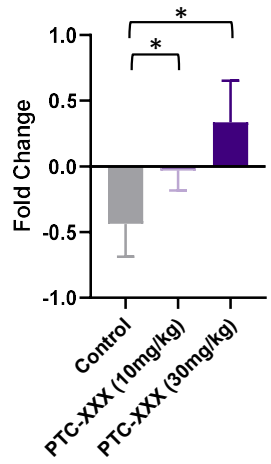
*P < 0.0001

Synaptic Plasticity (10 proteins)



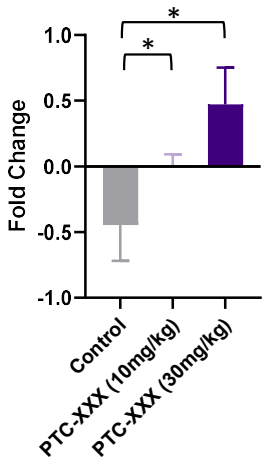
#P < 0.05, *p < 0.0001

Neurotransmission (26 proteins)



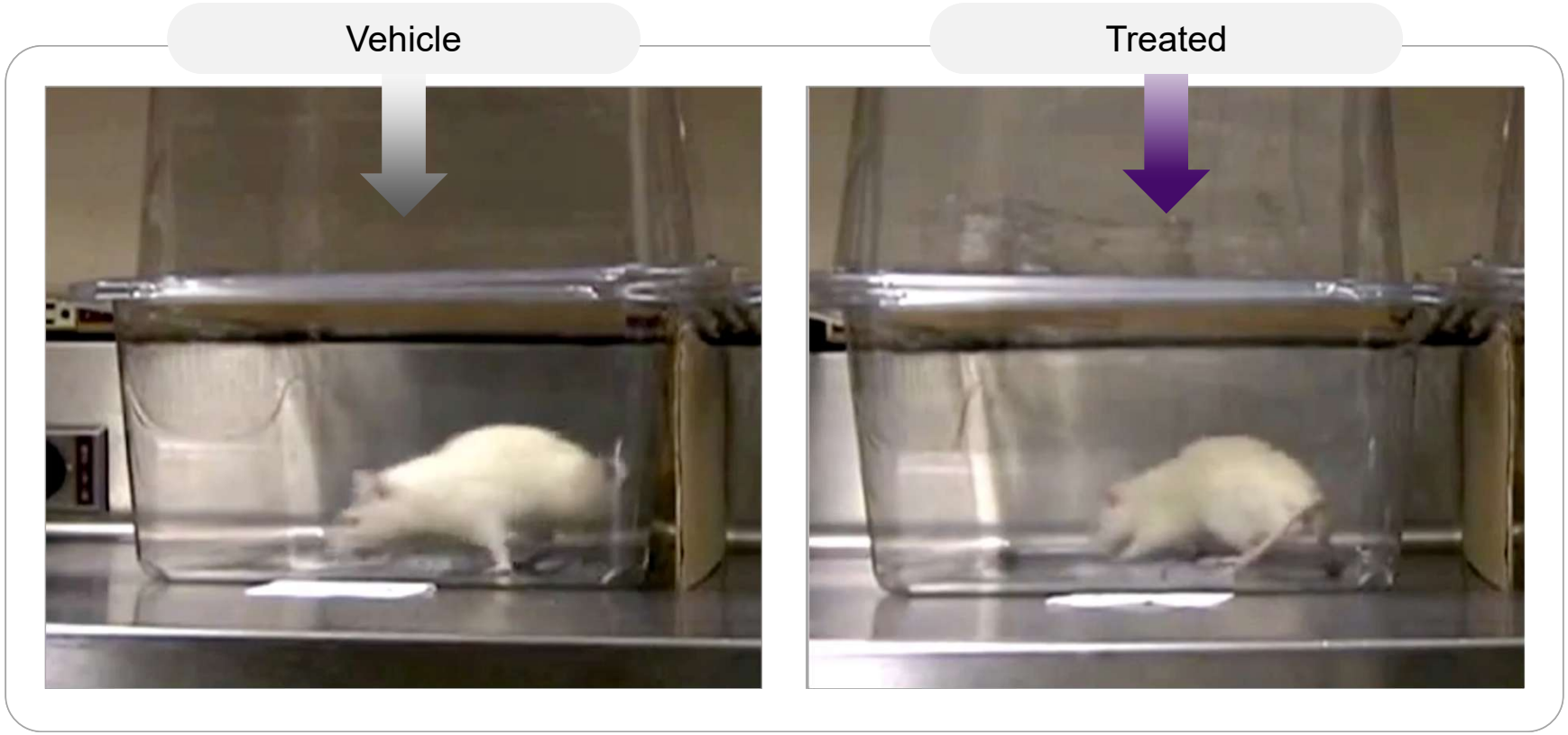
*P < 0.0001

Synapse Formation (9 proteins)

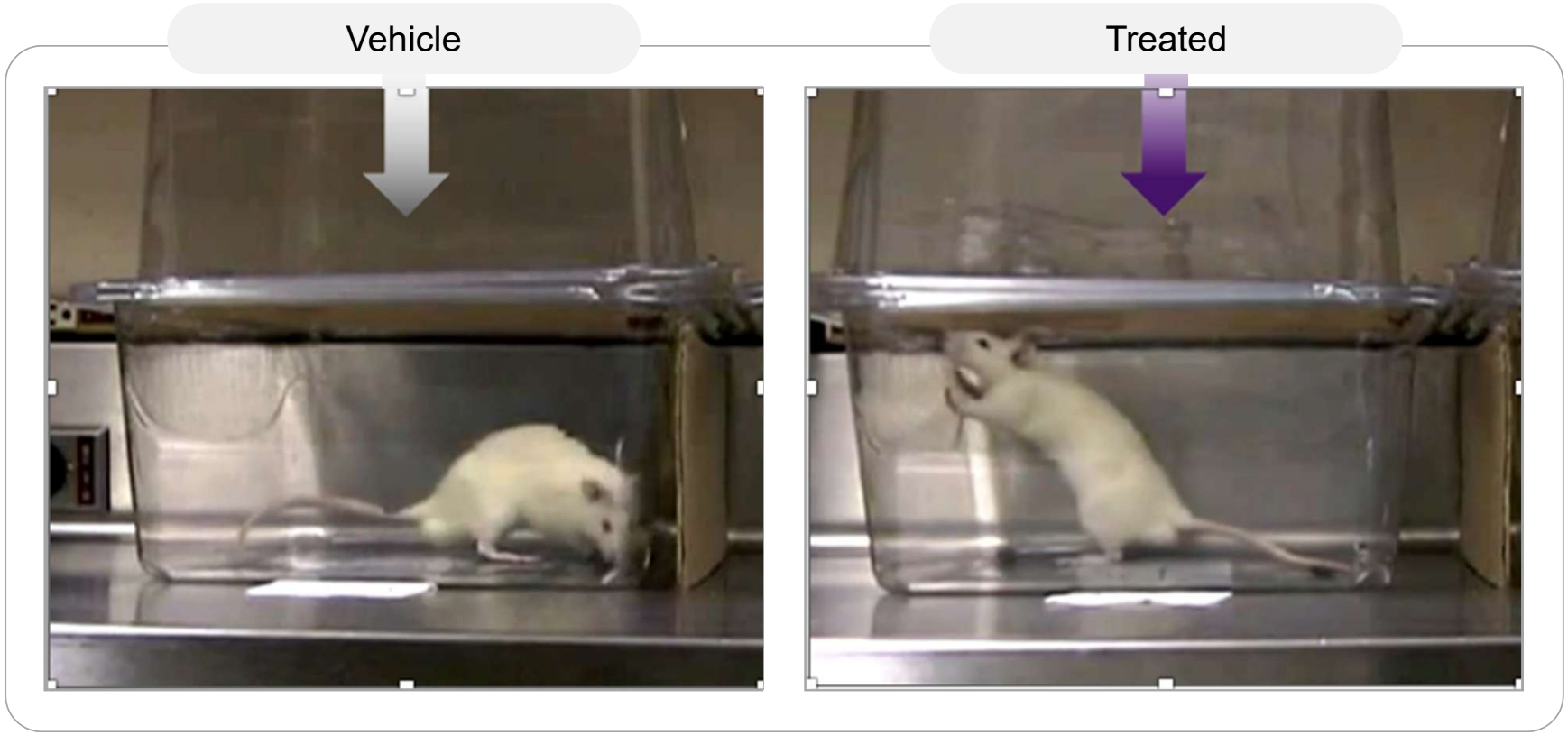


*P < 0.0001

PTC Compound Protects Locomotor Function in 6-OHDA Parkinson's Disease Model



PTC Compound Protects Locomotor Function in 6-OHDA Parkinson's Disease Model



Parkinson's Disease Program Status

- In vitro & in vivo POC established across several Parkinson's disease models
- Plan to select Development Candidate in Q1 2026
- Phase 1 initiation planned for H2 2026
- Translational biomarker program initiated to facilitate and accelerate clinical program

NRF2 Activation Program

NRF2 Program Leverages a Novel Mechanism to Provide Greater Anti-inflammatory Effects

- NRF2 is an intrinsic transcription factor that regulates cellular inflammation and stress response
- Program features differentiated mechanism of activation with enhanced selectivity and comprehensive NRF2 activation
  - Dose dependent NRF2 protein level increase
  - Selective target engagement
  - Modulation of both cellular stress response and inflammation pathways

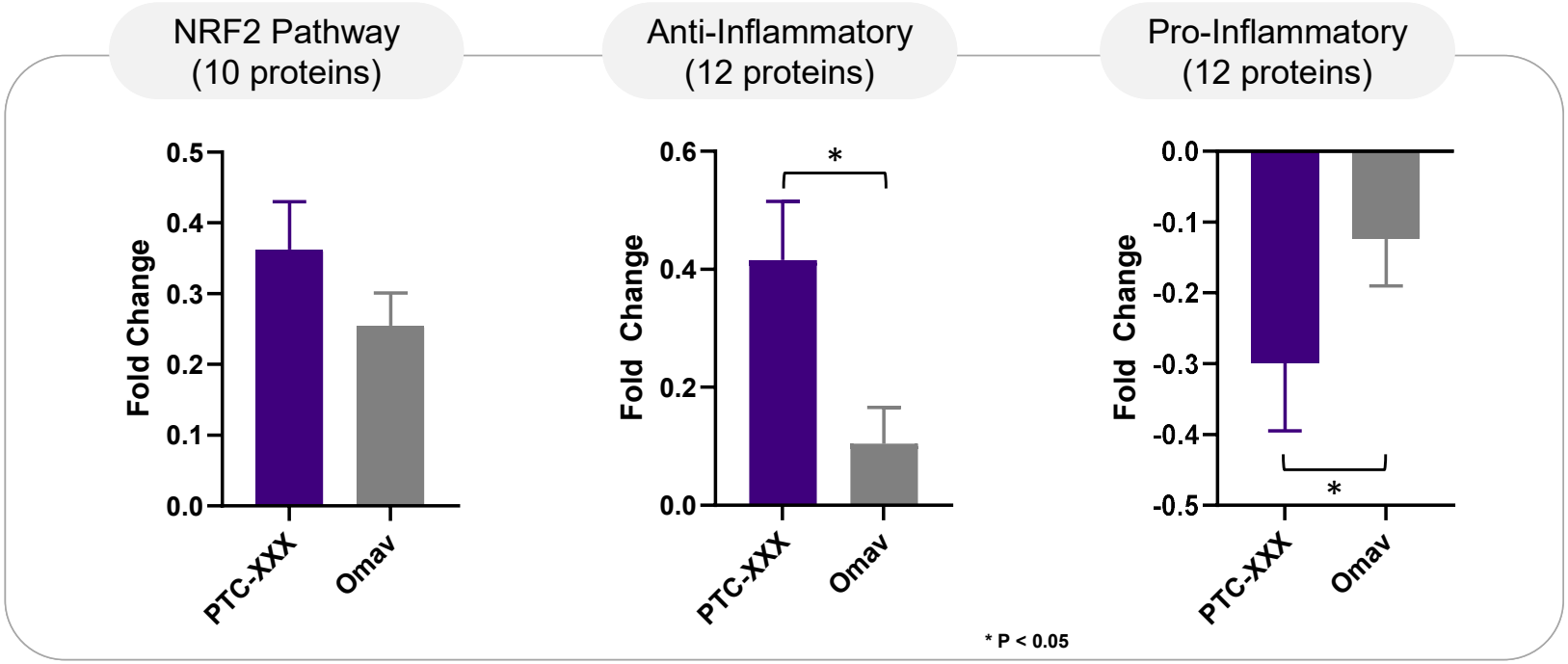
PTC Compounds Distinctly Modulate Inflammation Pathways Across a Range of Cell Types (*in vitro*)

Cell Type	Cytokine	PTC-XXX	Omav*
Human Astrocytes	IFNy	+	–
	IL4	+	–
	IL10	+	–
	IL-6	+	–
	C3	+	–
	MCP1	+	–

Cell Type	Cytokine	PTC-XXX	Omav*
ALS Human PBMCs	TNF	+	–
	MCP1	+	–
Human Microglia	MHCII	+	–
Human T-cells	IL2	+	–

*Omaveloxolone

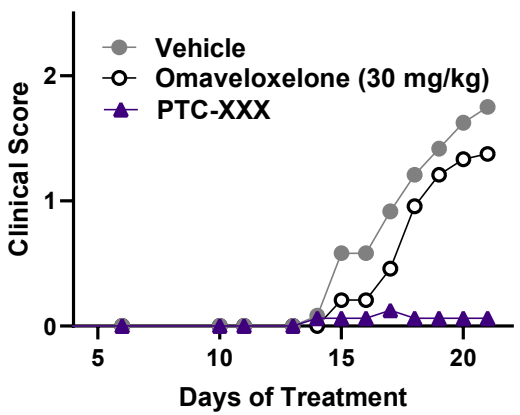
PTC Compounds Uniquely Modulate Inflammation Pathways Compared to Omaveloxolone (*in vitro*)

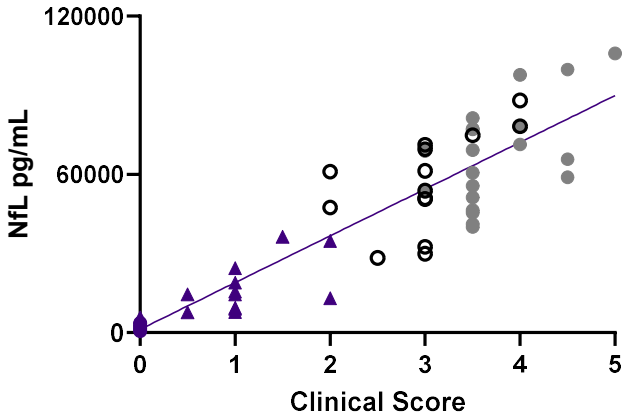


- PTC compounds increase expression of NRF2-related proteins and modulate inflammation pathways

PTC Compounds Provide Significant Protection in Relapsing Remitting MS Mouse Model

Prophylactic Dosing

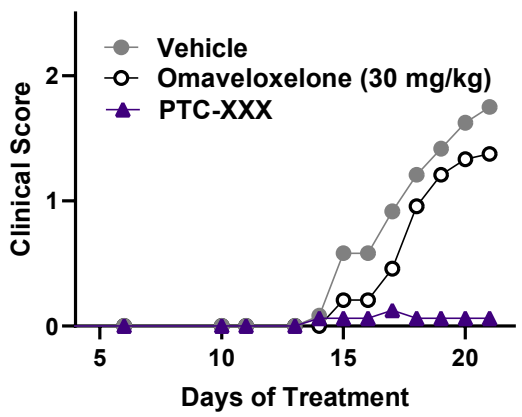


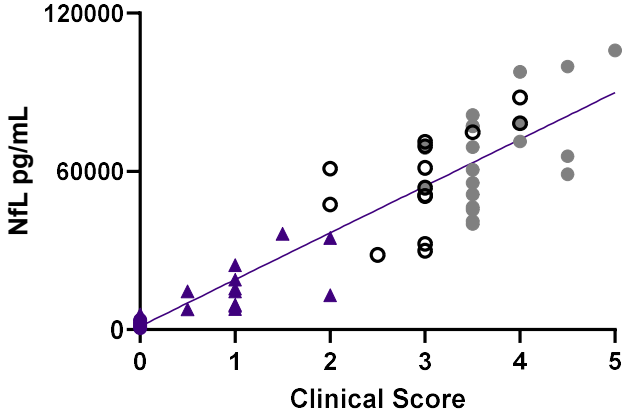


- PTC-compound administration protects when given before or after onset of disease presentation while Omaveloxolone confers no protection
- Clinical score correlates with biomarker of neuronal cell death—Neurofilament light chain (NfL)

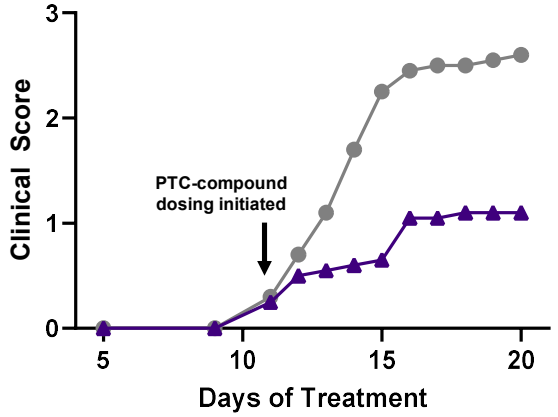
PTC Compounds Provide Significant Protection in Relapsing Remitting MS Mouse Model

Prophylactic Dosing





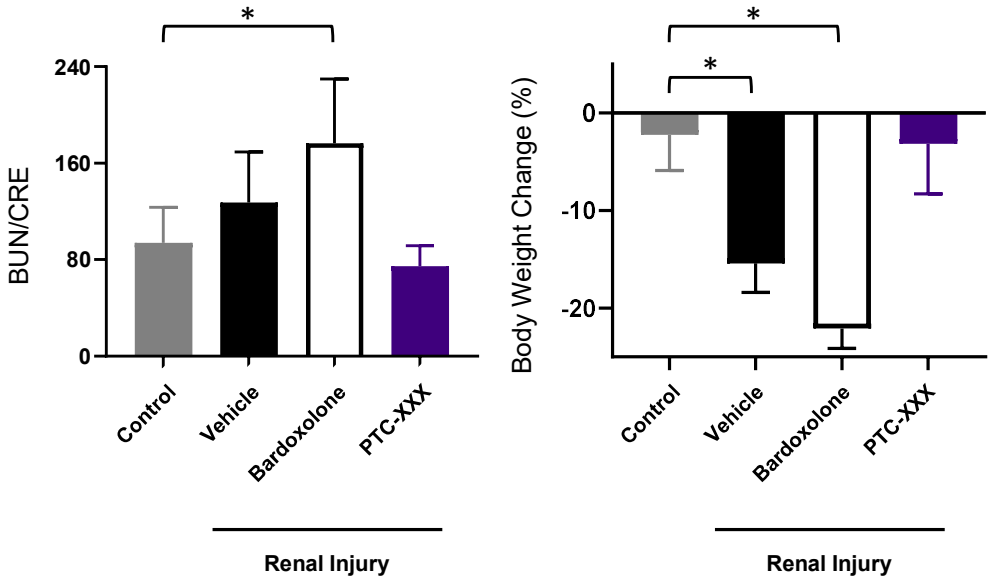
Therapeutic Dosing



- PTC-compound administration protects when given before or after onset of disease presentation while Omaveloxolone confers no protection
- Clinical score correlates with biomarker of neuronal cell death—Neurofilament light chain (NfL)

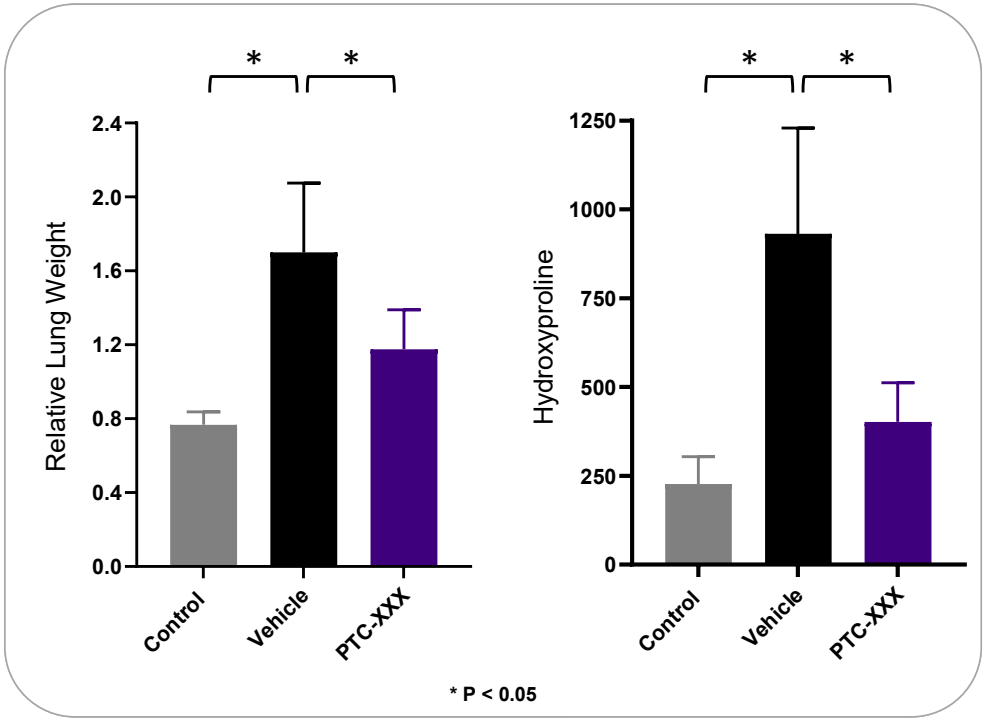
PTC Compounds Provide Significant Protection in Mouse Kidney Injury Model

- Renal inflammation model induces structural damage and fibrosis
- PTC compounds preserve kidney function and reverse weight loss
- Bardoxolone (a non-selective NRF2 activator) does not preserve kidney function and exacerbates weight loss



PTC Compounds Provide Significant Protection in Pulmonary Fibrosis Mouse Model

- Pulmonary fibrosis model induces structural damage and fibrosis
- PTC compounds preserve lung morphology and prevent fibrosis
- Supports NRF2 activation for indications in which fibrosis and tissue remodeling are known disease mechanisms



NRF2 Program Status

- Novel class of NRF2 activator small molecules identified and optimized
- Demonstrated competitive differentiation compared to existing NRF2 activators
- Expect Development Candidate nomination in 2026
- Indication selection work ongoing

PTC612 NLRP3 Inhibition Program

Mayzie Johnston, PharmD

NLRP3 - A Key Signaling Protein in the Innate Immune System

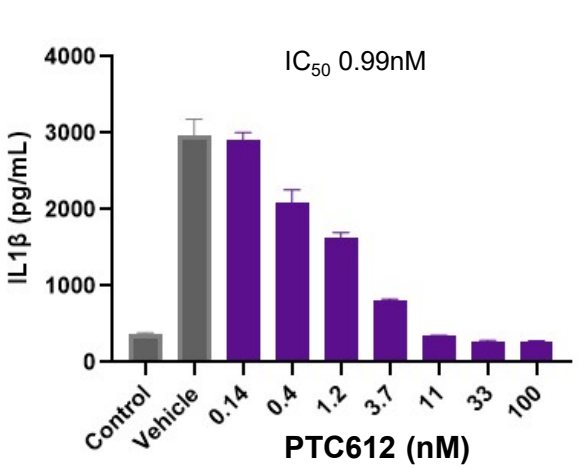
- NLRP3 is an Intracellular sensor protein in macrophages and other immune cells
- Detects infection, stress or tissue damage
- Upon detection, NLRP3 is activated triggering the assembly and activation of the NLRP3 inflammasome leading to elevated levels of IL-1β and IL-18
- Aberrant NLRP3 activation is implicated in a wide range of inflammatory diseases
- NLRP3 inhibitors block the NLRP3 protein from assembling into the inflammasome

PTC612 is a Highly Potent & Selective NLRP3 Inhibitor

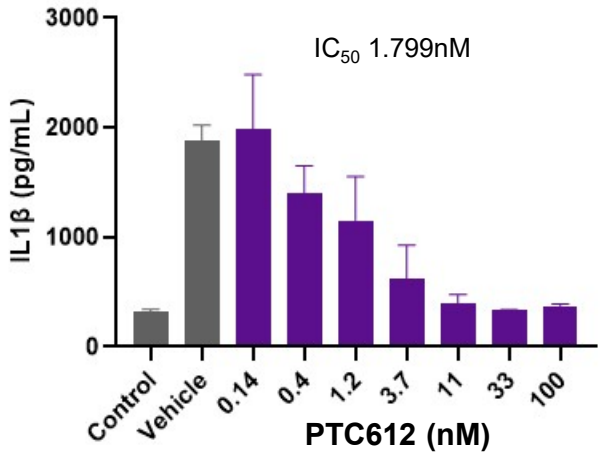
- Novel chemistry and favorable drug properties compared to other NLRP3 inhibitors leading to potential better safety and tolerability profile
- Demonstrates greater potency and selectivity for NLRP3 than many other NLRP3 inhibitors in development
- PTC612 demonstrated efficacy in multiple animal models, with evidence of NLRP3 pathway inhibition in vivo and defined PK-PD relationship

PTC612 Inhibits IL-1β Secretion in Multiple Cellular Models (*in vitro*)

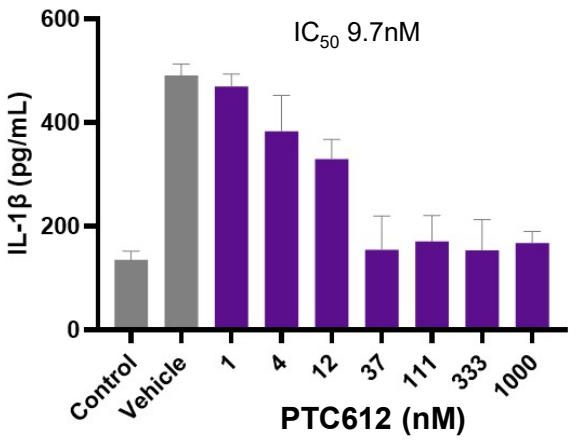
THP-1



hMDM



Human Whole Blood



THP-1: Myeloid tumor cell line

hMDM: Human monocyte derived macrophages

PTC612 Has Greater Potency Compared to Other NLRP3 Inhibitors

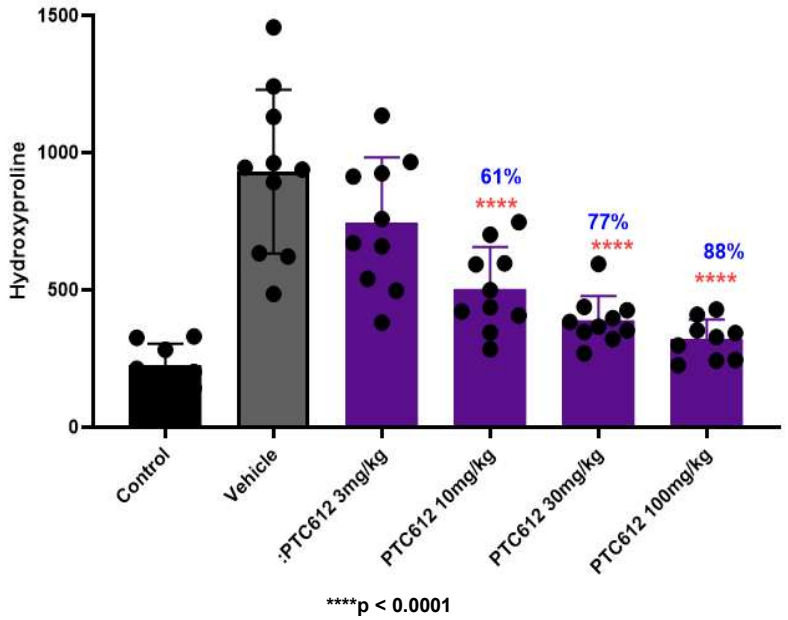
Compound	PTC612	Selnoflast[1]	DFV890[2]	Usnoflast[3]	AZD4144[4]
THP-1 IL1β IC_{50} (nM)	**0.99**	220	13	13	23-82

Compound	PTC612	Vent-01[5]	DFV890[2]	VTX-3232[6]	VTX-2735[6]
hWB IL1β IC_{50} (nM)	**9.7**	124	180	13	80

1. In house data; 2. JMC 2025; 3. Brain Res 2024; 4. JMC 2025
5. Infalmmasome Summit 2022; 6. Ventyx Corporate Presentation June 2023

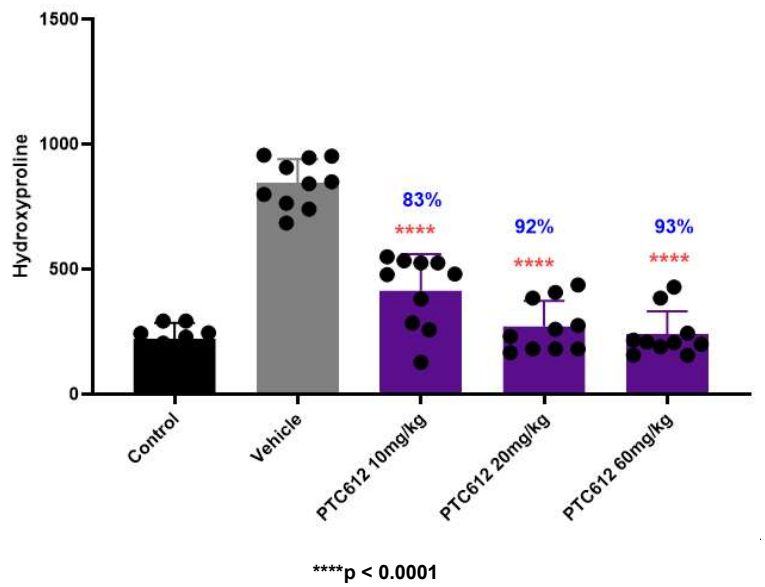
PTC612 Demonstrates Dose-Dependent Effect on Fibrosis in Murine IPF Model *(in vivo)*

Prophylactic Model



Treatment initiated on Day -1

Therapeutic Model



Treatment initiated on Day 7

PTC612 Summary and Program Status

- PTC612 is a highly selective NLRP3 inhibitor demonstrating significant reduction in inflammatory cytokines and pathology across multiple preclinical models
- PTC612 IND enabling studies ongoing
- Phase 1 study initiation planned for H1 2026
- Finalizing pulmonary inflammation indication selection

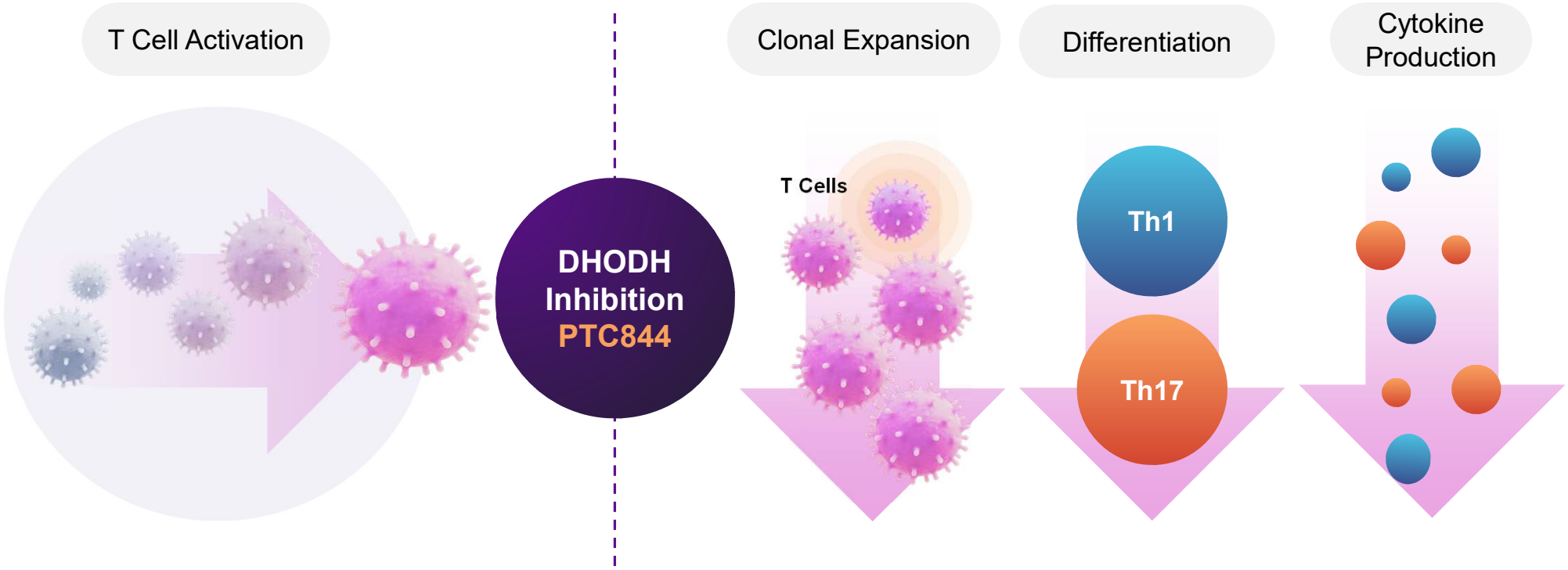
PTC844 DHODH Inhibition Program

Mayzie Johnston, PharmD

DHODH is a Key Regulator of T Cell Mediated Inflammation

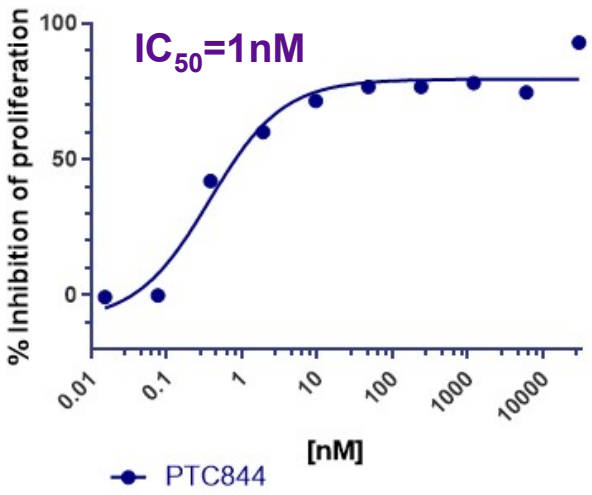
- DHODH plays critical role in inflammation by regulating the proliferation of immune cells and modulating cytokine production
- Inhibition starves activated T cells by depleting pyrimidine nucleotides
- Marketed DHODH inhibitors have limitations due to lack of specificity and associated toxicity
- PTC844 is a more potent and selective DHODH inhibitor potentially improving the efficacy and safety and tolerability profile

PTC844 Suppresses Proliferation of Activated T Cells

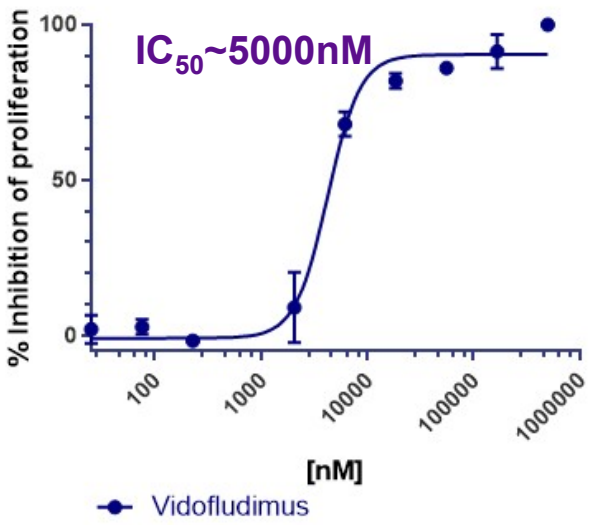


PTC844 Demonstrates Superior Potency Compared to Other DHODH Inhibitors

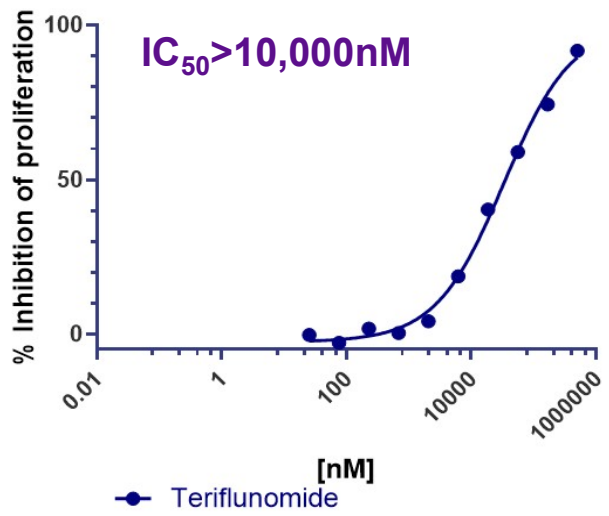
PTC844



Vidofludimus

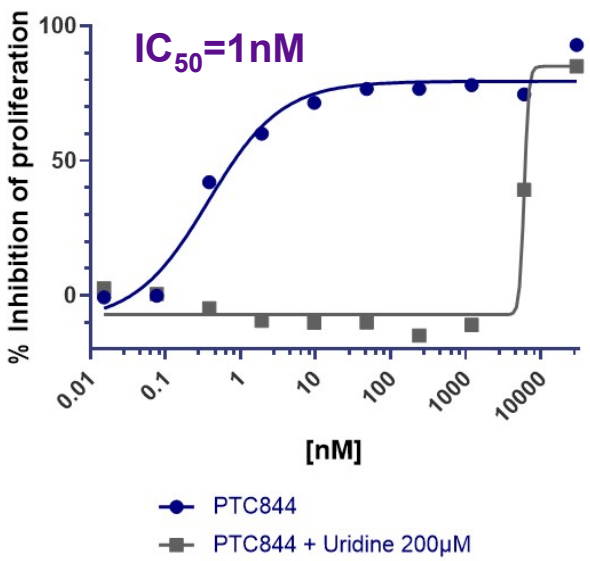


Teriflunomide

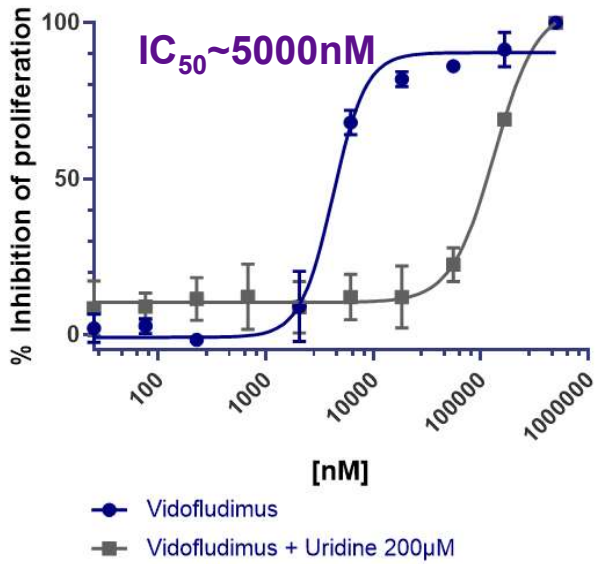


PTC844 Demonstrates Superior Selectivity Compared to Other DHODH Inhibitors

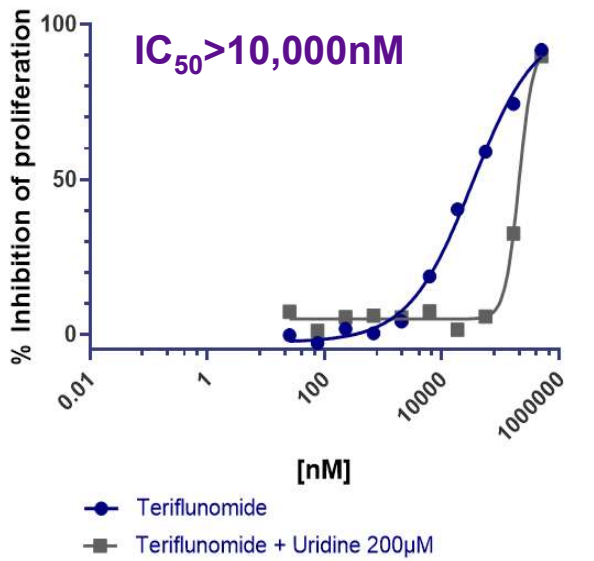
PTC844



Vidofludimus

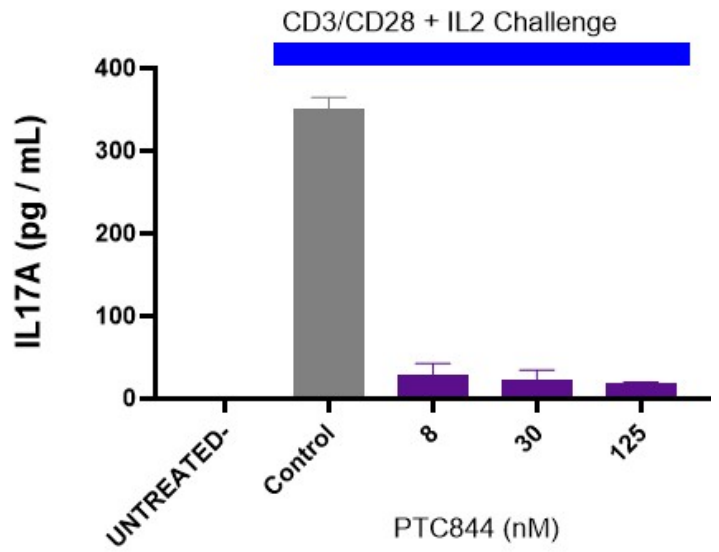


Teriflunomide

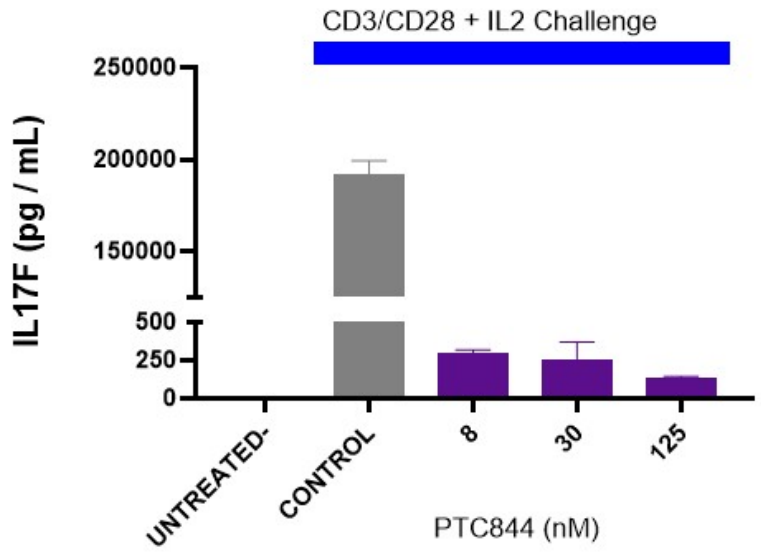


PTC844 Potently Inhibits the Proinflammatory Cytokine IL-17 in Human Cells *(in vitro)*

Human PBMCs IL-17A (CD3/CD28+ IL-2)

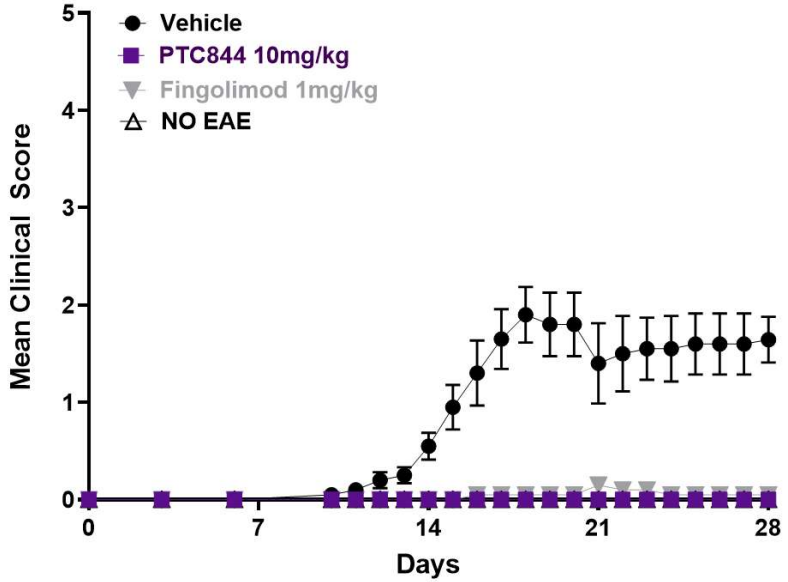


Human PBMCs IL-17F (CD3/CD28+ IL-2)

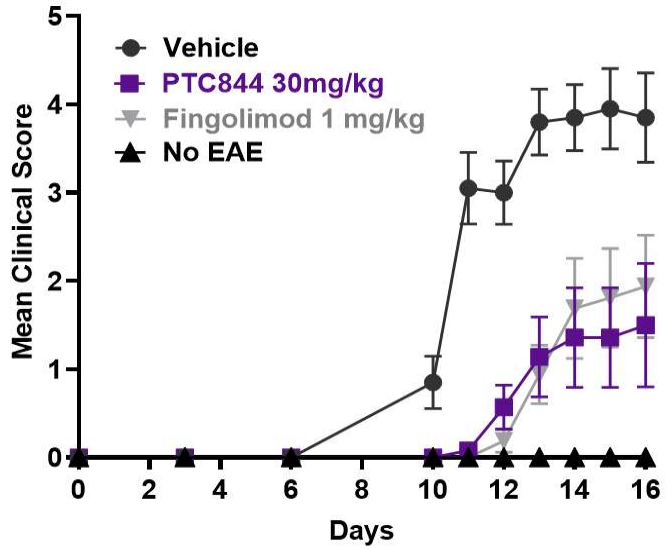


PTC844 Demonstrates Significant Efficacy in Murine Multiple Sclerosis Model *(in vivo)*

Myelin Oligodendrocyte Glycoprotein (MOG)



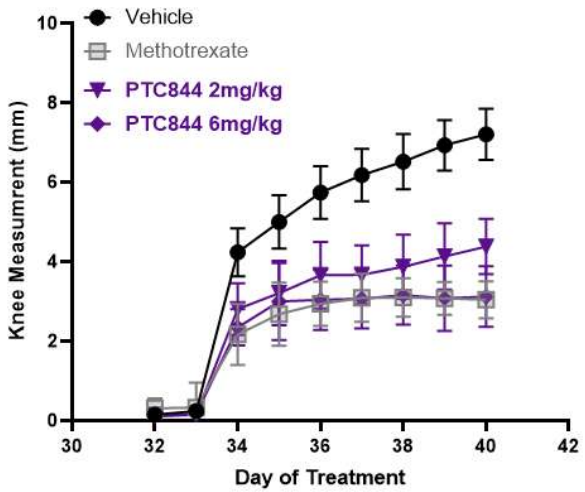
Proteolipid Protein (PLP)



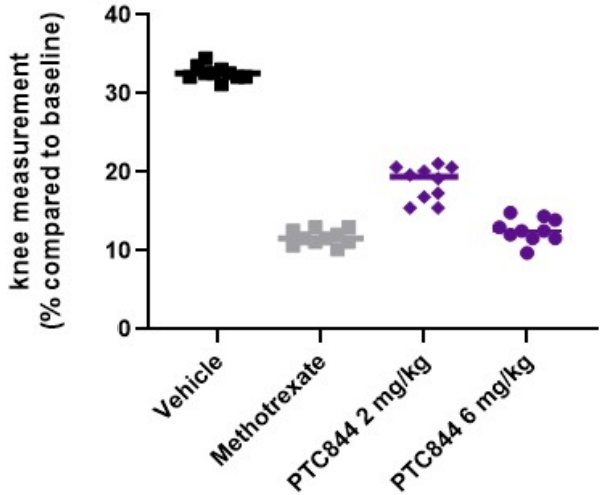
*PTC844 analog for murine model

PTC844 Demonstrates Efficacy in an Antigen Induced Model of Rheumatoid Arthritis *(in vivo)*

Knee, Change in Diameter



Knee, % Change in Diameter, Day 40



PTC844 was comparable to methotrexate in reducing knee inflammation after antigen challenge

Phase 1 Study Demonstrates Consistent Pharmacology, Favorable Safety Profile and Proof of Mechanism of Action

Single Ascending Dose (SAD)

SAD Doses	PK AUC (Day 1) (hr*ng/ml)	DHO* AUC (Day1) (hr*ng/ml)
1.5 mg	168	**1,590**
4.5 mg	380	**4,990**
13.5 mg	960	**20,000**
27 mg	1807	**37,400**
45 mg	3369	**62,500**

Multiple Ascending Dose (MAD)

Dose	PK AUC (Day 14) (hr*ng/ml)	DHO* AUC (Day 14) (hr*ng/ml)
4.5 mg	432	**10,417**
13.5 mg	1288	**27,400**
27 mg	2279	**35,100**

*DHO (dihydroorotate; substrate of DHODH)

DHO target ~ 30,000 at steady state

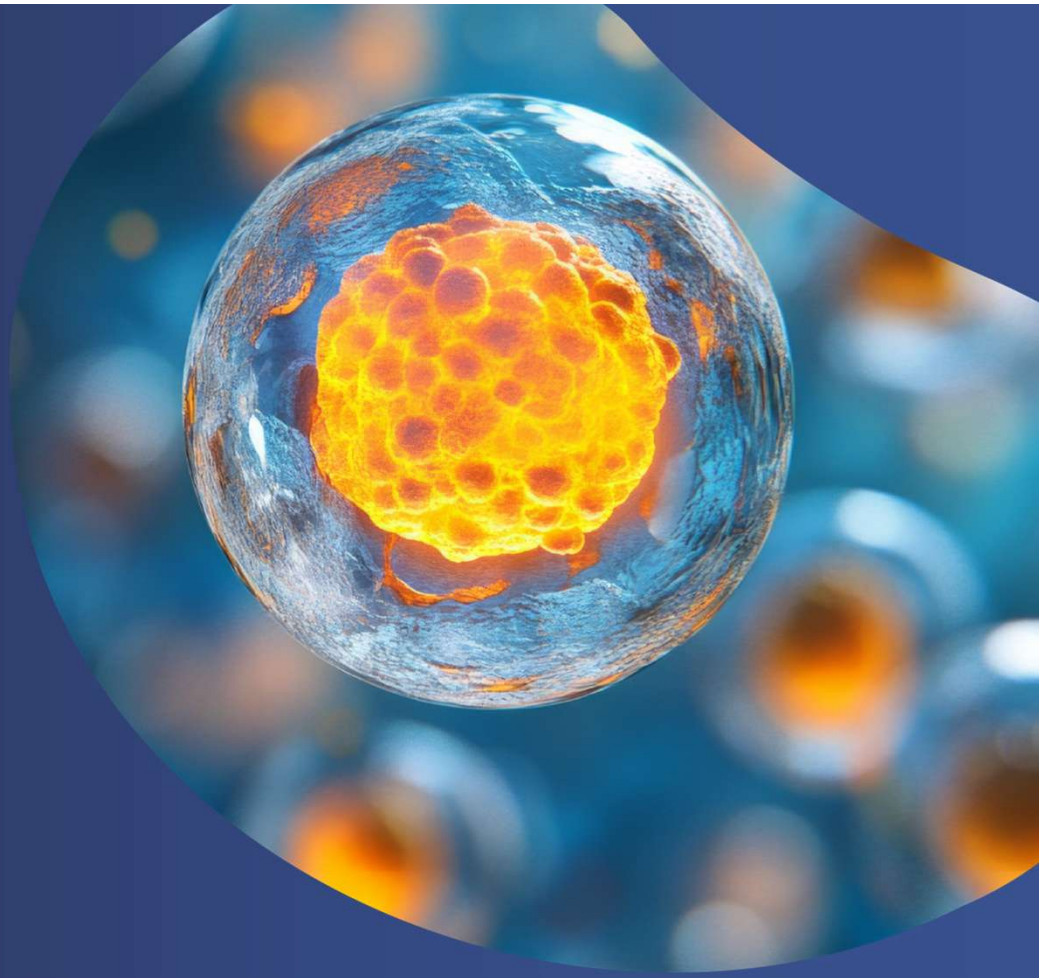
PTC844 Program Status

- PTC844 demonstrated safety in GLP toxicology studies
- SAD/MAD completed
- Food Effect study ongoing
- Finalizing indication selection
- Expect to initiate Phase 2A PK/PD study in mid-2026

Summary of Inflammation Platform Programs

- **15-Lipoxygenase inhibition:** Prevention of ferroptosis-mediated cell death and alpha-synuclein aggregation to deliver a disease modifying treatment for Parkinson's disease
- **NRF2 activation**: Activate NRF2 to mitigate oxidative stress and inflammation for CNS and non-CNS indications
- **NLRP3 inhibition:** Highly potent and selective NLRP3 inflammasome inhibitor to target peripheral (non-CNS) autoimmune and inflammatory indications
- **DHODH inhibition:** Highly potent and selective DHODH inhibitor with improved safety and tolerability profile to target T cell mediated pathology

Inflammation and Ferroptosis Q&A



Questions and Closing Remarks