Splicing Platform Deep Dive

July 24, 2020

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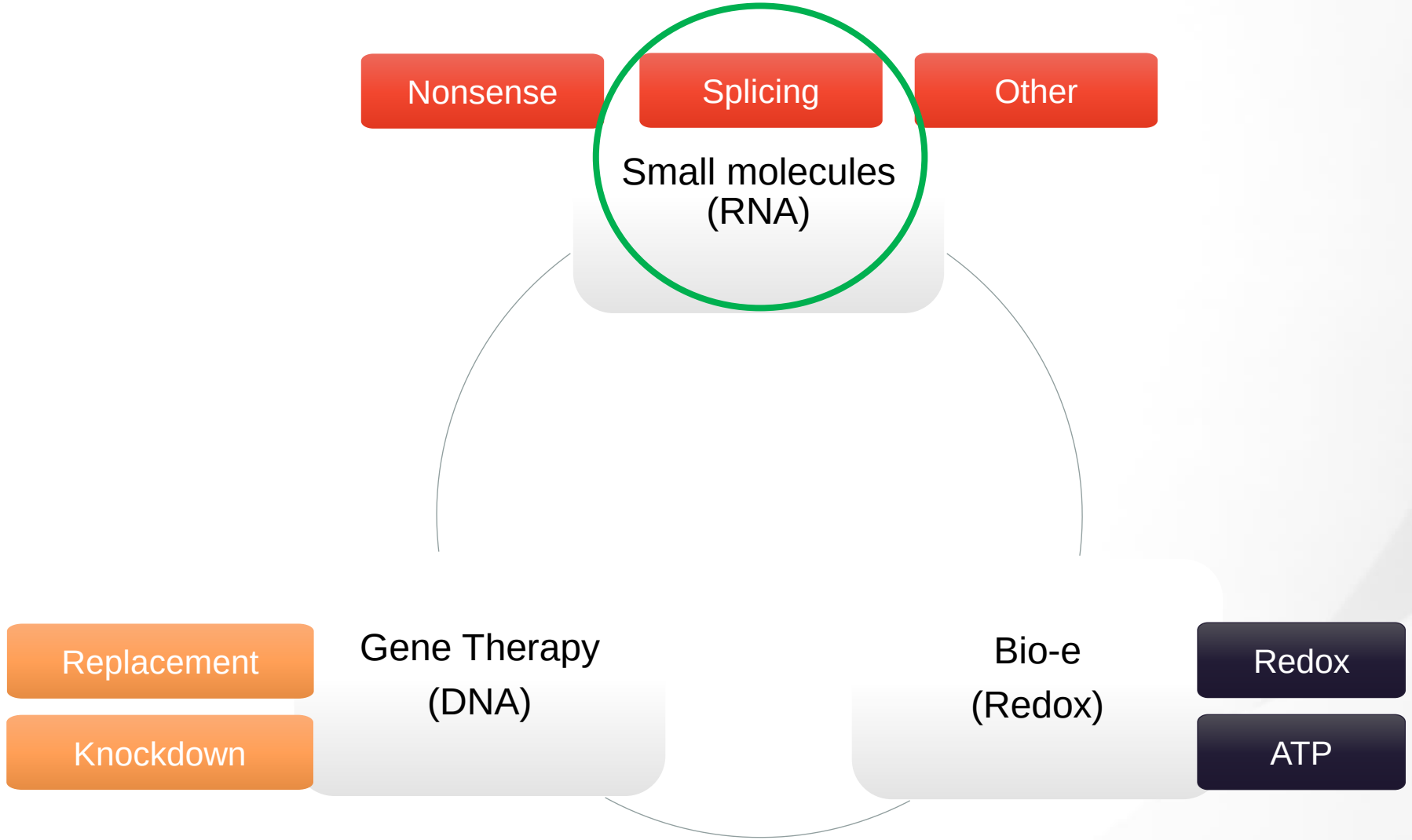
Splicing Platform Overview

Mark J. Pykett
V.M.D., Ph.D., Chief Scientific Officer

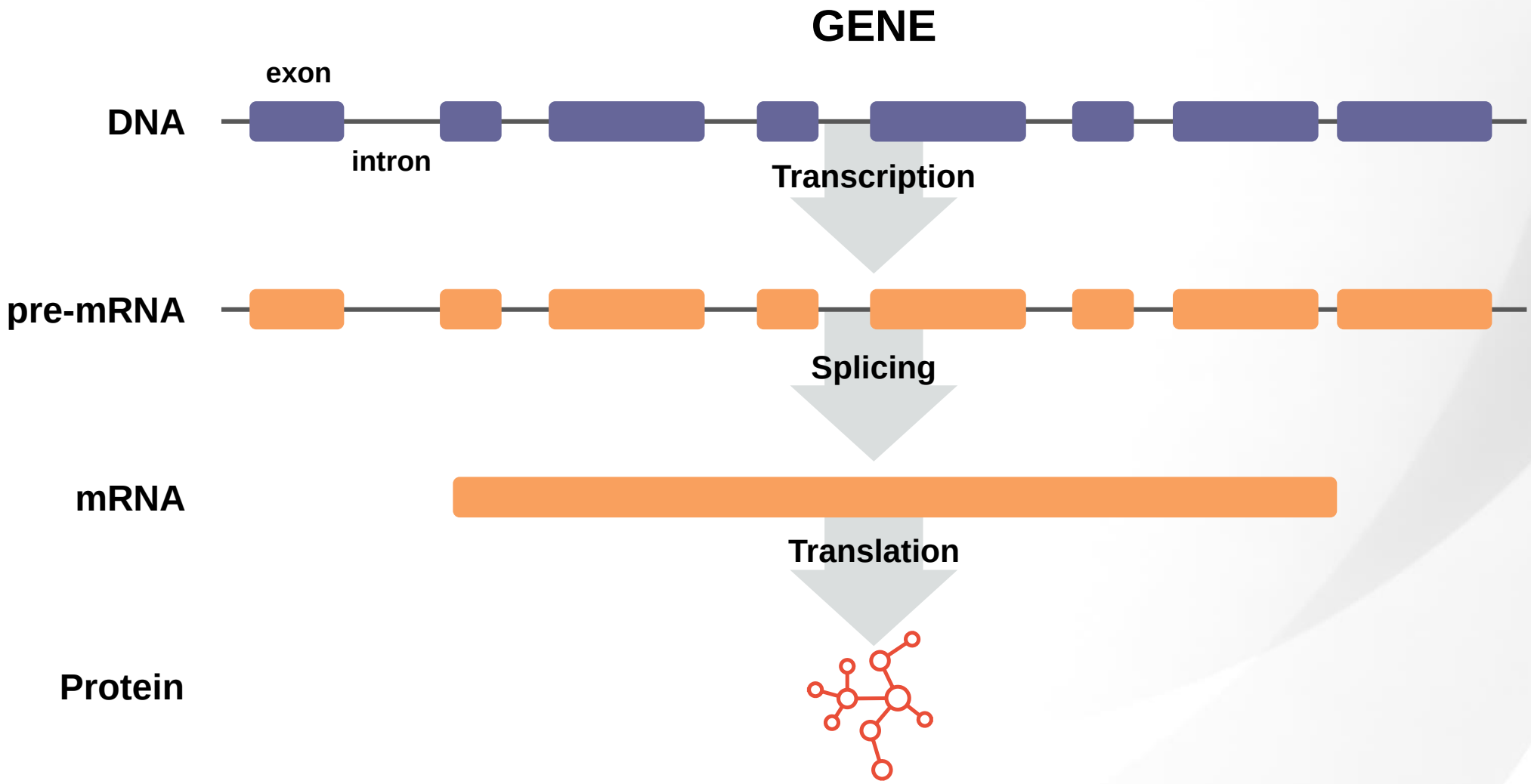
Splicing Platform Deep Dive Agenda

Splicing Platform Overview	**Mark J. Pykett** *V.M.D., Ph.D., Chief Scientific Officer*
Risdiplam Validates Targeting Splicing	**Nikolai Naryshkin** *Ph.D., VP External Innovation*
PTC's Unique & Proprietary Library	**Matt Woll** *Ph.D., VP & Head of Chemistry*
Splicing Platform Development & Programs	**Chris Trotta** *Ph.D., VP Biology*
Closing Remarks	**Stuart W. Peltz** *Ph.D., Chief Executive Officer*

PTC is the Leader in Small-Molecule RNA Biology

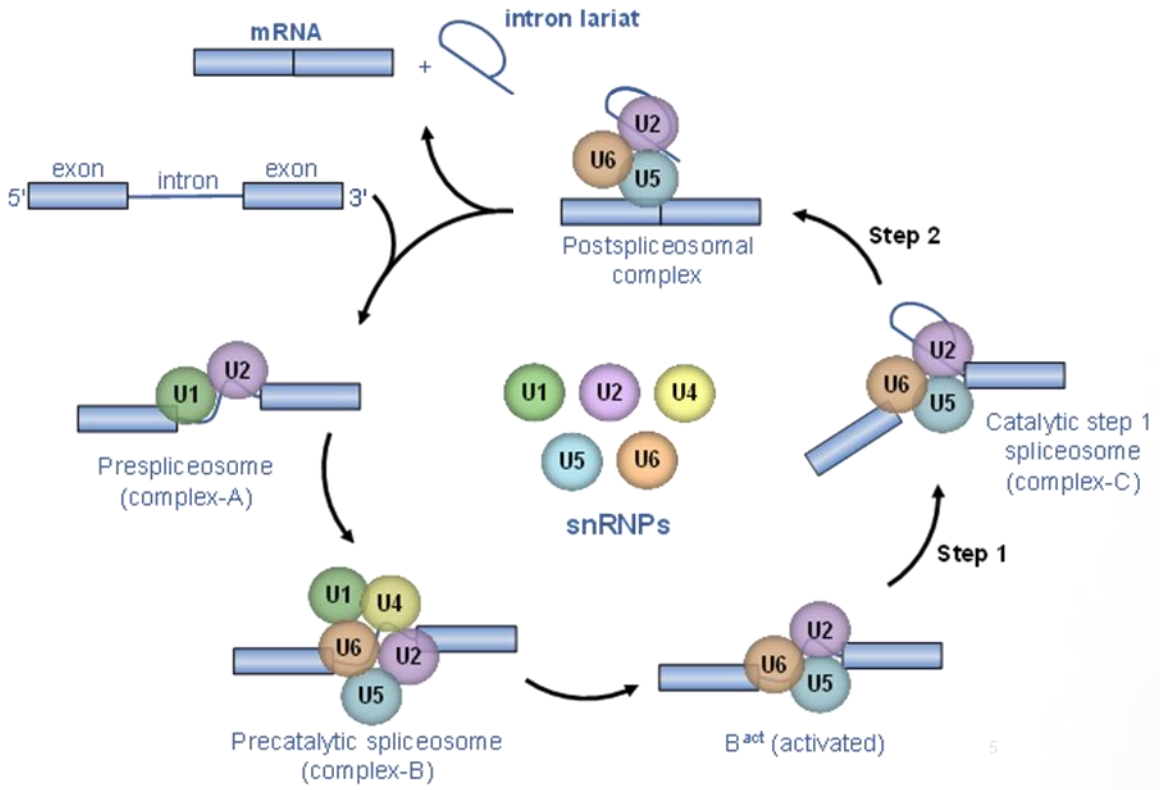


Pre-mRNA Splicing is Required for Gene Expression



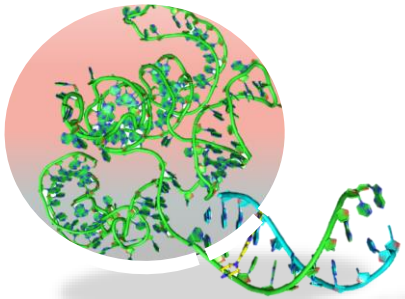
Pre-mRNA Splicing is a Complex Process, Rich in Potential Targets

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



There is a rich source of potential drug targets in these mechanisms

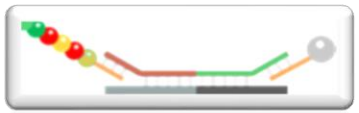
PTC is the Leader in Splicing With 15+ Years of Expertise And A Proven Track Record



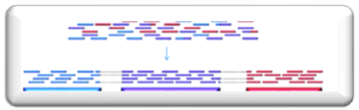
2005

Exploiting splicing

Databases of Splicing Targets

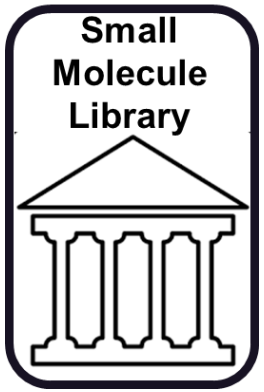


Isoform plex



HTSpliceseq

Proprietary systems and specialty libraries



2019

2020 and beyond

- risdiplam
- Familial dysautonomia
- Huntington disease

Many additional targets

Splicing Platform's Potential Extends Across PTC's Core Areas of Expertise

CNS

NEUROMUSCULAR

METABOLIC

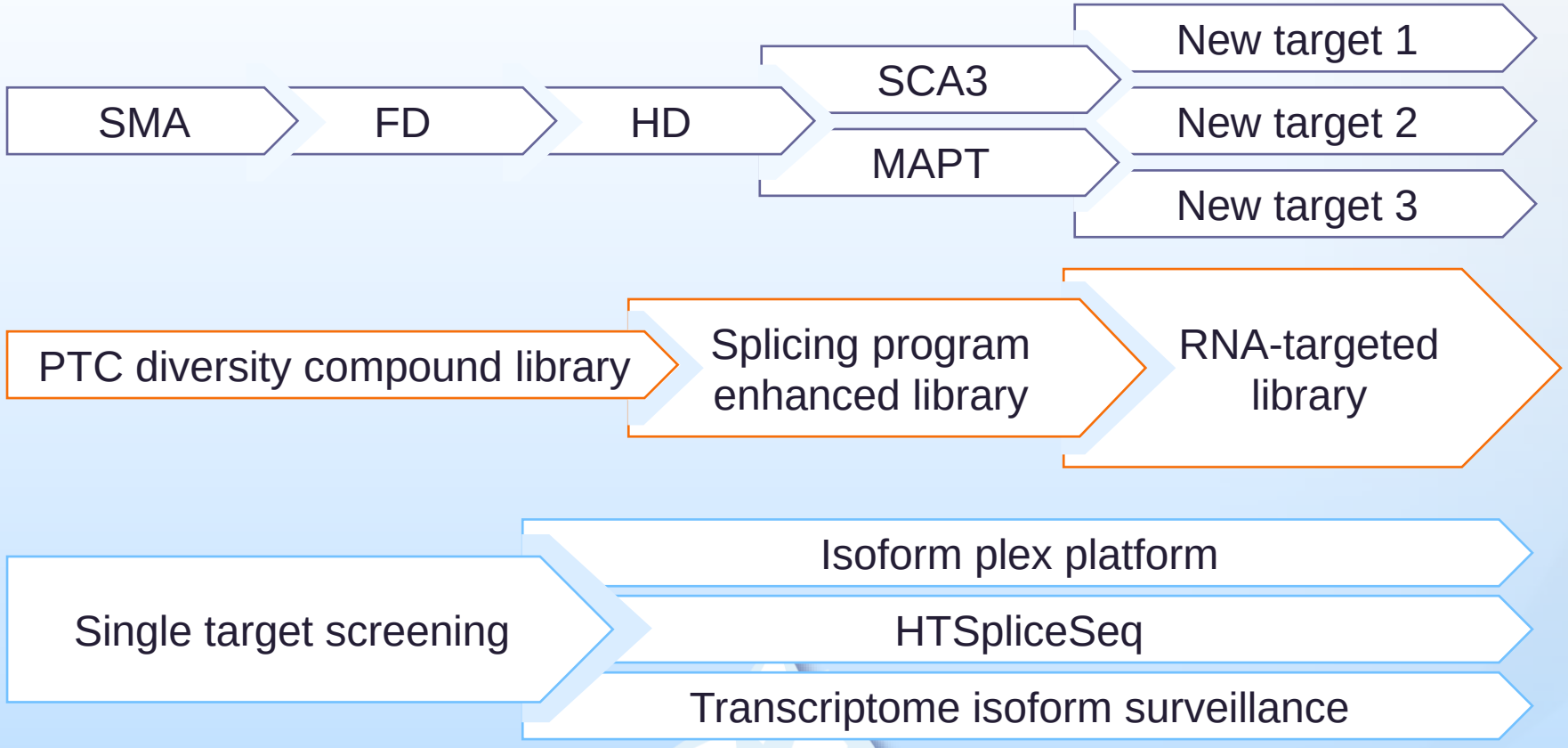
OPHTHALMOLOGY

Hundreds of identified targets with therapeutic tractability

Dozens of discovery assets

Multiple indications moving through POC

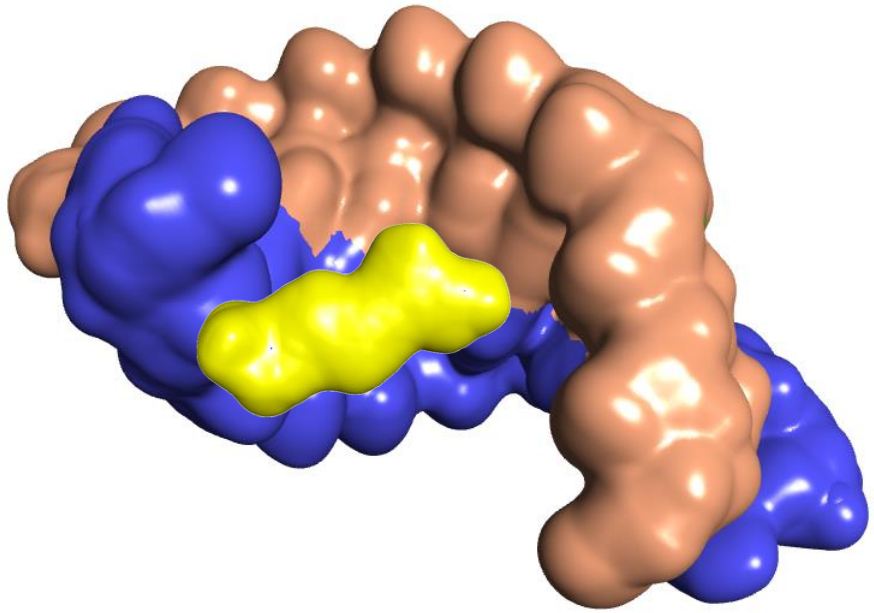
Building the PTC Splicing Platform



Risdiplam Validates Targeting Splicing

Nikolai Naryshkin, Ph.D.
VP External Innovation

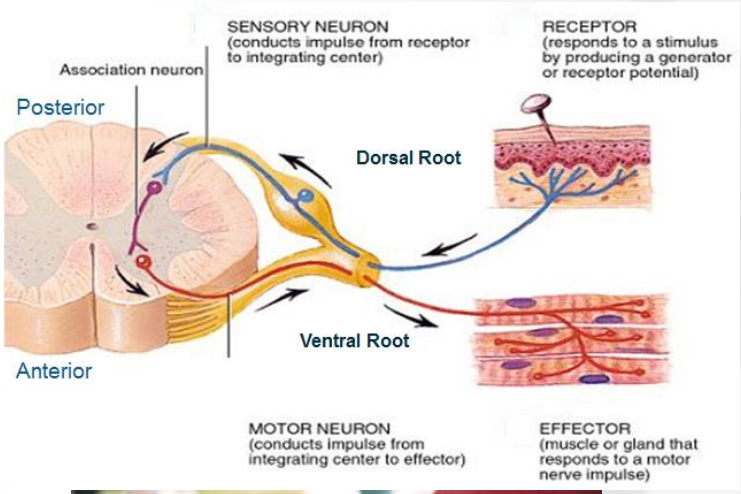
Risdiplam Validates Targeting pre-mRNA Splicing



- Strong translational foundation, consistent target engagement from in vitro and in vivo to humans
- Demonstrated selective modulation of splicing
- Enabled screening tier and key assays
- Defined mechanism of action; principles are expandable to other noncanonical sequences
- Laid the foundation of the PTC splicing platform, built unique and critical insights

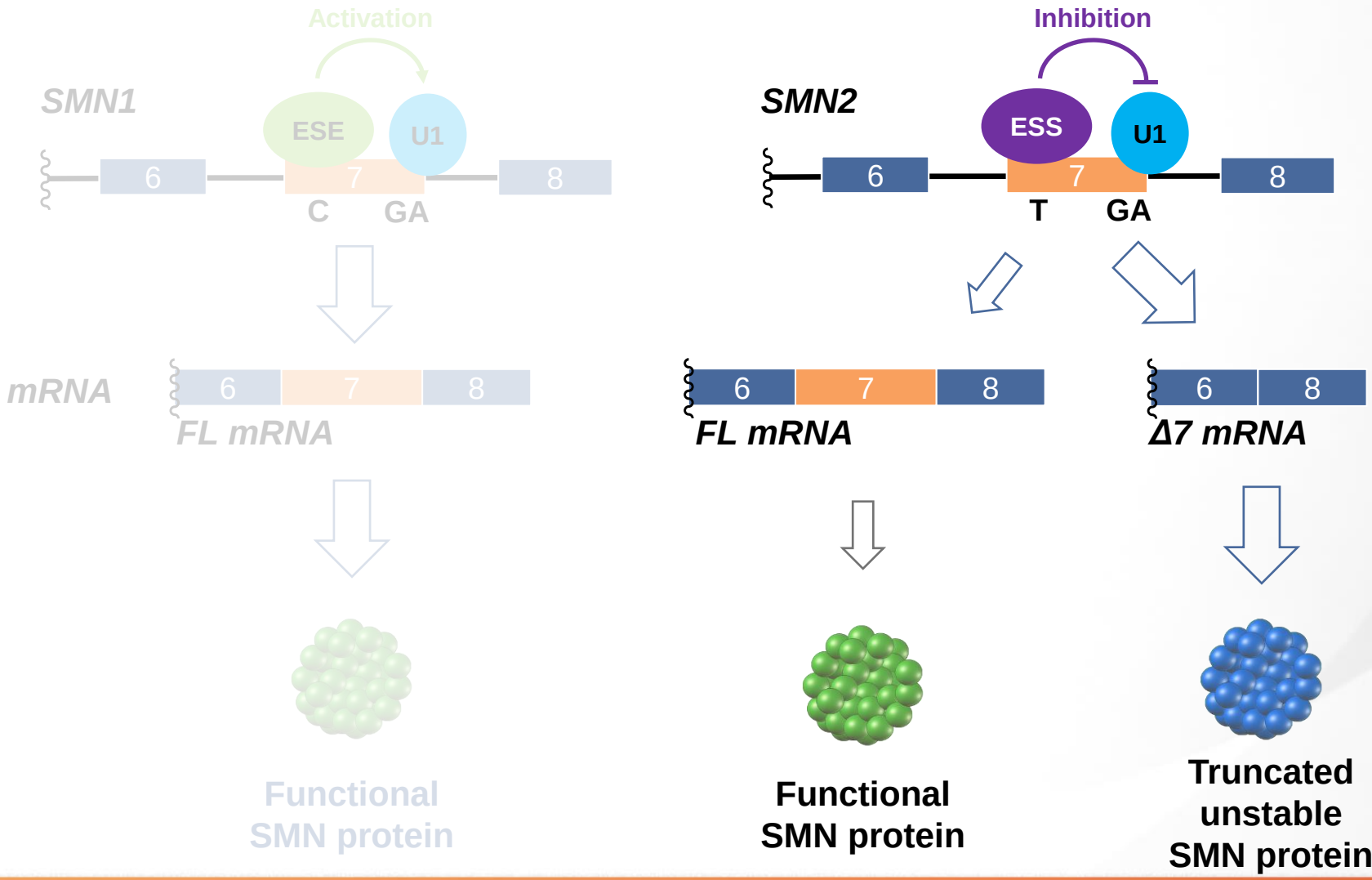
Spinal Muscular Atrophy Overview: The Leading Genetic Cause of Mortality in Infants

- Genetic disorder primarily affecting the central nervous system and muscles
- Overall muscle weakness, reduced body weight, weak reflexes, difficulty swallowing
- Autosomal recessive, 1 in 50 people are carriers[1]
- One in every 11,000 newborn children is affected with the disorder[1]
- PTC is collaborating with the SMA Foundation and Roche to advance treatments for SMA



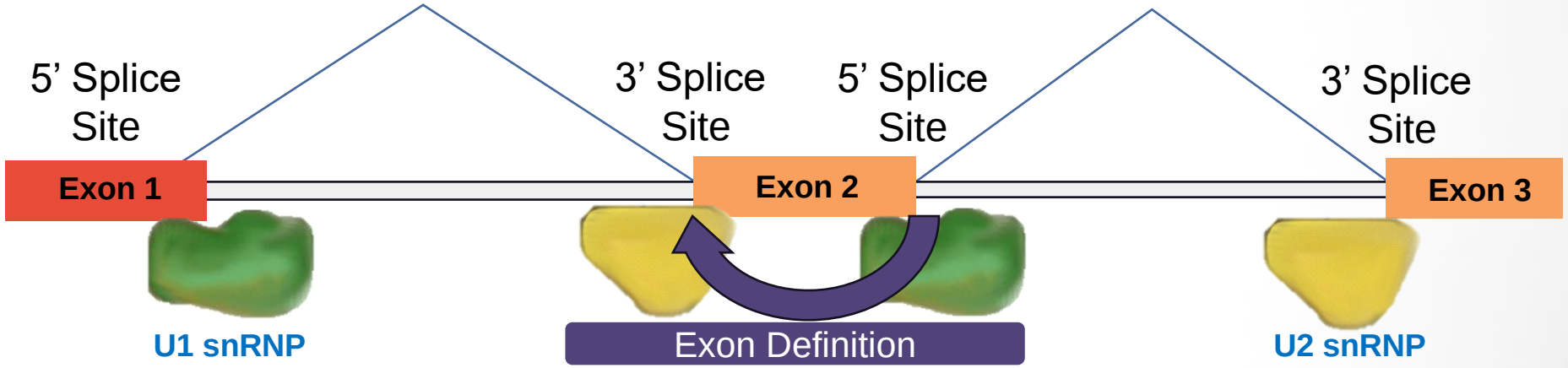
Sugarman EA, et al. *Eur J Hum Genet*. 2012;20(1):27-32.

Unique Molecular Genetics as Driver for SMA



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

Interactions between 5’- and 3’-Splice Sites Drive Exon Definition



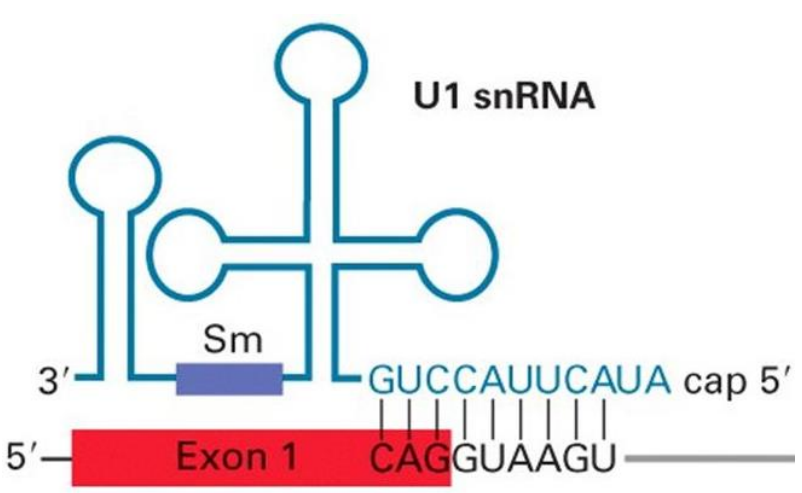
U1 recognizes the 5’ splice site at each exon

U2 recognizes the branch site near the 3’ splice site

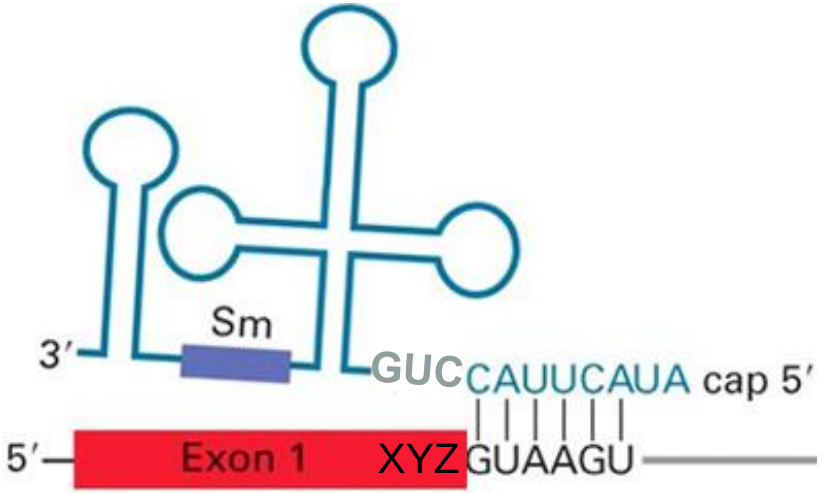
Xi et al. Nature (2019)
Buratti et al. NAR (2006)

Noncanonical 5’ Splice Sites Represent a Unique Class of Targets With Significant Sequence Specificity

Canonical exons
Perfect complementarity at the 5’ss

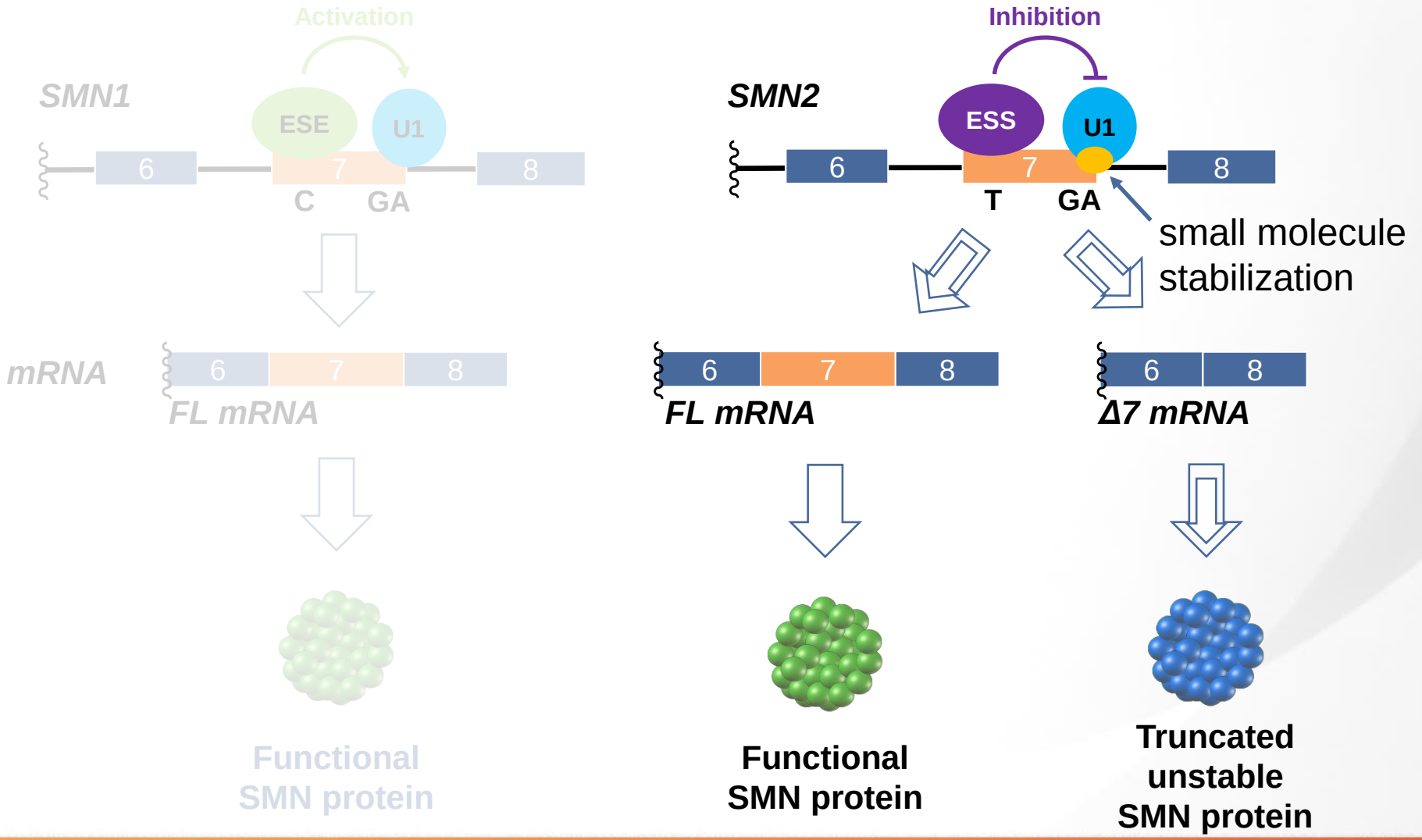


Noncanonical exons
Altered structure at the 5’ss



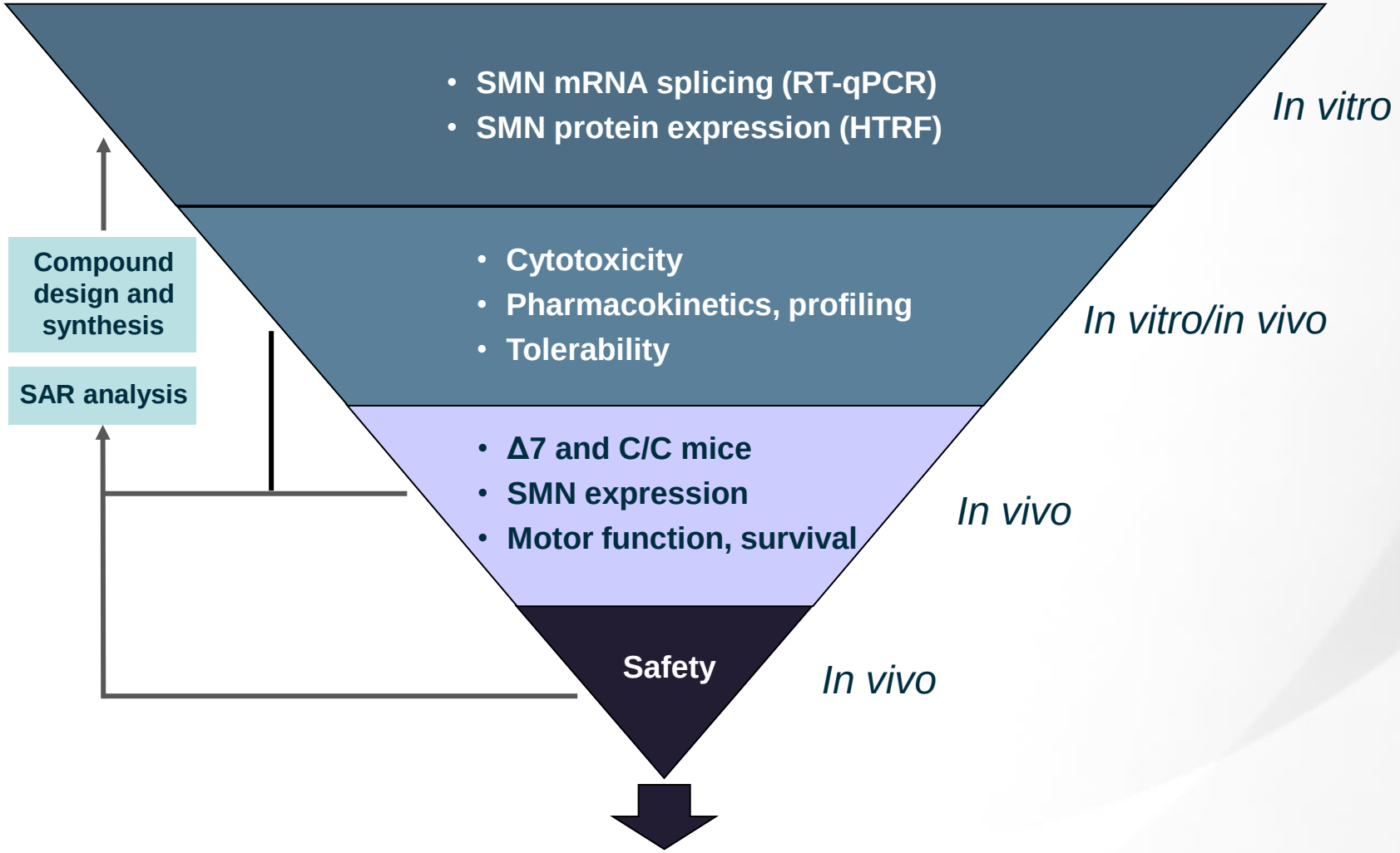
Science 2019 364, 362
Nat. Chem. Biol. 2019 15, 1191

Targeting Alternative Splicing of SMN2 in SMA



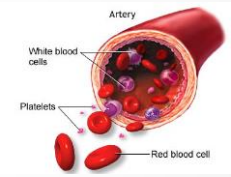
Singh et al. Crit rev euk gene expr (2004)
Cho and Dreyfuss. Genes Dev. (2010)

Comprehensive Lead Optimization Approach for Risdiplam Has Broad Application Across Splicing Platform

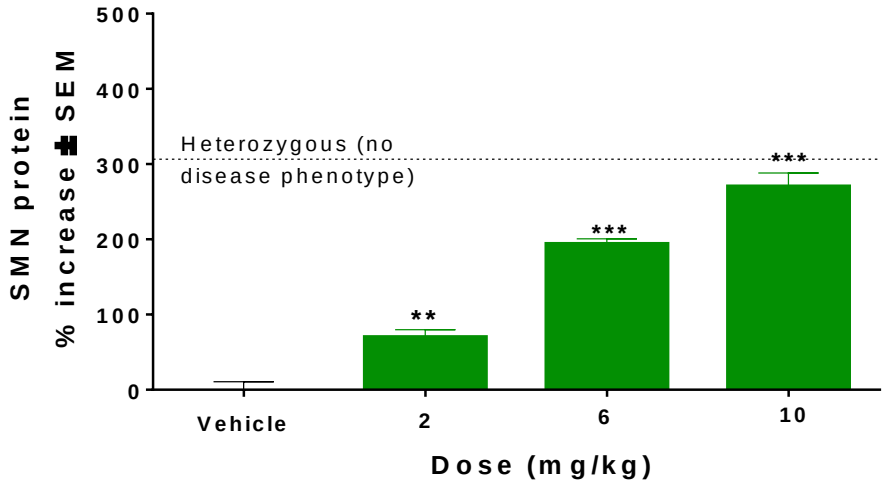


Compound Increases SMN Protein in Multiple Tissues to Near or Above Heterozygous Levels

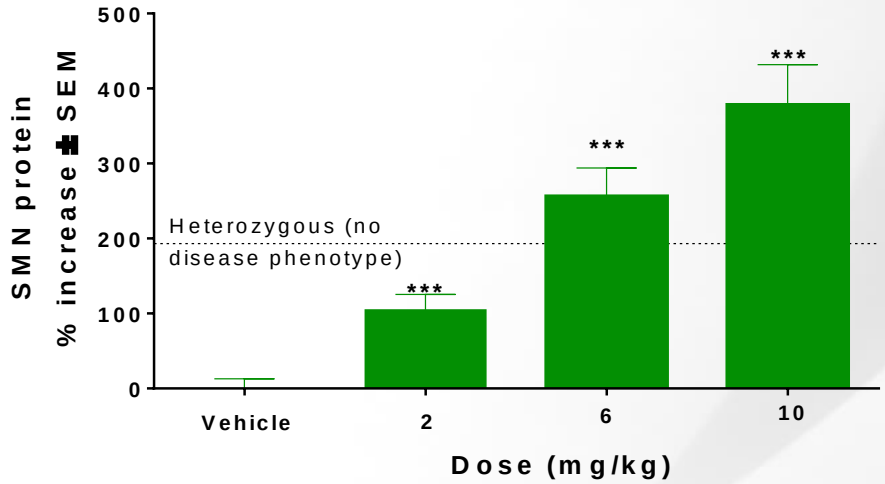
Oral dosing for 10 days in mild SMA mouse model



Brain



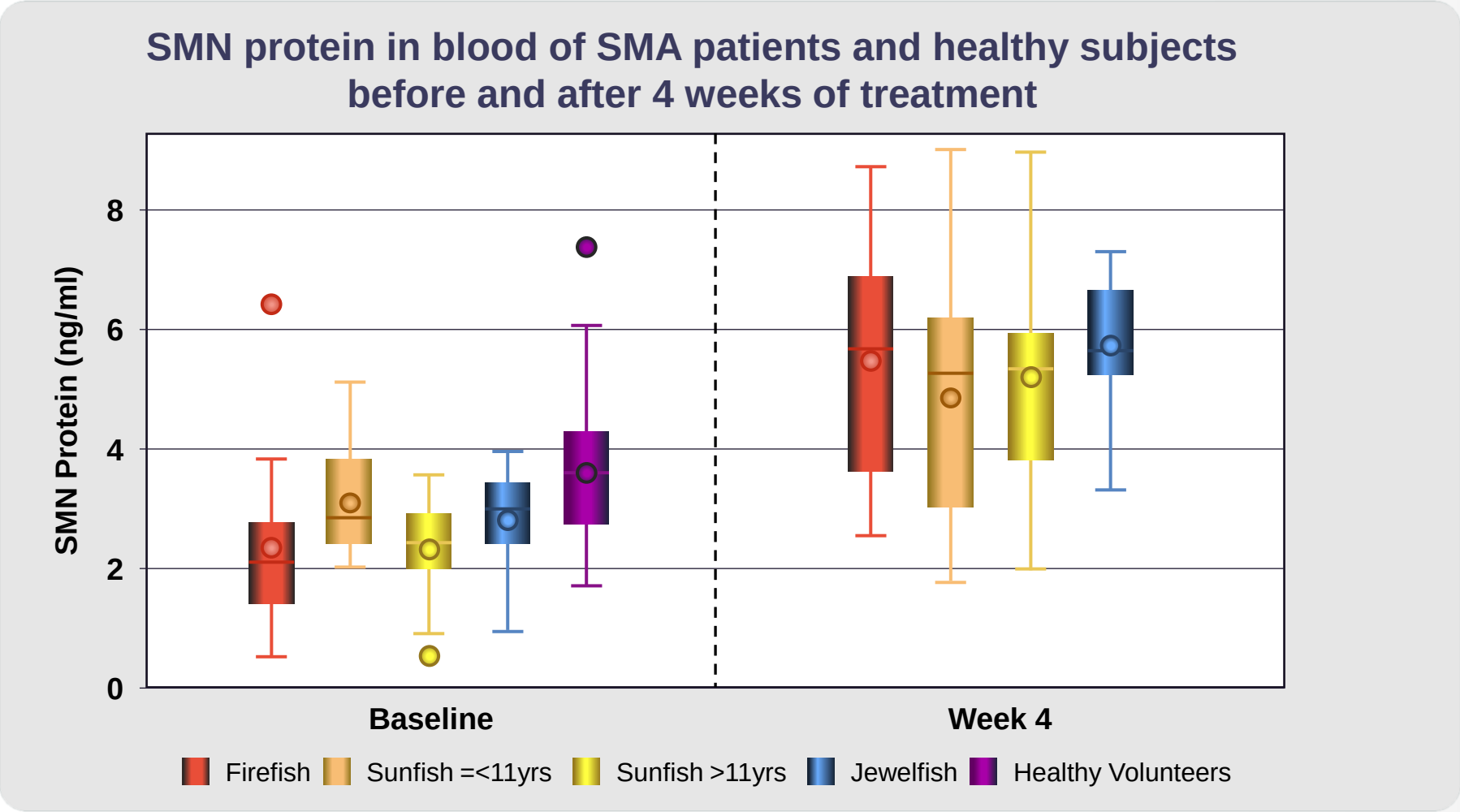
Peripheral Blood Mononuclear Cells



- 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

Risdiplam Increases SMN Protein Levels in All SMA Types to the Level in Adult Healthy Subjects



Kletzl et al. WMS 2018 poster

Healthy subjects n=49, age 18 - 60 years. Patients with SMA n=84, age 3.3 months - 52 years. Firefish part 1 (n=21), Sunfish part 1 (n=51), Jewelfish (n=12)

Risdiplam – Most Competitive Commercial Profile Across Broadest Population

FIREFISH – Type 1 SMA

FIREFISH Part 2 demonstrated statistically significant improvement in proportion of infants sitting for at least 5 seconds at 12 months

29%

12 of 41 infants were able to sit for at least 5 seconds without support at month 12; p<0.0001

85%

35 of 41 infants were event-free at month 12

95%

of infants alive maintained the ability to swallow after 12 months

Results confirm risdiplam's clinically meaningful efficacy in infants with advanced and difficult to treat disease

FIREFISH Part 2 met primary & key secondary endpoints

SUNFISH – Type 2 and 3 SMA

Part 2 pivotal study demonstrated statistically significant improvement in MFM-32 scores compared to placebo

1.55

point change compared to placebo (p=0.0156) in MFM-32 scores

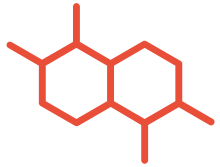
1.59

Point change compared to placebo (p=0.0028) in RULM scores

Included broadest group of SMA patients studied, age 2-25, representative of real-world spectrum of people living with SMA

SUNFISH Part 2 met primary & key secondary endpoints

Risdiplam – Most Competitive Commercial Profile Across Broadest Population



Small Molecule with systemic mode of action

Oral, at home-administration

Full target engagement - SMN2 full-length ↑, Δ7 mRNA ↓

Durable increase of SMN protein level in CNS and periphery

Studied in >450 patients from newborns to 60 years of age

Clinically meaningful efficacy in real world patient population

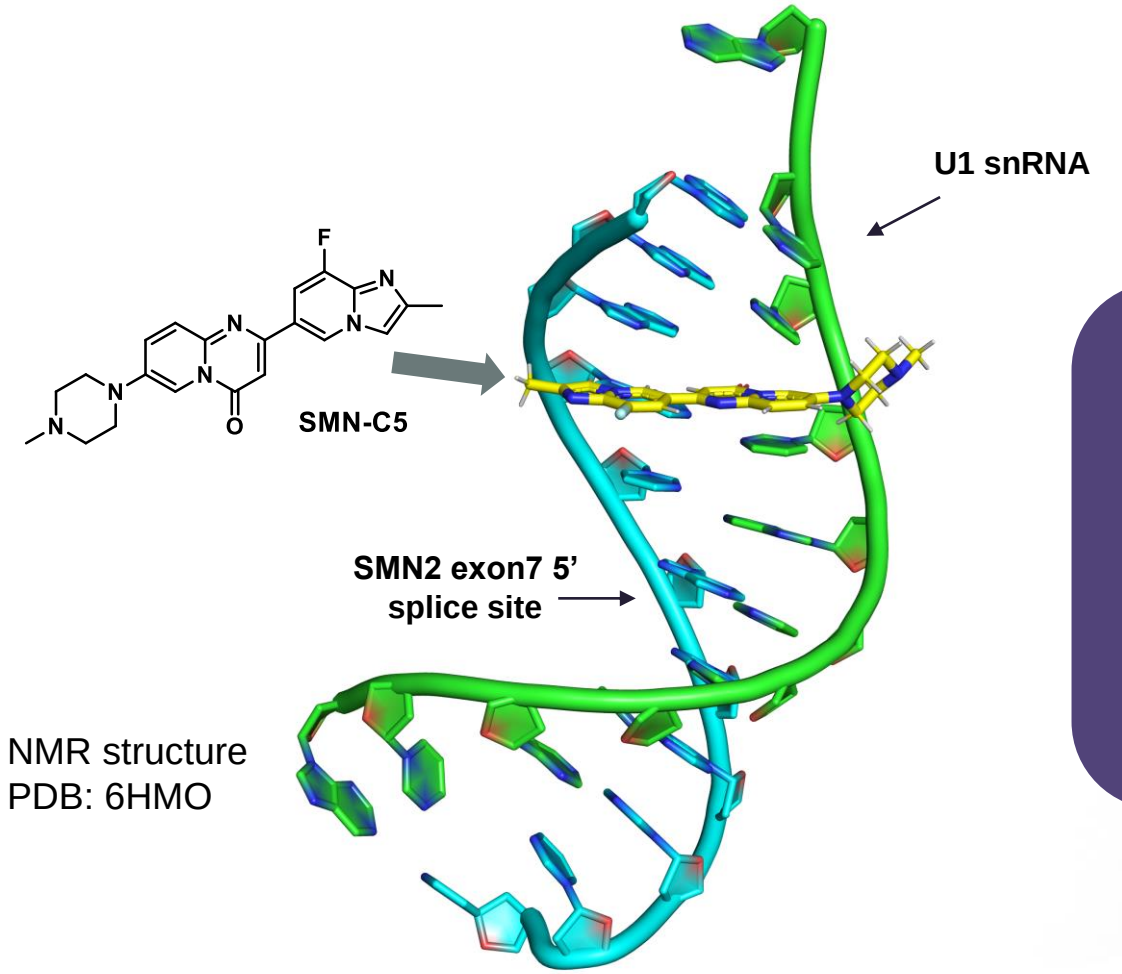
Strong safety profile

PDUFA date: August 24, 2020

PTC's Unique & Proprietary Library

Matt Woll, Ph.D.
VP Chemistry

Splicing Modifiers Bind at a Specific RNA Interface

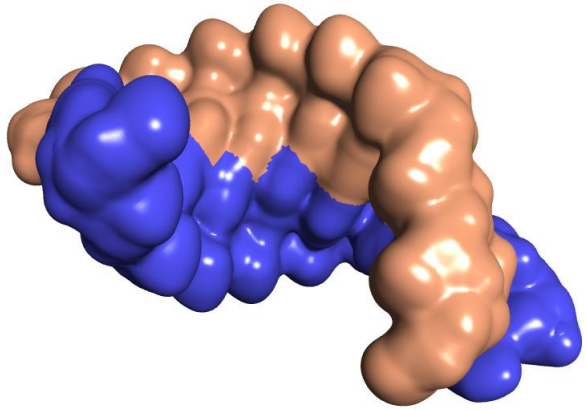


SMN splicing modifier binds at the interface of U1/pre-mRNA at the noncanonical 5’ splice site of exon 7

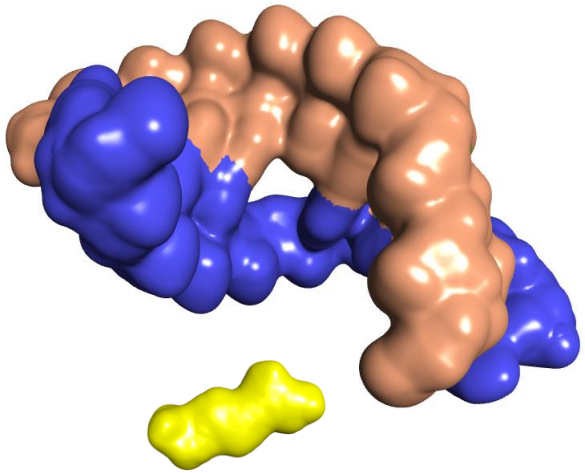
Nat. Chem. Biol. 2019 15, 1191

Noncanonical 5’-Splice Sites Present Unique Structural Interfaces for Small Molecule Binding

Canonical duplex



Noncanonical duplex 1

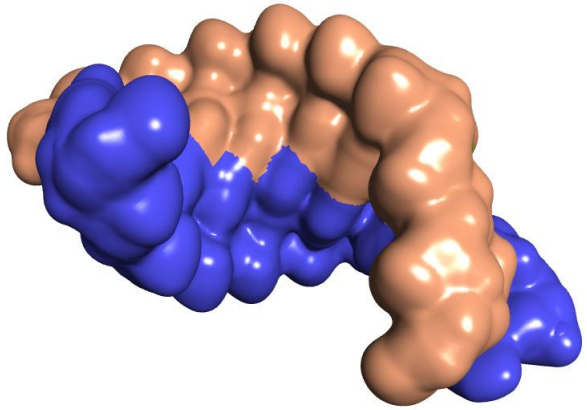


Small molecule 1

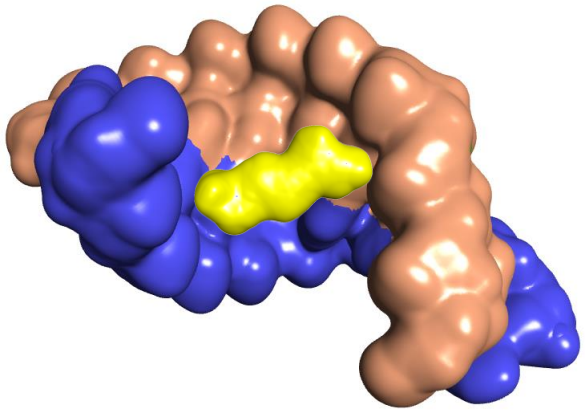
Molecules are designed to match a unique **pre-mRNA/U1** interface and serve as molecular glue to help initiate splicing events

Noncanonical 5’-Splice Sites Present Unique Structural Interfaces for Small Molecule Binding

Canonical duplex

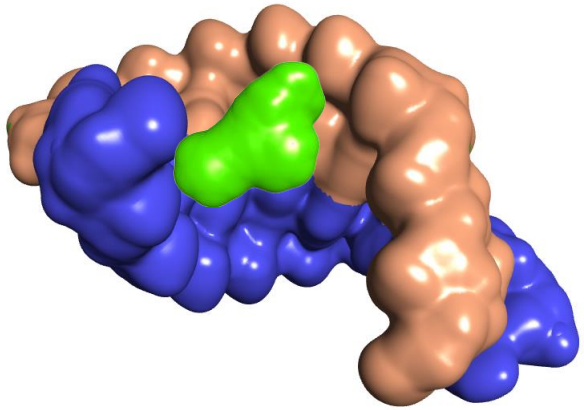


Noncanonical duplex 1



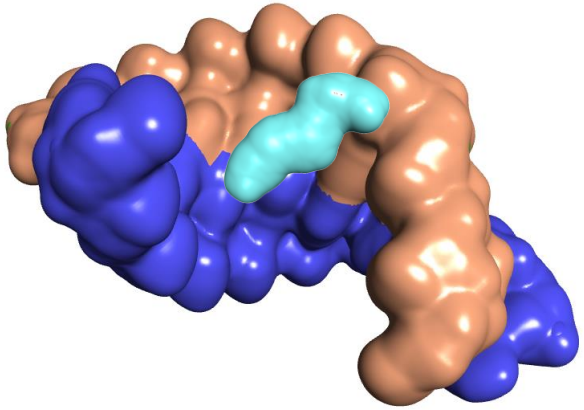
Small molecule 1

Noncanonical duplex 2



Small molecule 2

Noncanonical duplex 3



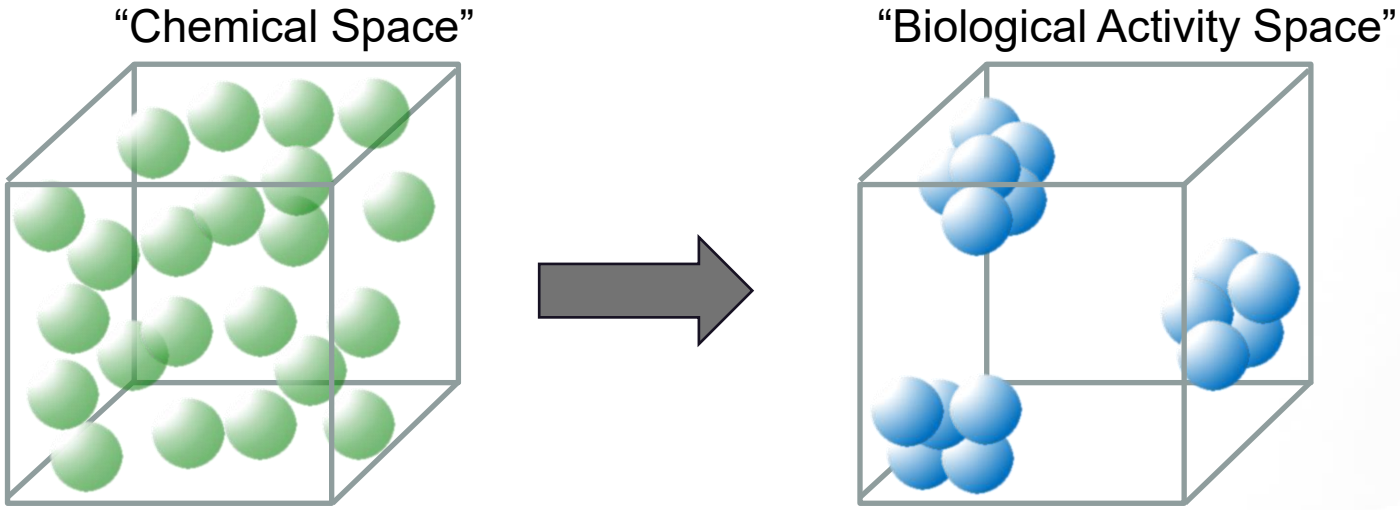
Small molecule 3

Molecules are designed to match a unique **pre-mRNA/U1** interface and serve as molecular glue to help initiate splicing events

Discovery of Next Generation Splicing Modifiers Requires A Purpose-Built Library

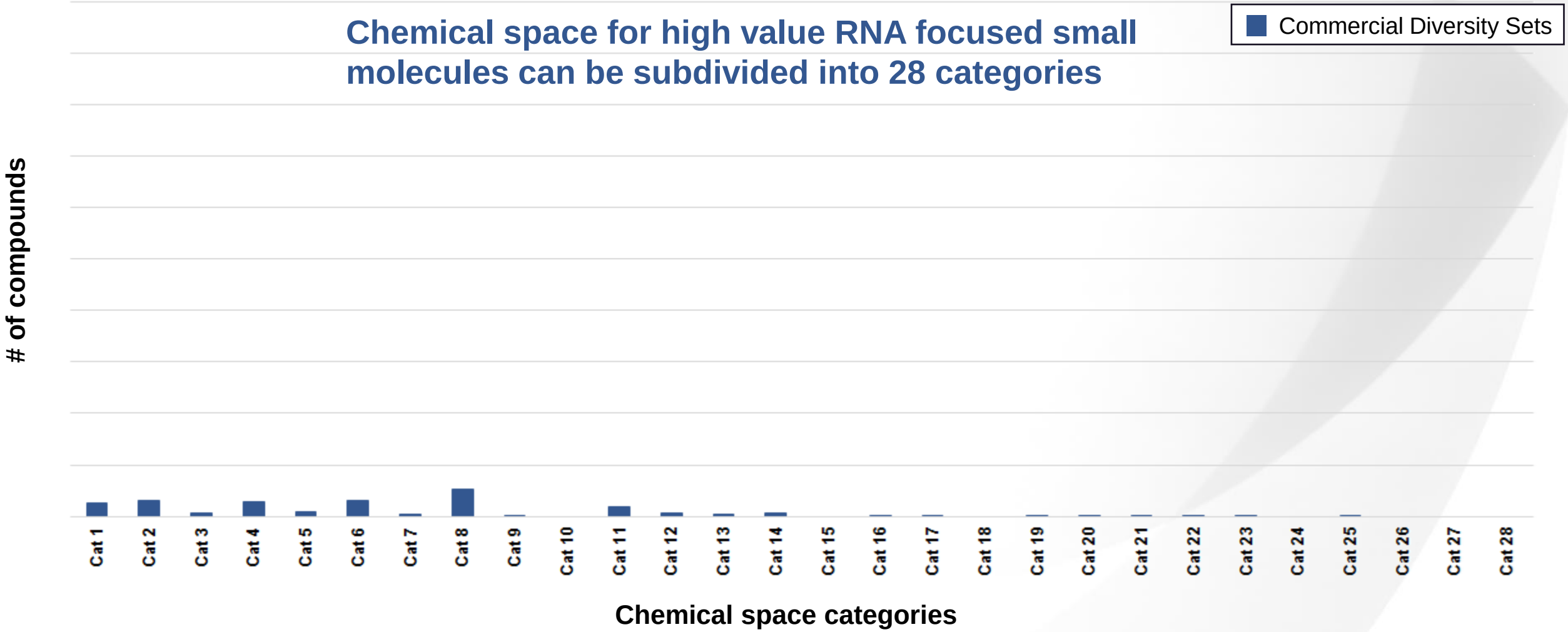
Standard approach:

- Use molecular property descriptors to stratify compounds

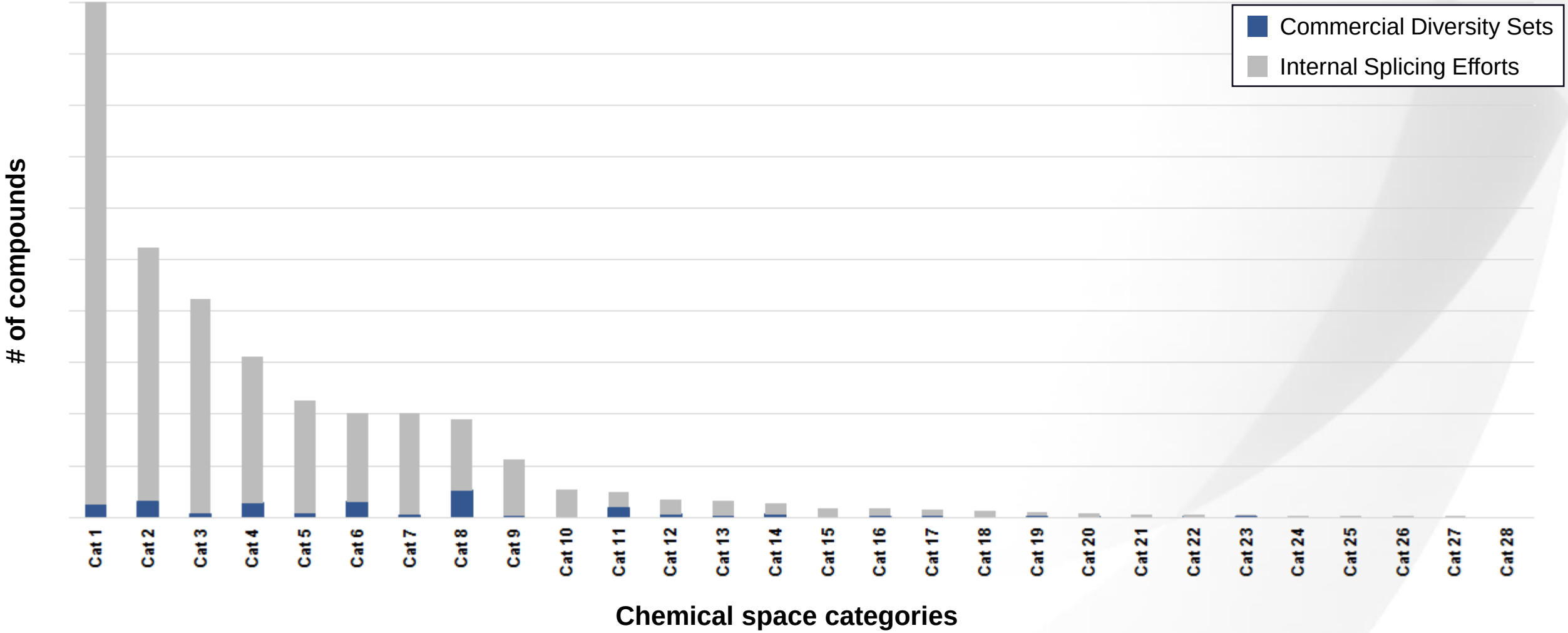


Low probability of finding hits with unique biological activity

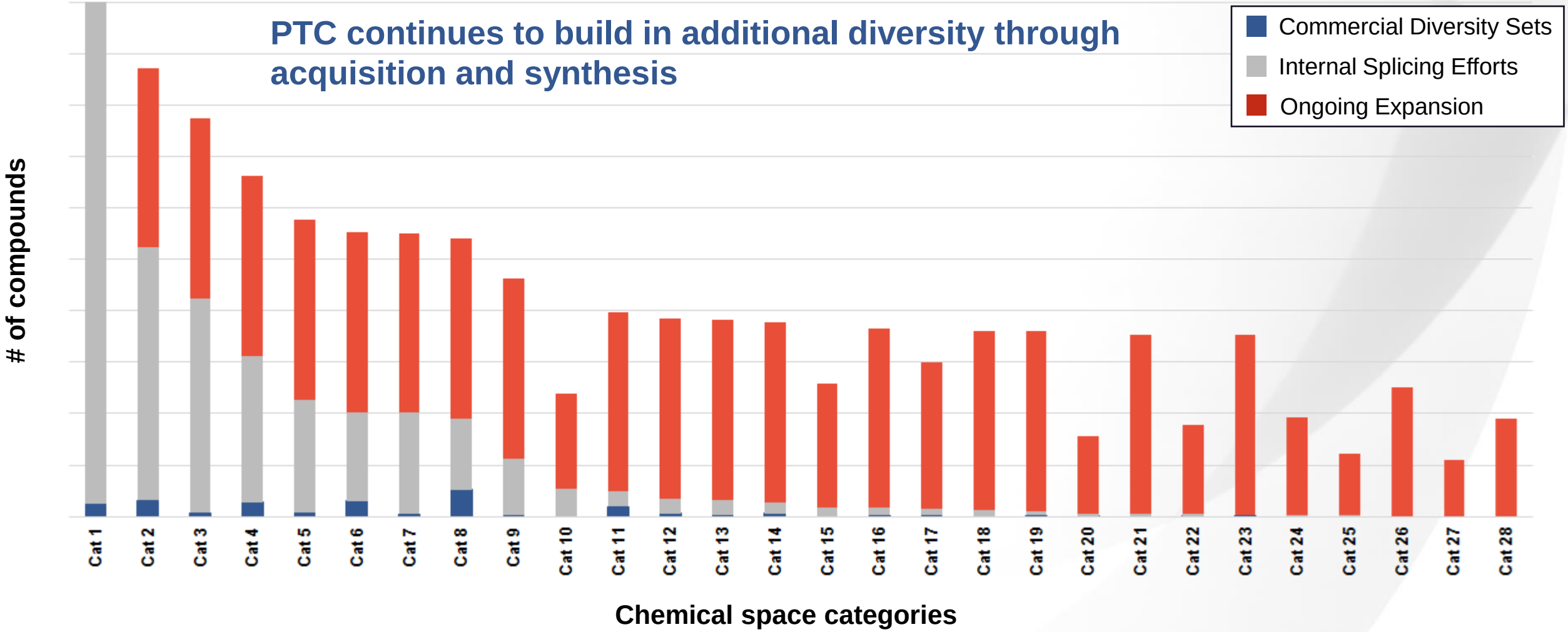
Commercially Available Diversity Sets Have Very Few Splicing Focused Small Molecules



Internal Splicing Efforts Contribute High Value Compounds to Categories



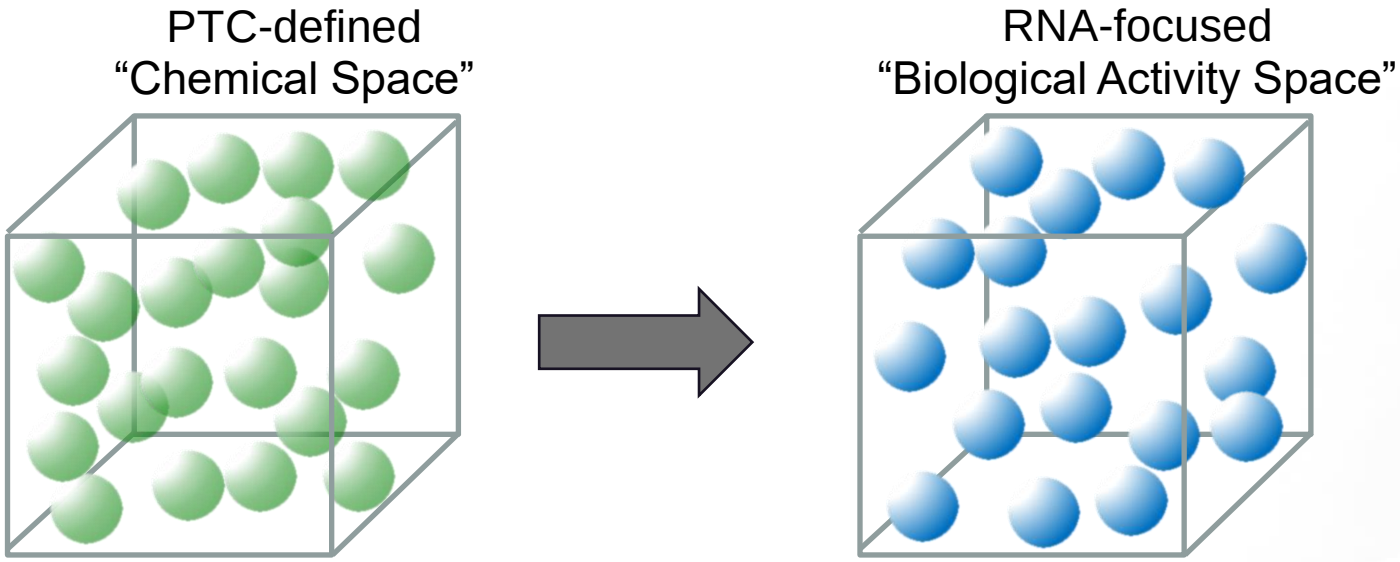
Ongoing Efforts are Expanding the Library Diversity Across All Categories



PTC's Optimized Strategy for a Purpose-Built Splicing Modifier Library

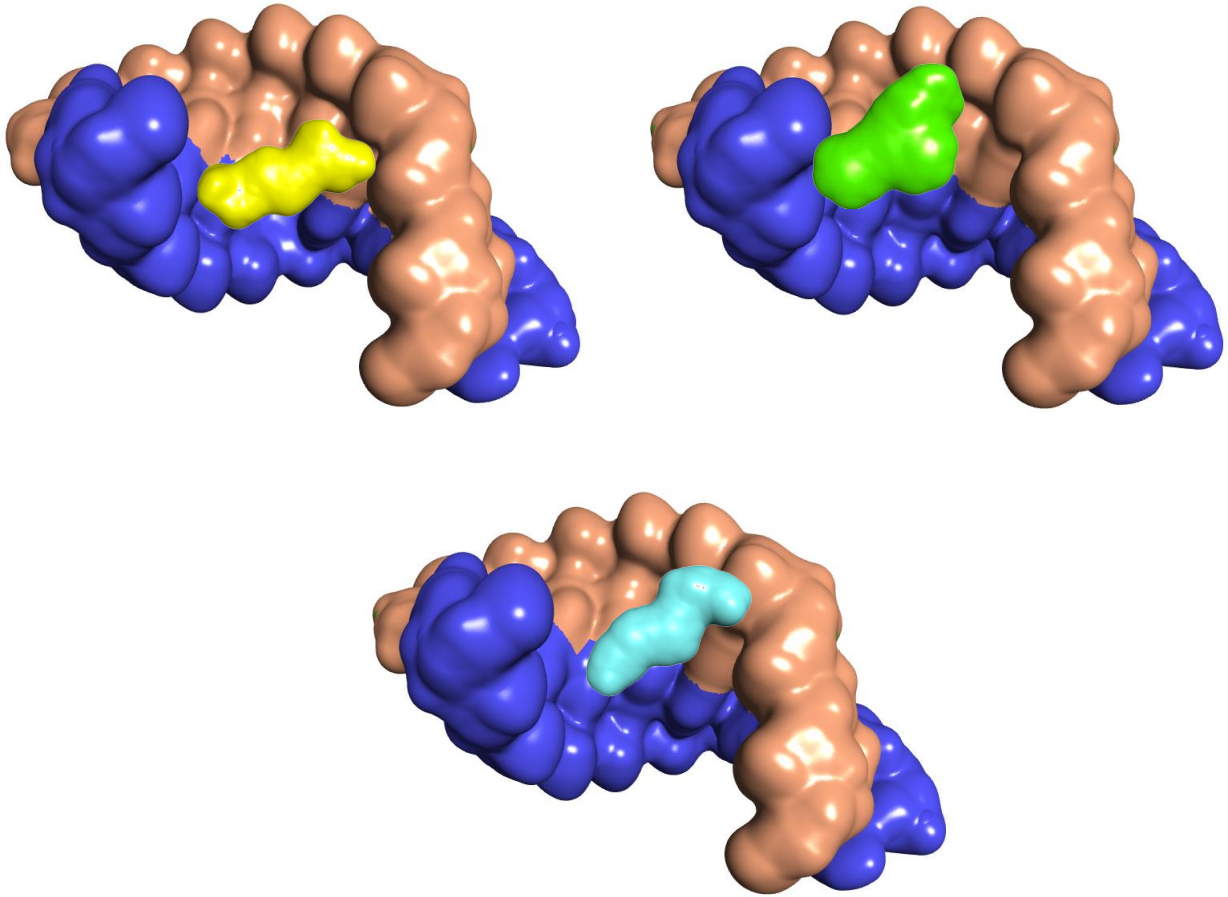
PTC approach:

- Classify molecules using the 3-D orientation of key structural motifs deemed critical for RNA-directed small molecules



Higher probability of finding hits with unique biological activity

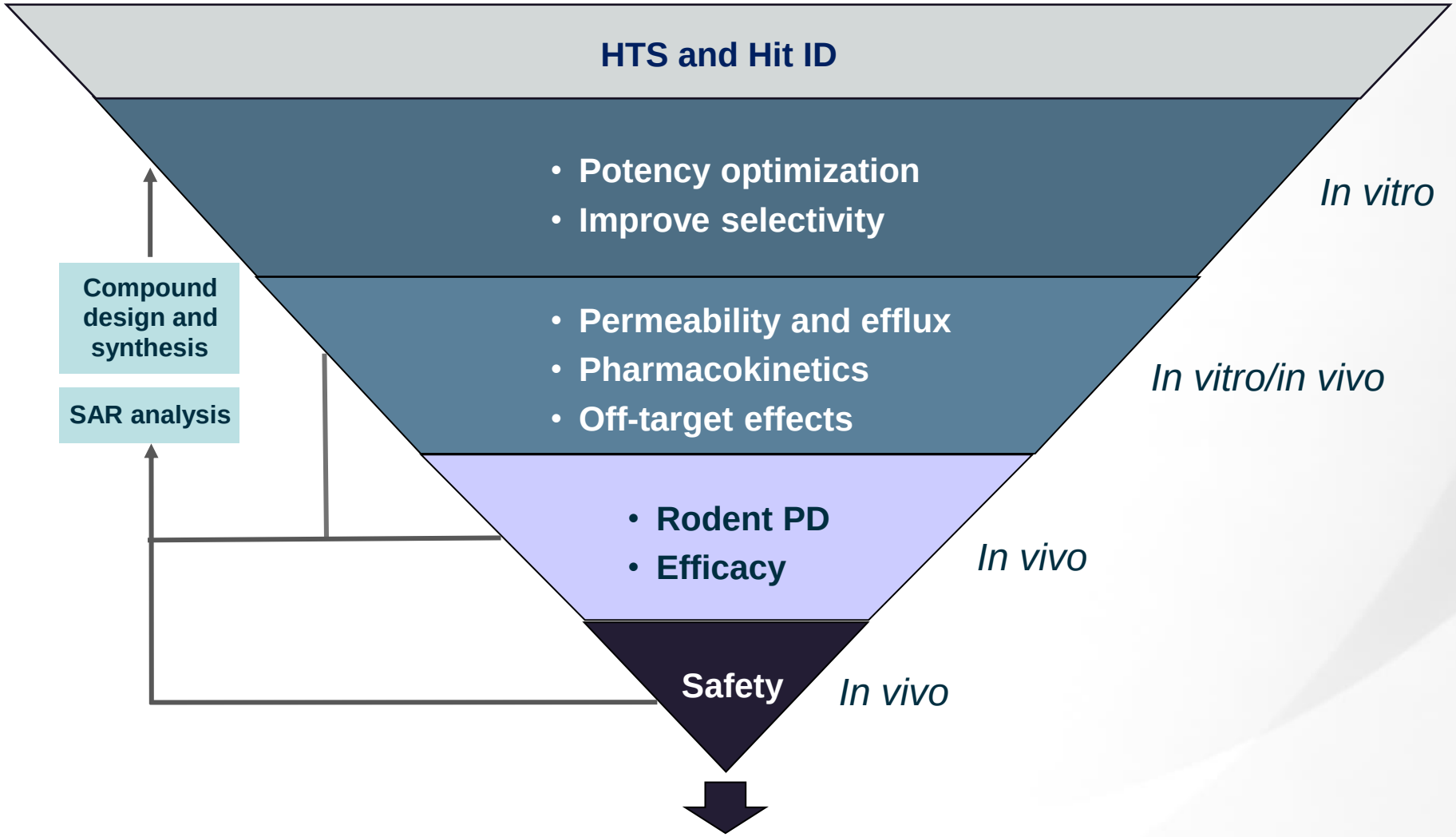
PTC Has a Library Built for Success in Splicing Modulation



What makes our library unique?

- Largest collection of molecules synthesized for successful splicing programs
- Hand-picked commercial molecules that have splicing-centric properties
- Bold efforts to synthesize novel screening molecules in unchartered PTC-defined chemical space
- Purpose-built based on principles learned from selective splicing modifiers

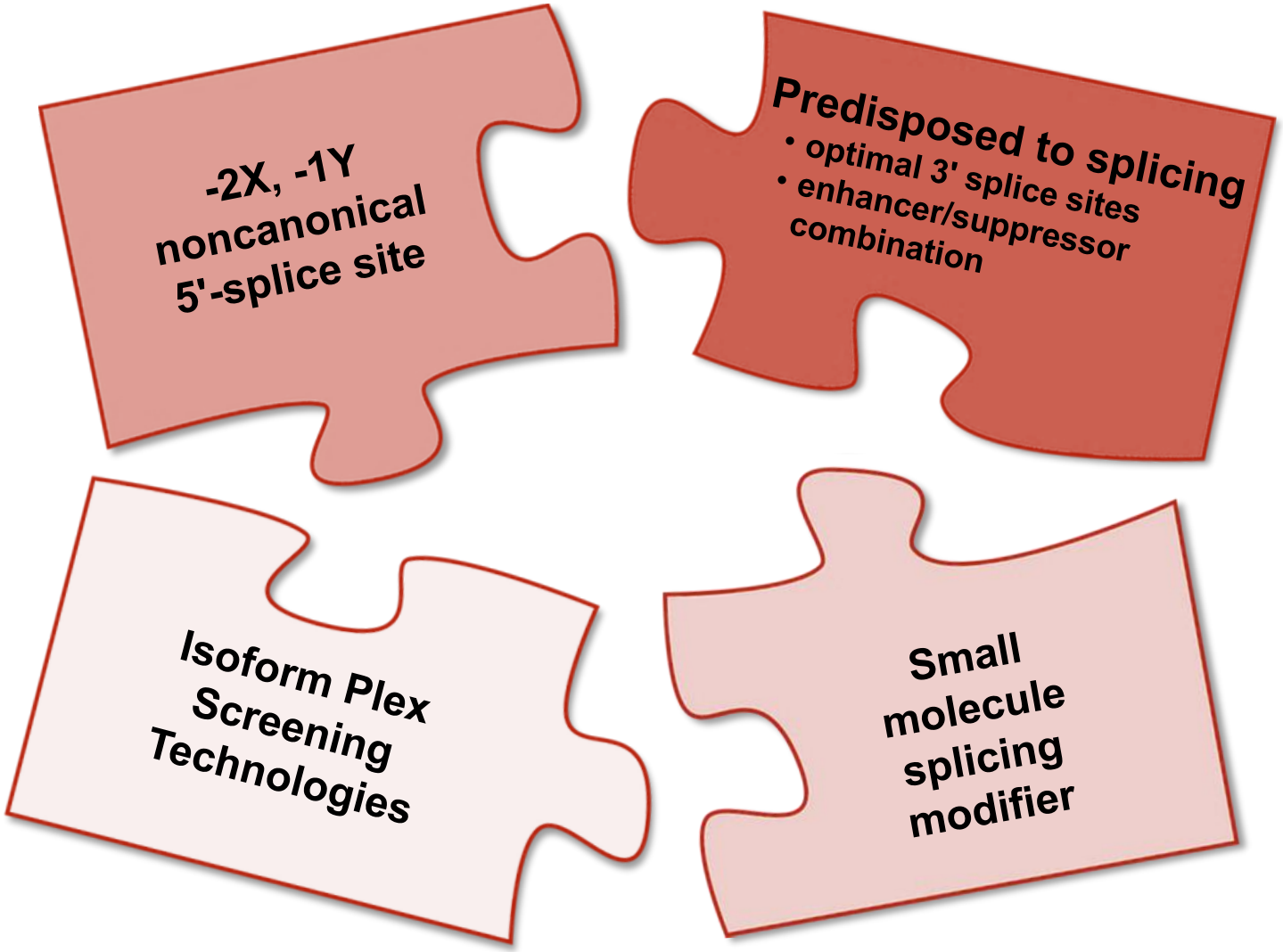
PTC Has the Infrastructure and Capabilities to Rapidly Transform Hits to Development Candidates



Splicing Platform Development & Programs

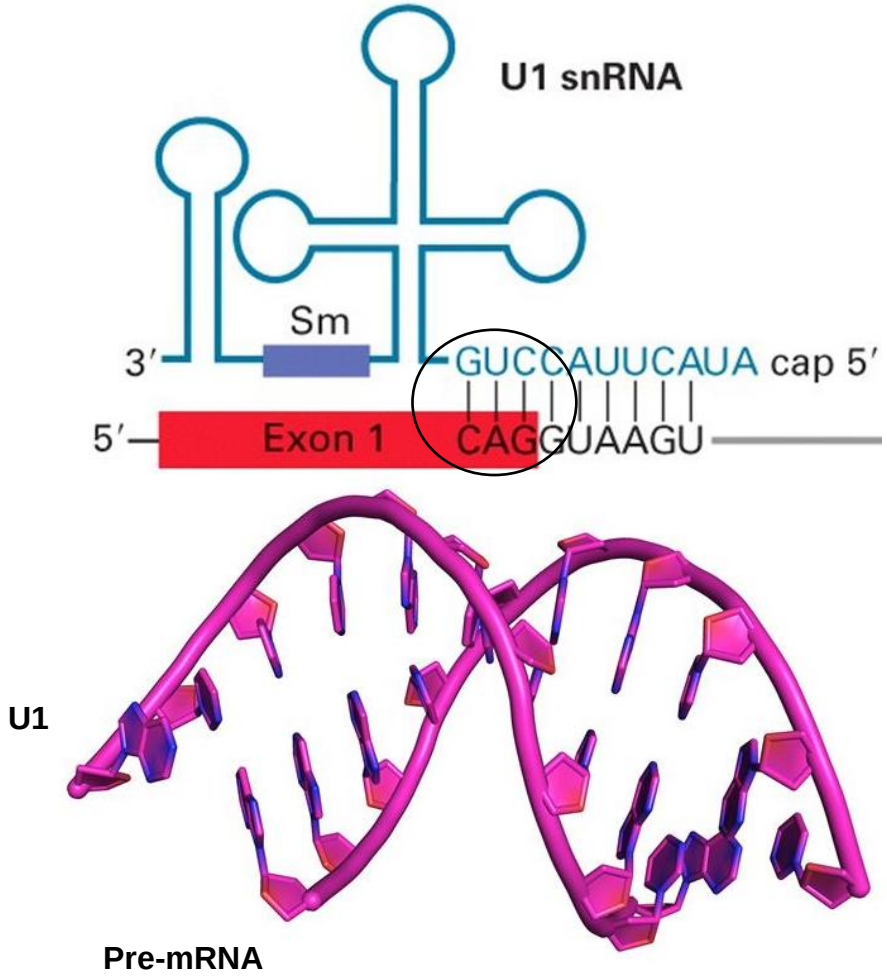
Chris Trotta, Ph.D.
VP Biology

Proprietary PTC Knowledge of Splicing Modifiers Enables Platform Technologies



PTC's understanding of the mechanism of action of small molecule splicing modifiers has enabled platform technologies to identify new therapeutics to target splicing

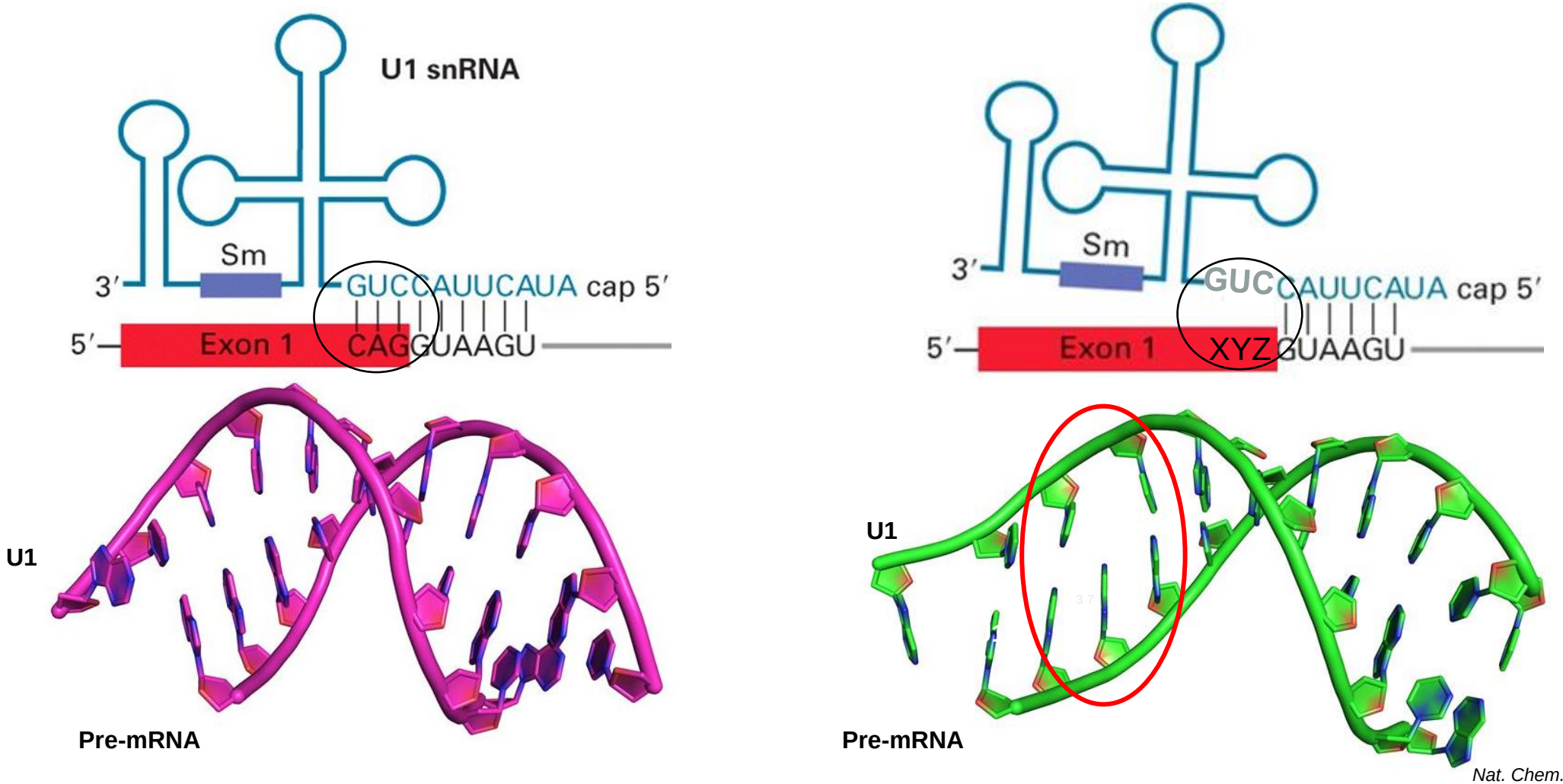
Therapeutic Potential Lies within Noncanonical 5’ Splice Sites



Canonical 5’ splice site

55% of 5’ splice sites are canonical

Therapeutic Potential Lies within Noncanonical 5’ Splice Sites

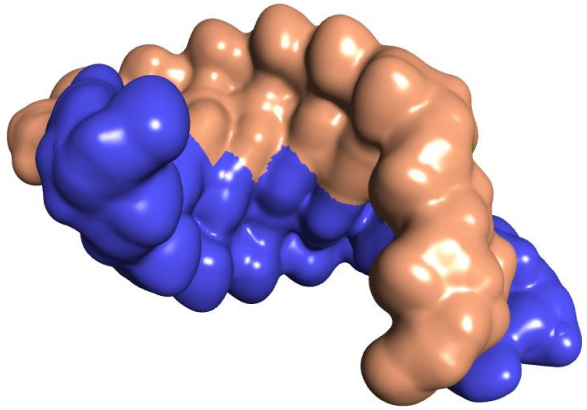


Nat. Chem. Biol. **2019** 15, 1191
Science **2019** 364, 362

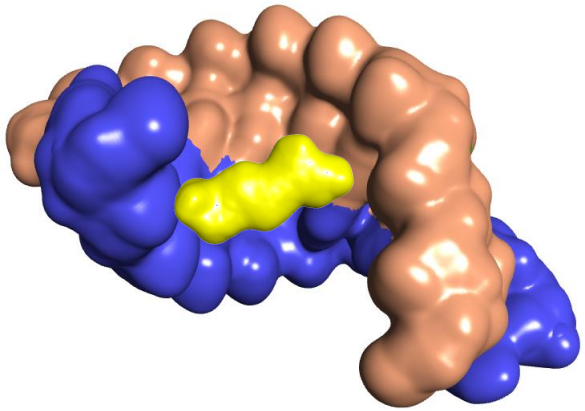
45% of 5’ splice sites are noncanonical

Discovery of a Comprehensive & Diverse Catalog of Druggable Noncanonical 5’ Splice Sites

Canonical duplex



Noncanonical duplex 1

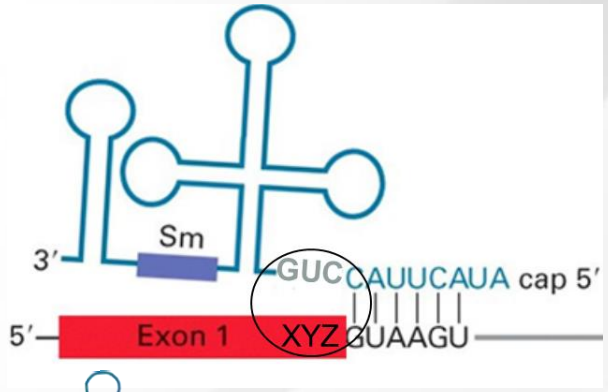


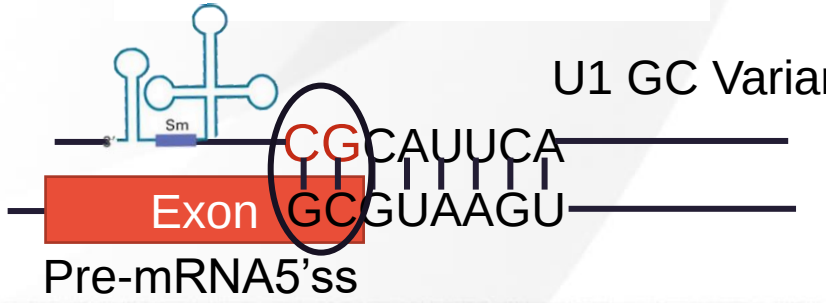
Splicing Modifier

5’ splice site
AG
UG
GG
CG
AA
CU
AU
CA
GA
AC
GU
UU
CC
GC
UA
UC

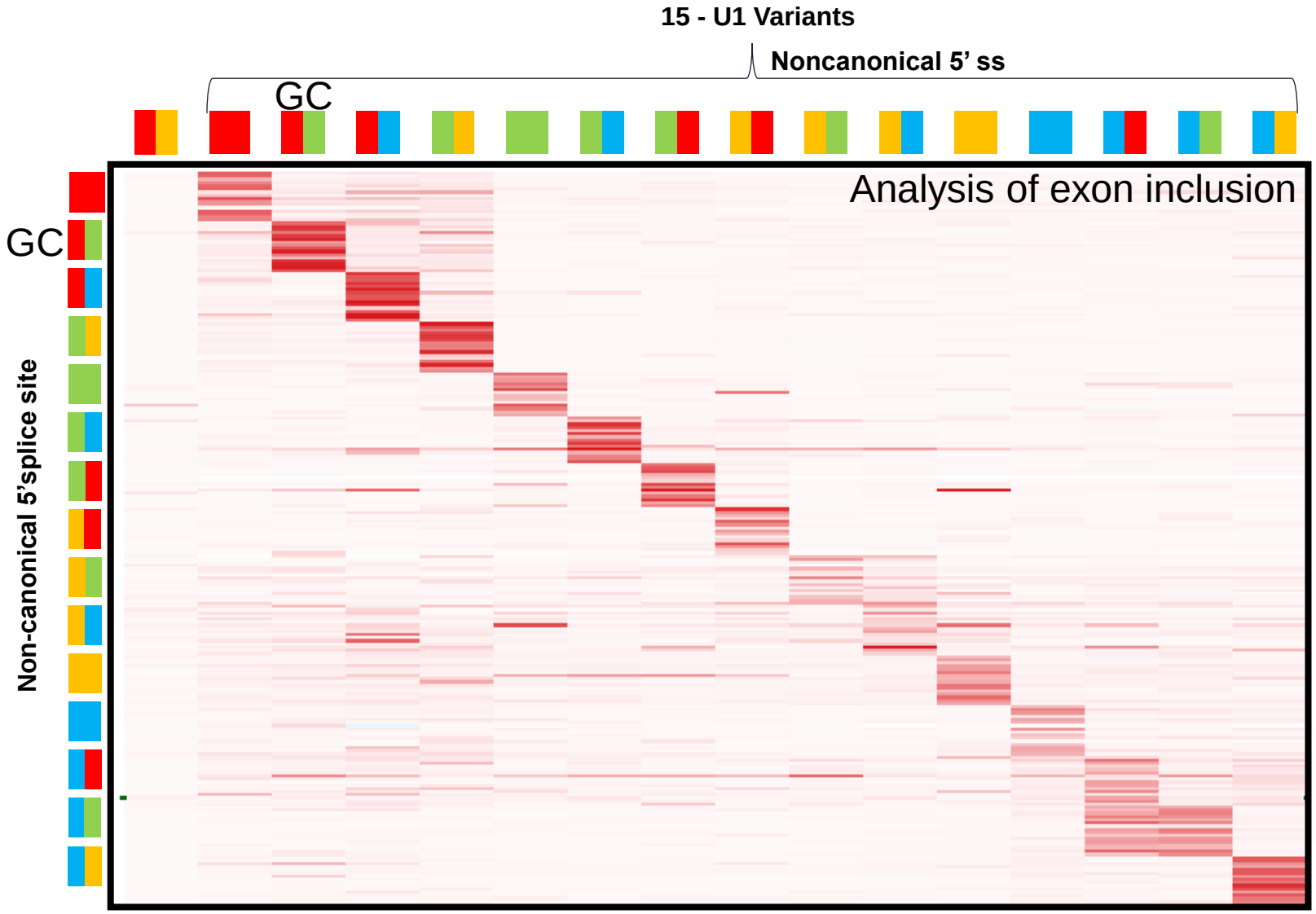
15 subclasses of noncanonical 5’ splice sites (45% of all splice sites)

Genetic reprogramming U1 to discover splicing competent exons for all potential noncanonical 5’ splice sites



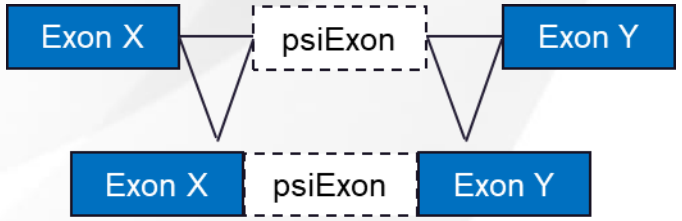


Discovery of Non-canonical Splicing Genome-wide



Several thousand splicing events

- **Inclusion cassette exons**
- **Exclusion of cassette exons**
- **Inclusion of a new class of exons called psiExons**



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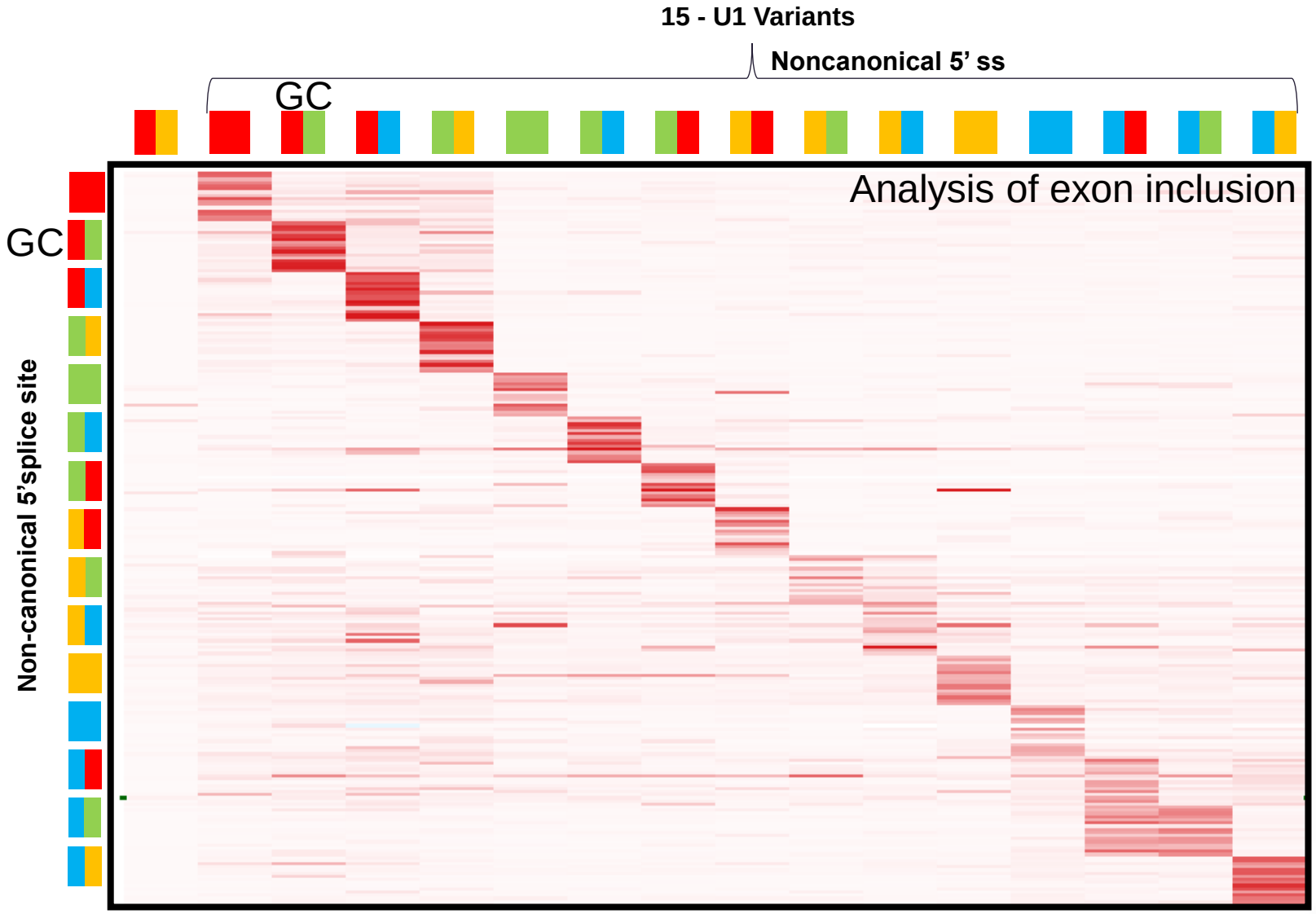
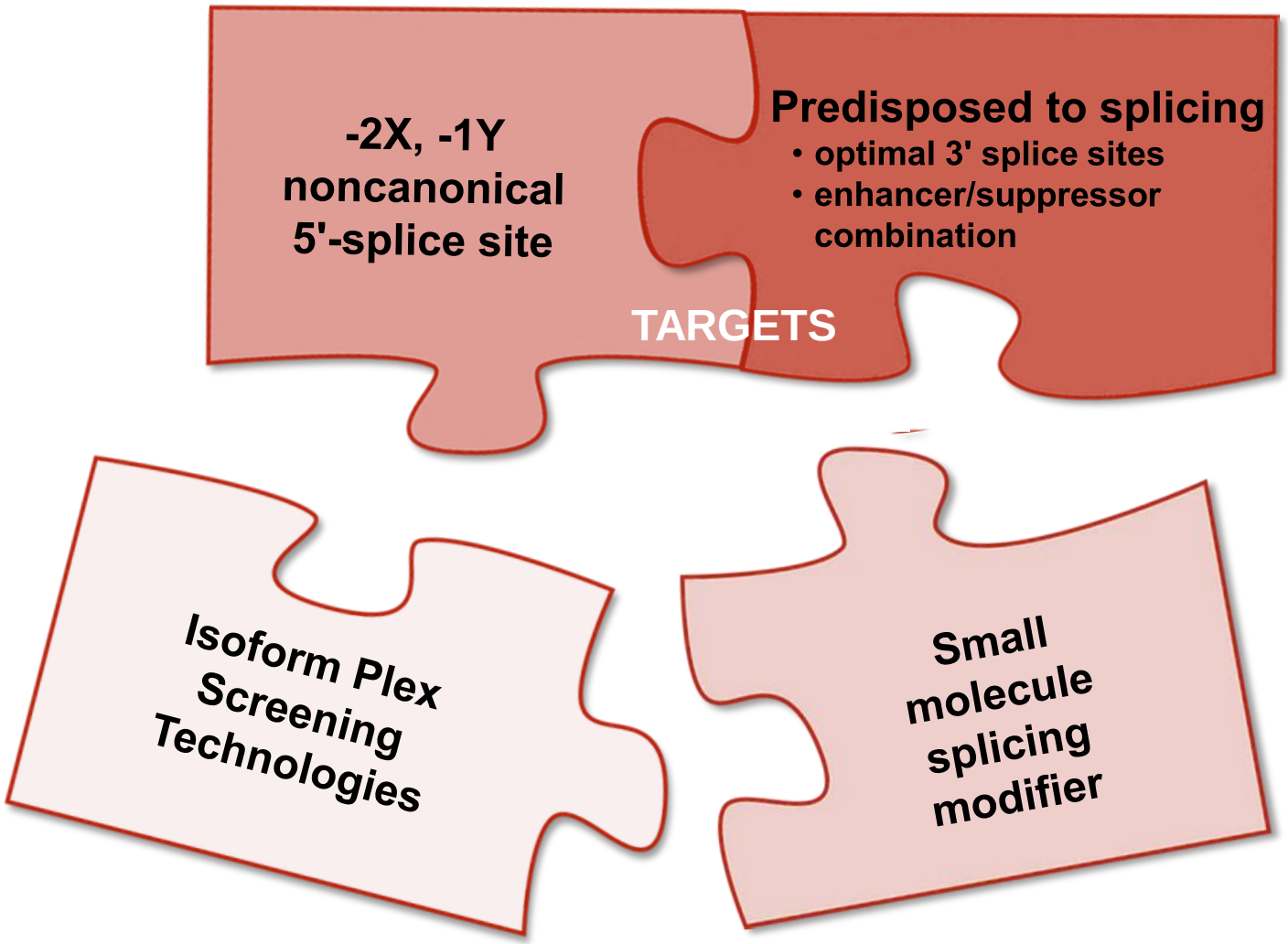


Several thousand splicing events

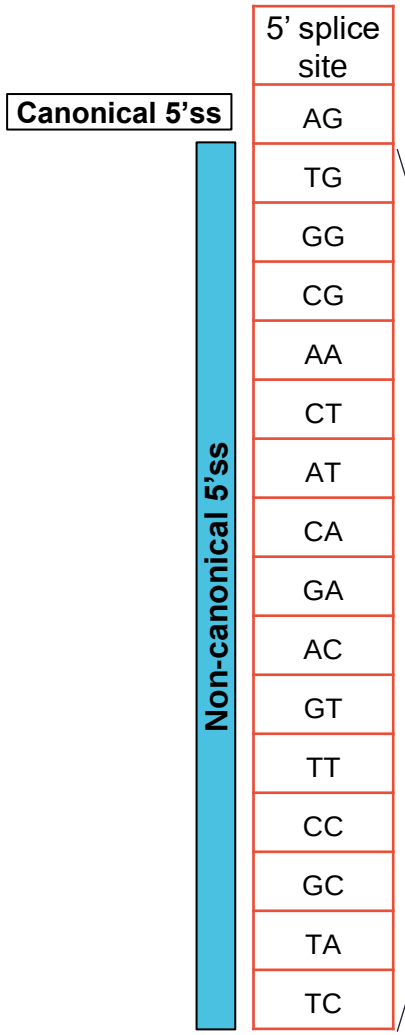
- **Inclusion cassette exons**
- **Exclusion of cassette exons**
- **Inclusion of a new class of exons called psiExons**
- **Proprietary bioinformatic pipeline to discover additional druggable noncanonical exons**

Proprietary PTC Knowledge of Splicing Modifiers Enables Platform Technologies



- Cross compare exons to:
  - Dominant genetic diseases
  - Haploinsufficiency diseases
  - Splicing driven diseases
- Unlocking the **therapeutic tractability** for 100s of potential targets

Building a Database of Druggable Splicing Targets



5' splice site
AG
TG
GG
CG
AA
CT
AT
CA
GA
AC
GT
TT
CC
GC
TA
TC

splicing change | Desired | Disease

Gene	splicing change caused by mutation?	Mutation_code	Desired Splicing	target disease	Affected tissue	Disease prevalence category
SMN2	no	AS -4A>C|AS +2G>A	inclusion	Spinal muscular atrophy (SMA)	Nervous system	>1/100k
IKBKAP	yes, 5'ss+6T>C	DS +6T>C	inclusion	Familial dysautonomia	Nervous system	<1/1M
HTT	no	WT	inclusion	Huntington's disease	Nervous system	>1/100k
ATXN3	no	WT	skipping	Spinocerebellar ataxia type 3	Muscle	>1/100k
MAPT	yes and no	WT	skipping	FTDP-17	Nervous system	>1/100k
Undisclosed	no	WT	skipping	Undisclosed	Muscle	>1/100k
Undisclosed	no	WT	skipping	Undisclosed	Nervous system	>1/100k
Undisclosed	no	WT	inclusion	Undisclosed	Nervous system	>1/100k
Undisclosed	no	WT	inclusion	Undisclosed	Muscle	>1/100k
Undisclosed	no	WT	inclusion	Undisclosed	Nervous system	
Undisclosed	no	WT	skipping	Undisclosed	Nervous system	
Undisclosed	no	WT	inclusion	Undisclosed	Nervous system	
Undisclosed	c.964-1G>C	AS -1G>C	AS	Undisclosed	Development	>1/100k
Undisclosed	no	WT	inclusion	Undisclosed	Nervous system	>1/1k
Undisclosed	no	WT	inclusion	Undisclosed	Nervous system	>1/1k
Undisclosed	c.815-27T>C	AS -27T>C	inclusion	Undisclosed	Metabolic	>1/100k
Undisclosed	c.-32-13T>G	AS -13T>G	inclusion	Undisclosed	Metabolic	>1/100k
Undisclosed	no	WT	skipping	Undisclosed	Kidney	>1/100k
Undisclosed	no	WT	skipping	Undisclosed	Muscle	>1/10k
Undisclosed	c.5714+5G>A	DS +5G>A	inclusion	Undisclosed	Eye	>1/10k
Undisclosed	c.1092+5G>A	DS +5G>A	inclusion	Undisclosed	Eye	<1/1M
Undisclosed	no	WT	inclusion	Undisclosed	Nervous system	>1/10k
Undisclosed	no	WT	inclusion	Undisclosed	Muscle	>1/100k
Undisclosed	c.2588G>C	AS +1G>C	inclusion	Undisclosed	Eye	>1/10k
Undisclosed	c.1909+22G>A	DS +22G>A	DS	Undisclosed	Nervous system	>1/100k
Undisclosed	c.4253+43G>A	DS +43G>A	inclusion	Undisclosed	Eye	>1/10k
Undisclosed	c.4539+2001G>A	AS +111G>A	skipping	Undisclosed	Eye	>1/10k
Undisclosed	no	WT	skipping	Undisclosed	Nervous system	>1/100k
Undisclosed	no	WT	skipping	Undisclosed	systemic	>1/10k

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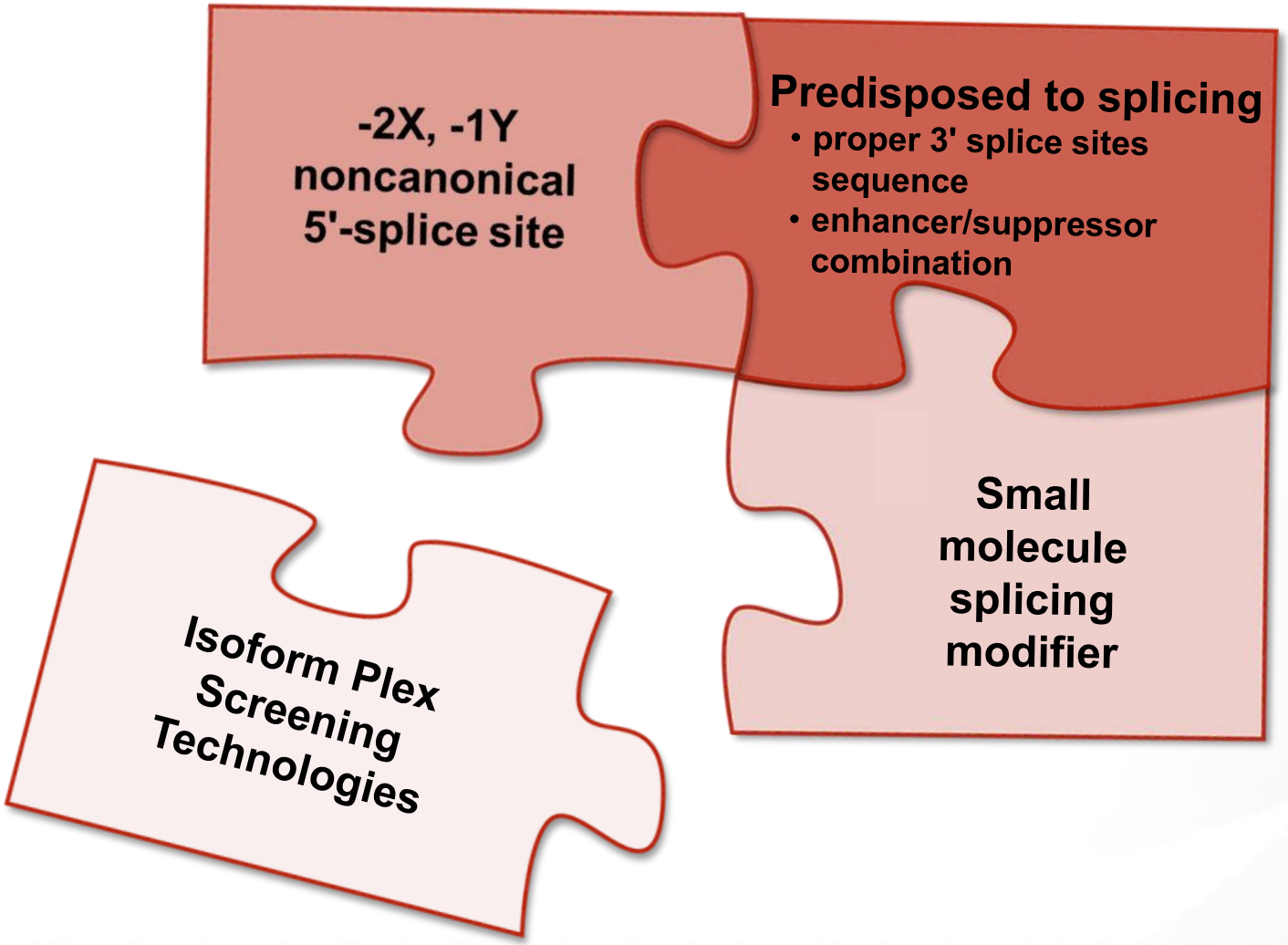
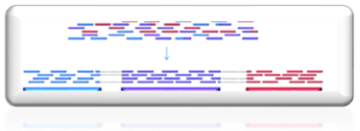
PTC Experience & Insights Lead to Proprietary Splicing Technologies



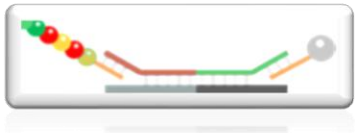
PTC Splicing Platform Technologies

Transcriptome mRNA isoform detection platforms for the discovery of small molecule splicing modifiers



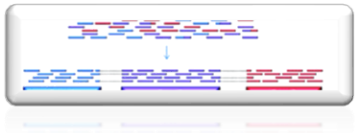
Splicing Isoform Detection

Proprietary bioinformatics pipeline of genome-wide, small-molecule induced splicing changes



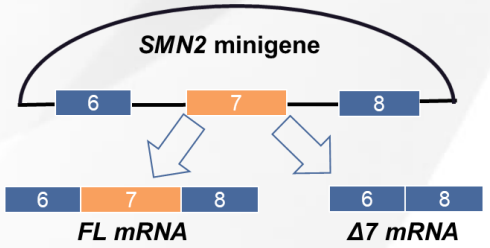
Isoform plex

Measurement of splicing changes to hundreds of disease-causing mRNA splice isoforms

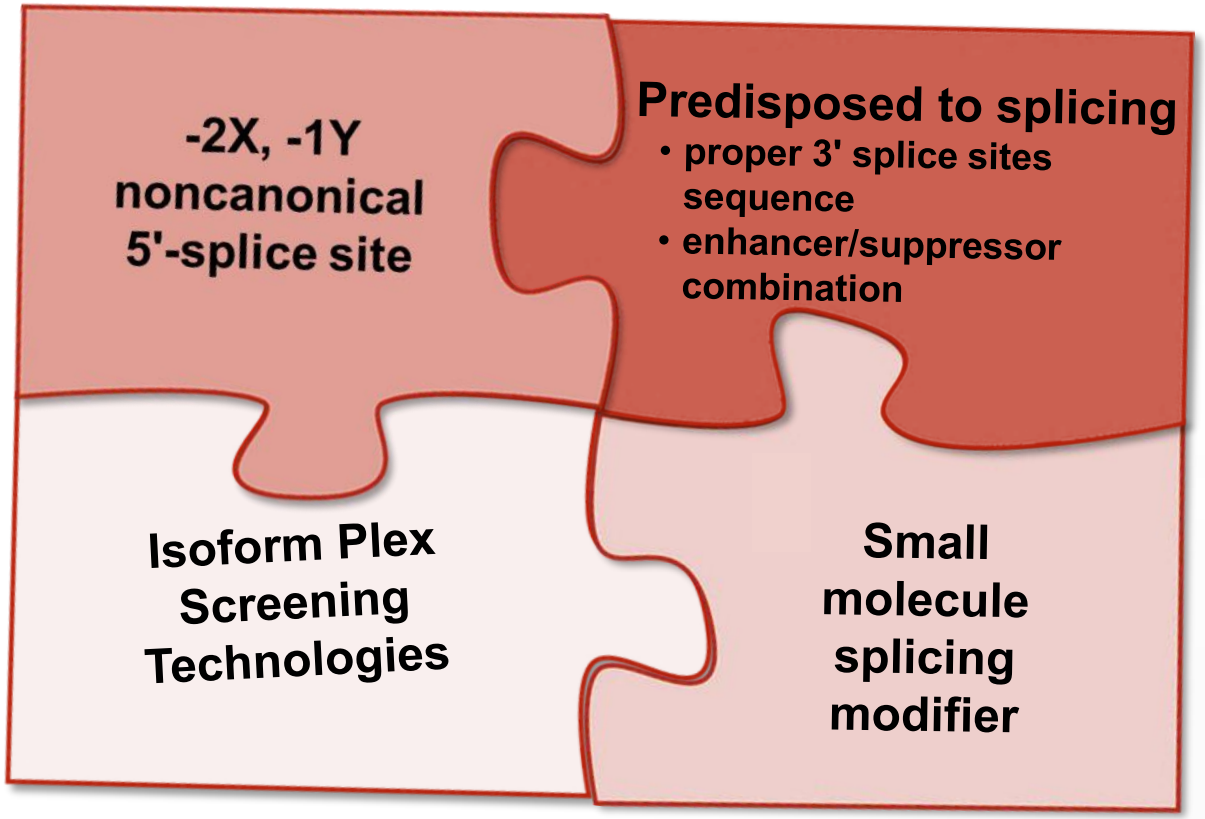


HTSpliceseq

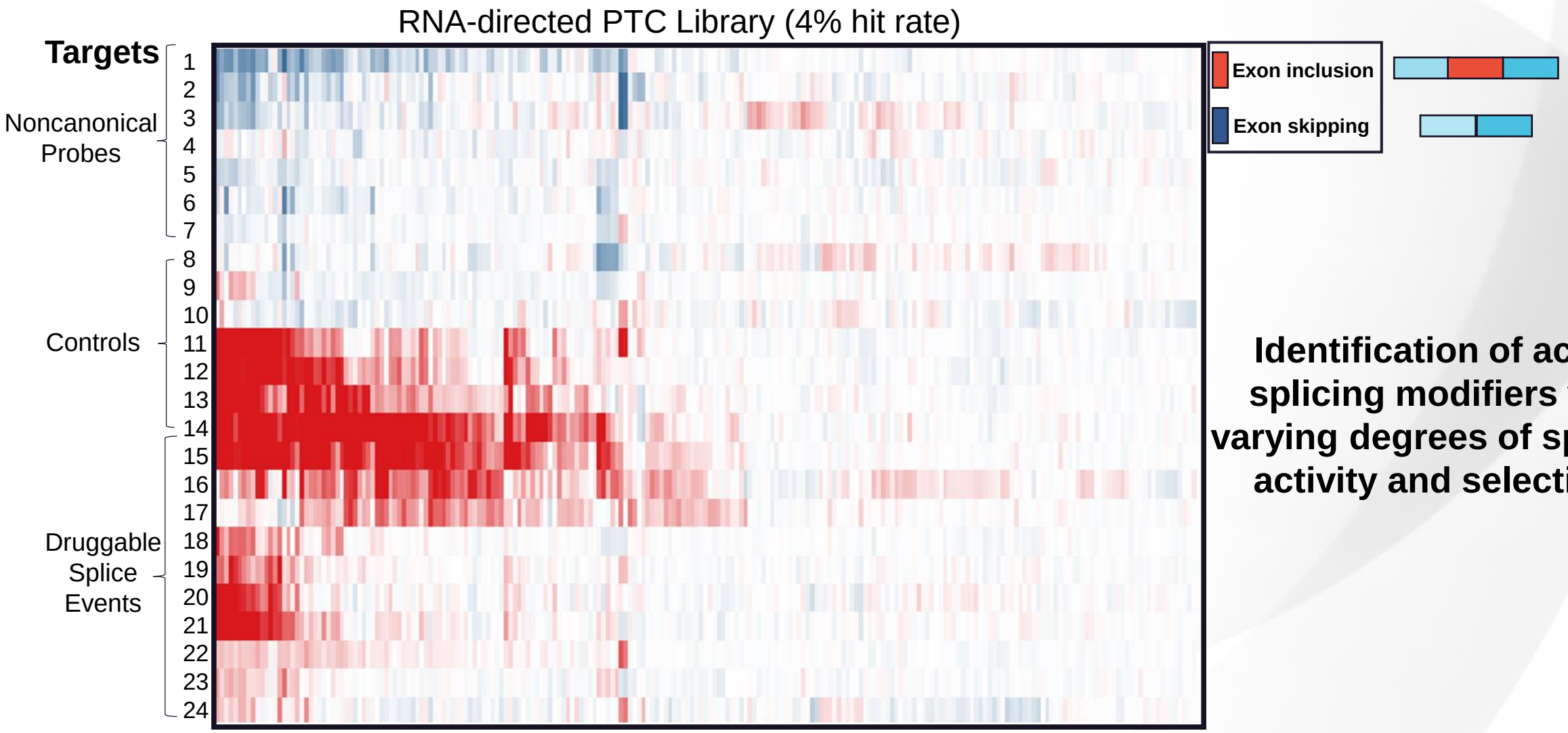
Minigene models of splicing for hundreds of disease-causing splicing defects



PTC Experience & Insights Lead to Proprietary Splicing Technologies



Isoform Plex Platform Enhances Ability to Identify Splicing Modifiers



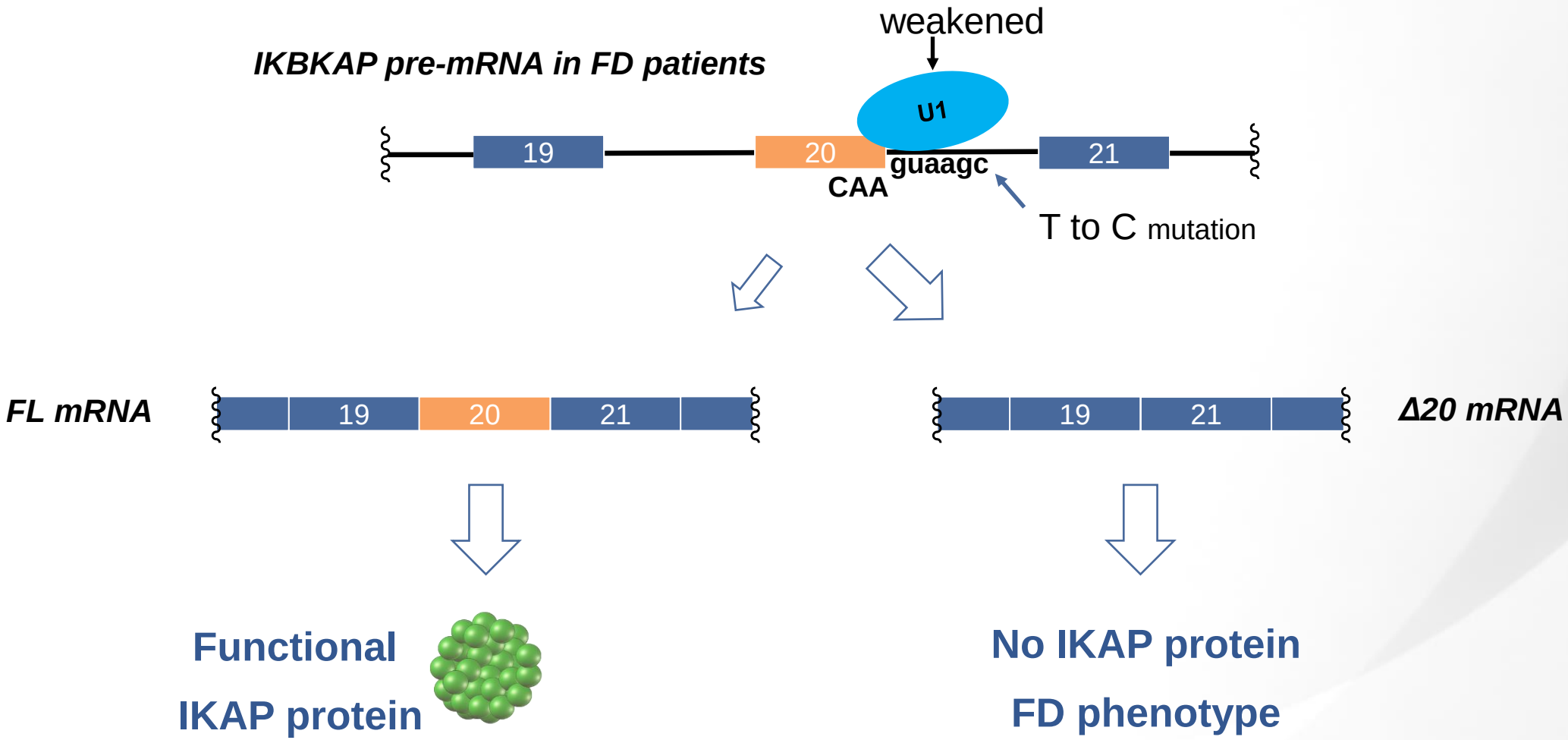
Identification of active splicing modifiers with varying degrees of splicing activity and selectivity

Targeting Noncanonical 5’ Splice Sites to Develop Therapies for Human Disease

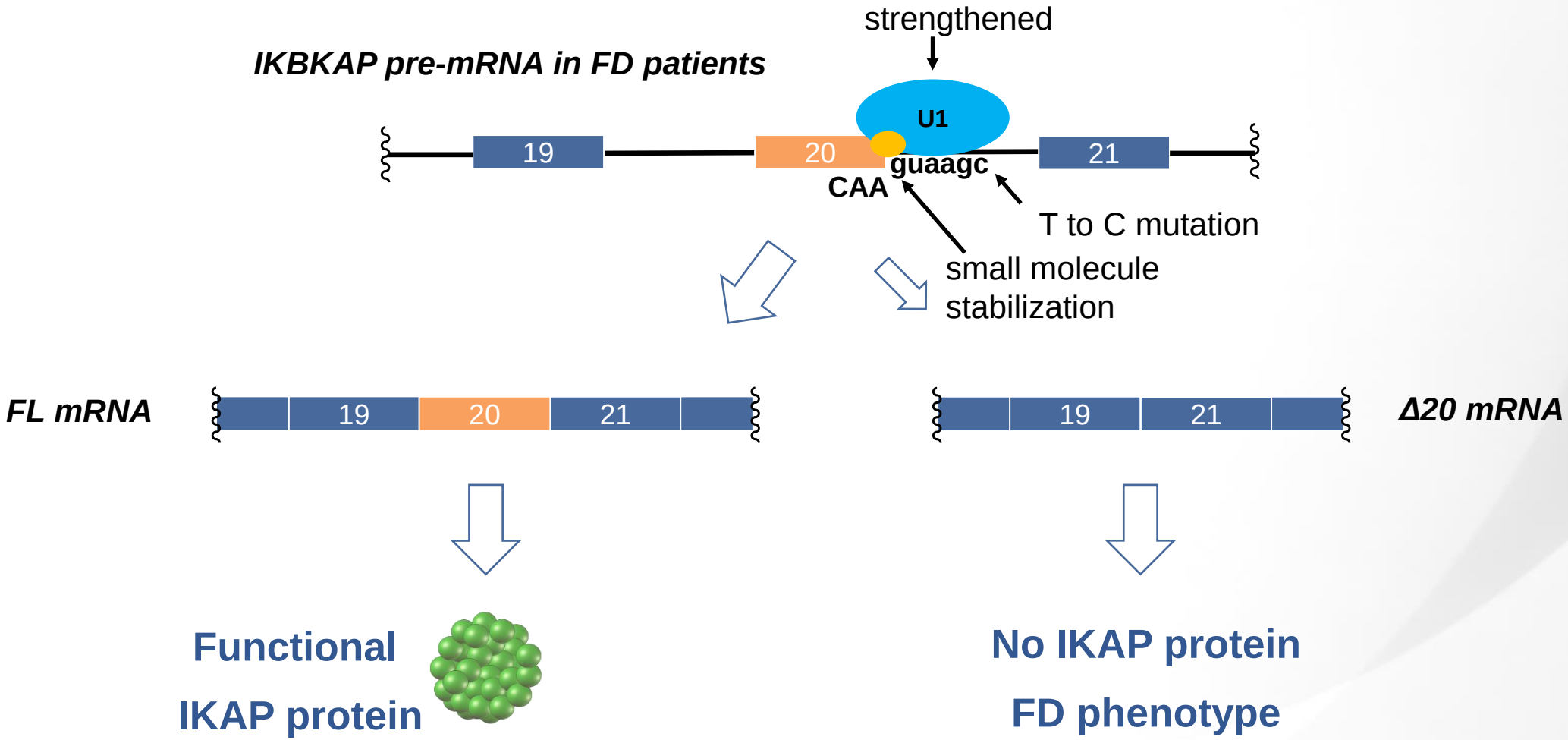
Targeting noncanonical exons allows us to develop small molecule therapies to:

- Restore protein
  - Promote inclusion of endogenous “weak” exons
    - SMN2 exon 7 to treat **SMA**
    - Mutations that create a “weak” noncanonical 5’ splice site such as **Familial dysautonomia**
      - 15-50% of disease-causing mutations effect splicing
- Reduce protein
  - Promote inclusion of psiExons
    - Pseudoexon inclusion leads to loss of pre-mRNA to treat diseases such as **Huntington’s Disease**
  - Promote exon skipping
    - Leads to frameshift or decay of pre-mRNA to treat diseases such as **Spinocerebellar Ataxia 3** and **Tauopathies**

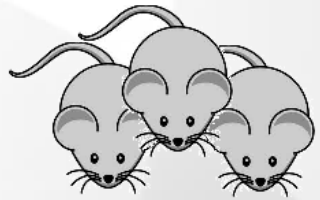
Targeting Alternative Splicing to Treat FD

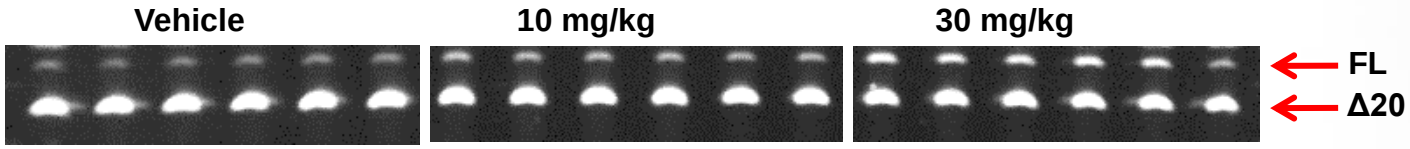


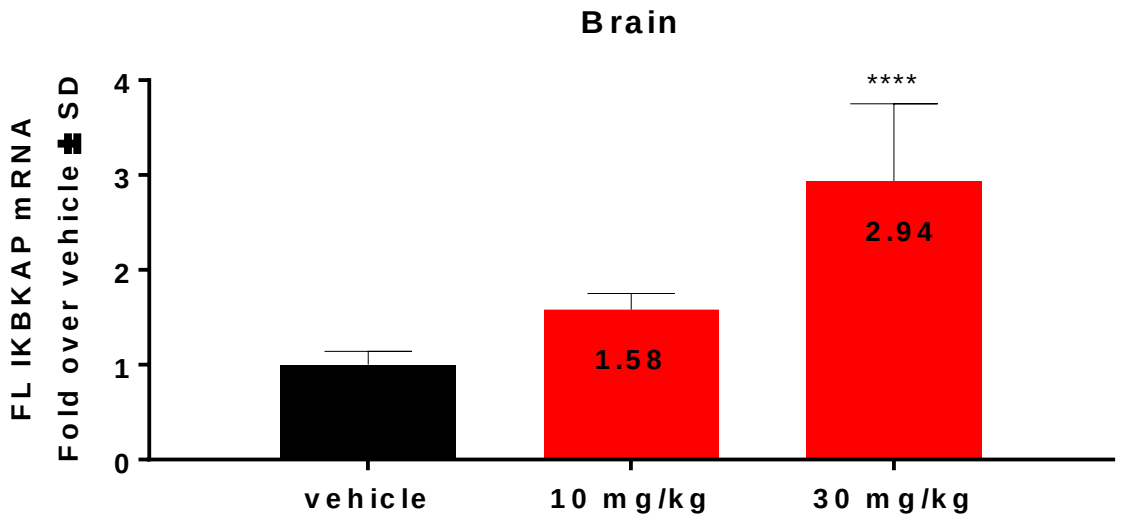
Targeting Alternative Splicing to Treat FD

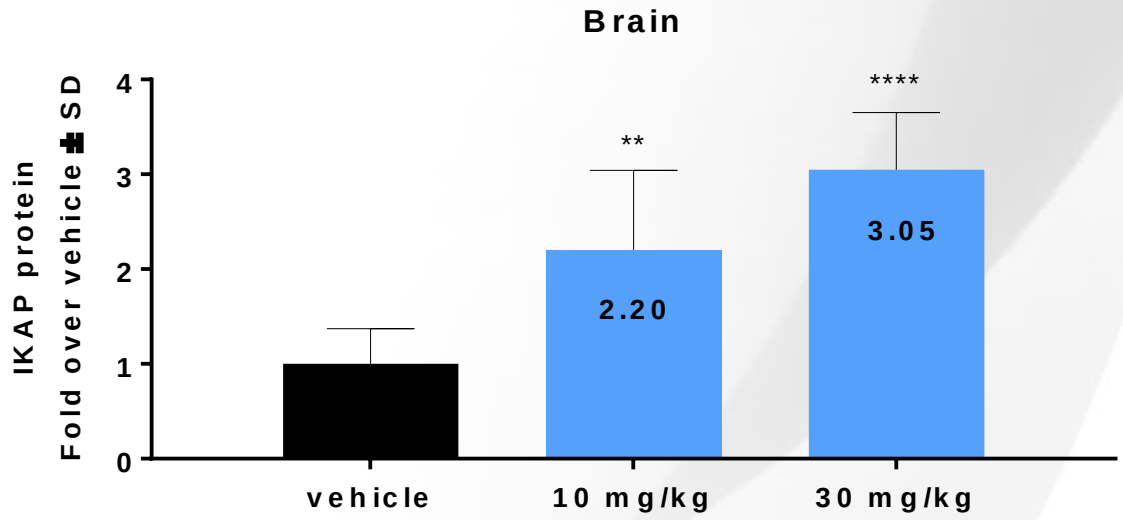


Compound Increases Full Length IKBKAP mRNA and IKAP Protein Levels *In Vivo*





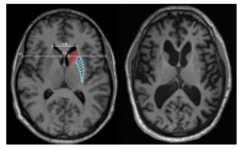




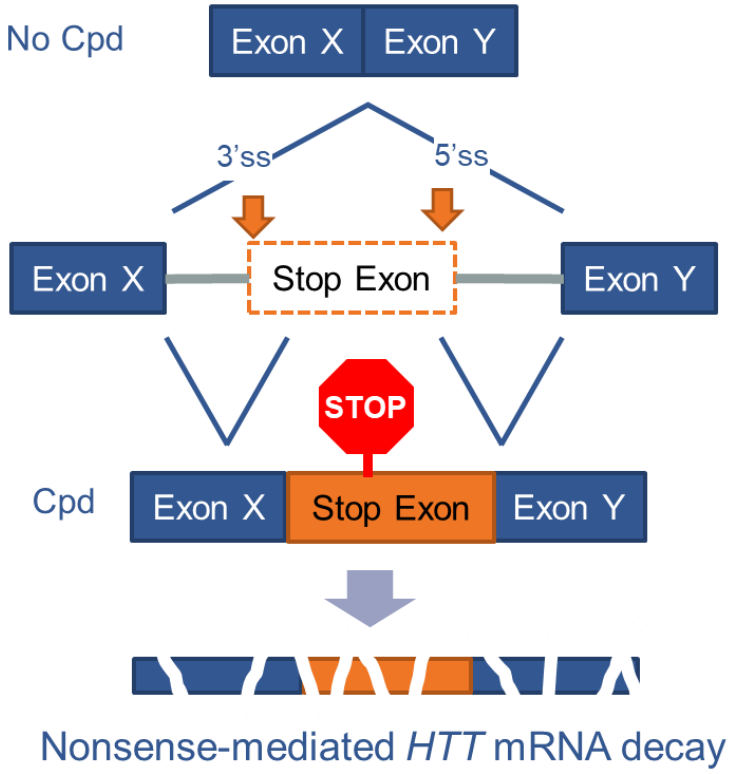
Second example of targeting a noncanonical 5' splice site

Hims MM, et al. *Genomics*. 2007;90(3):389-396.

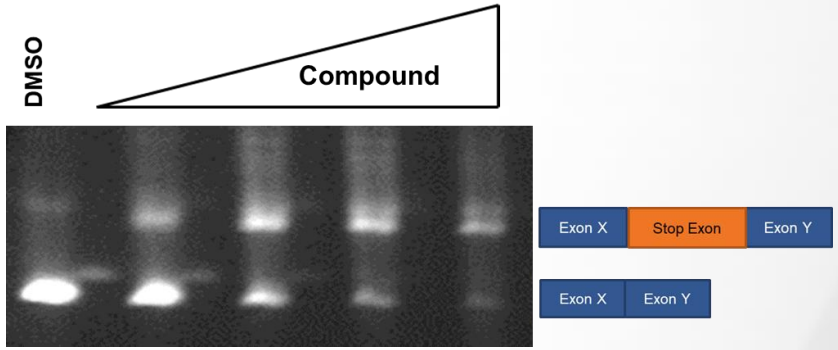
Splicing Modifiers Activate a Stop Exon Within the *HTT* mRNA Leading to mRNA Degradation

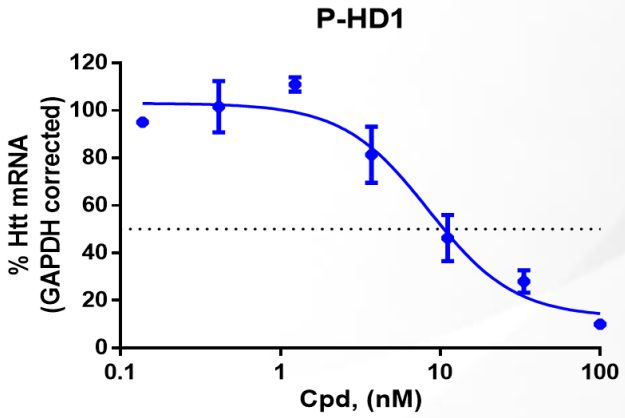


HD is a neurodegenerative disease caused by a toxic gain-of-function triplet repeat (CAG) expansion in the huntingtin gene



Nonsense-mediated *HTT* mRNA decay

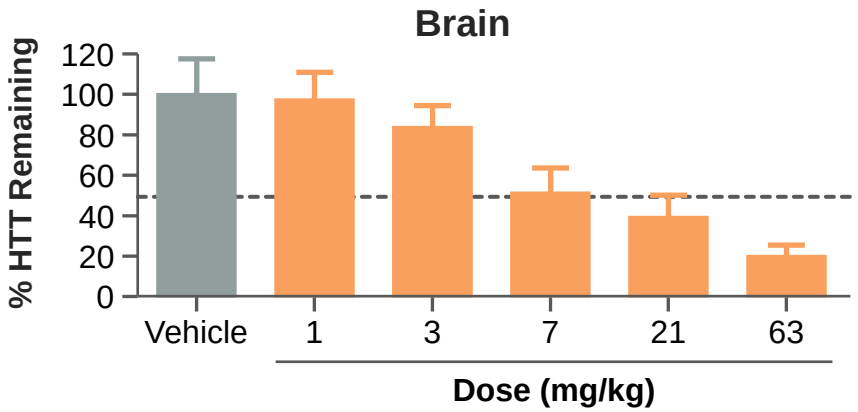




HTT mRNA lowering

HD Splicing Small Molecules Demonstrate Broad Tissue Distribution in BACHD Mice

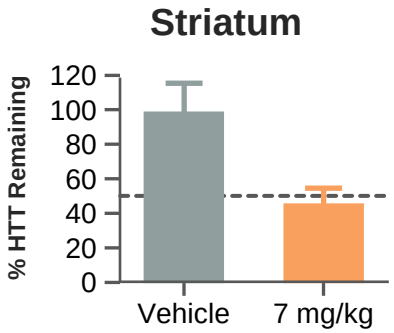
Dose dependent HTT lowering in the brain in BACHD mice

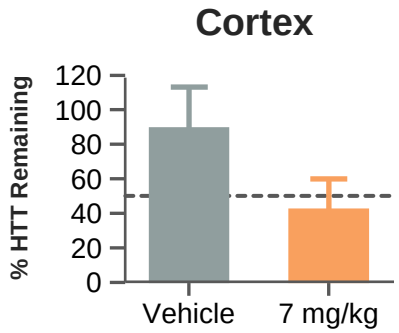


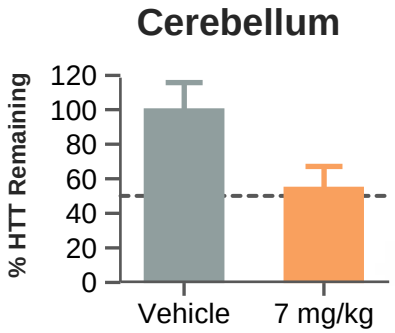
Ph1 trial planned for 4Q 2020

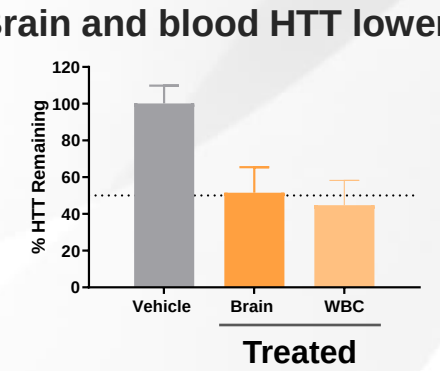
- Oral, crosses BBB
- Titratable
- IND toxicology studies ongoing
- Ability to measure mRNA and protein in blood in healthy volunteers

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



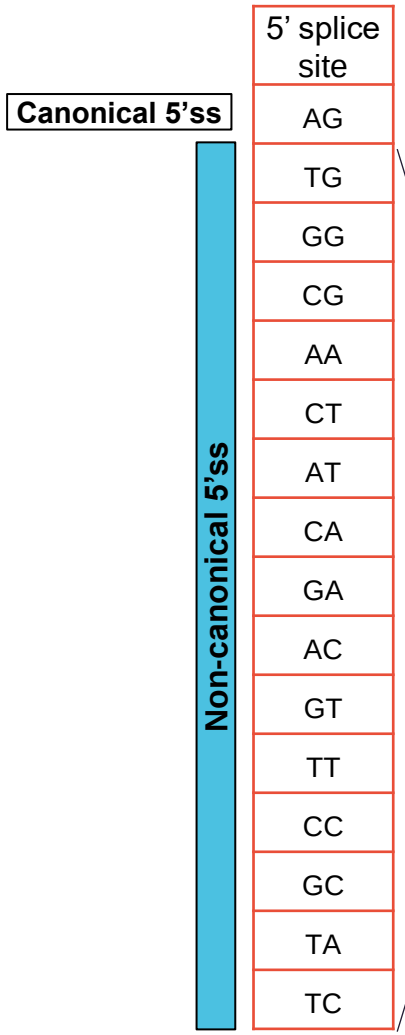






*Data on file from multiple studies

Building a Database of Druggable Splicing Targets



5' splice site
AG
TG
GG
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splicing change | Desired | Disease

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MAPT	yes and no	WT	skipping	FTDP-17	Nervous system	>1/100k
Undisclosed	no	WT	skipping	Undisclosed	Muscle	>1/100k
Undisclosed	no	WT	skipping	Undisclosed	Nervous system	>1/100k
Undisclosed	no	WT	inclusion	Undisclosed	Nervous system	>1/100k
Undisclosed	no	WT	inclusion	Undisclosed	Muscle	>1/100k
Undisclosed	no	WT	inclusion	Undisclosed	Nervous system	
Undisclosed	no	WT	skipping	Undisclosed	Nervous system	
Undisclosed	no	WT	inclusion	Undisclosed	Nervous system	
Undisclosed	c.964-1G>C	AS -1G>C	AS	Undisclosed	Development	>1/100k
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Undisclosed	c.815-27T>C	AS -27T>C	inclusion	Undisclosed	Metabolic	>1/100k
Undisclosed	c.-32-13T>G	AS -13T>G	inclusion	Undisclosed	Metabolic	>1/100k
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Undisclosed	no	WT	skipping	Undisclosed	Muscle	>1/10k
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Undisclosed	c.1092+5G>A	DS +5G>A	inclusion	Undisclosed	Eye	<1/1M
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Undisclosed	c.1909+22G>A	DS +22G>A	DS	Undisclosed	Nervous system	>1/100k
Undisclosed	c.4253+43G>A	DS +43G>A	inclusion	Undisclosed	Eye	>1/10k
Undisclosed	c.4539+2001G>A	AS +111G>A	skipping	Undisclosed	Eye	>1/10k
Undisclosed	no	WT	skipping	Undisclosed	Nervous system	>1/100k
Undisclosed	no	WT	skipping	Undisclosed	systemic	>1/10k

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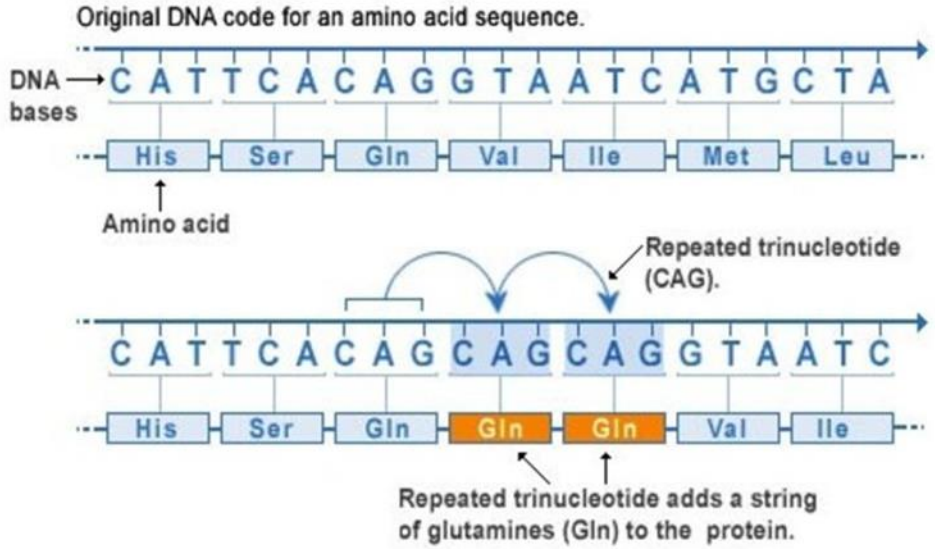
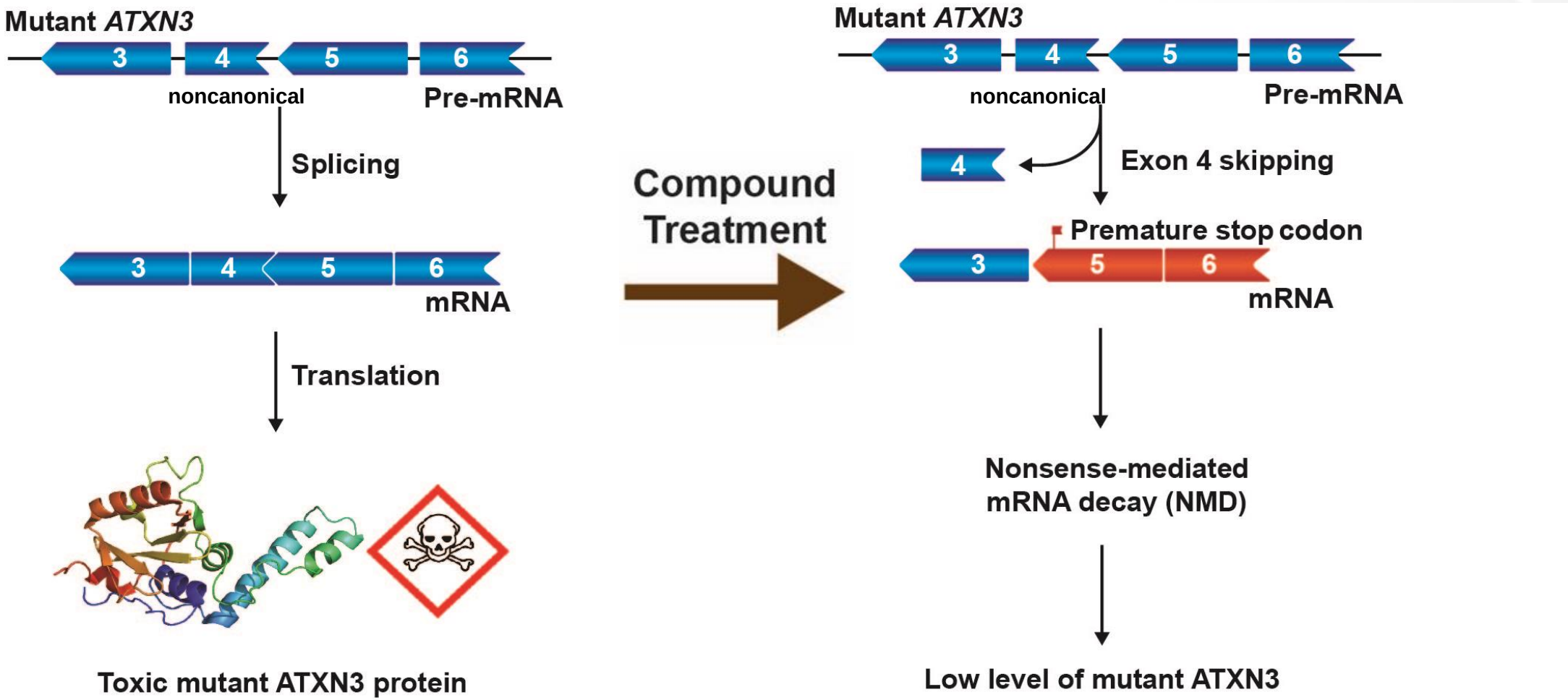
Spinocerebellar Ataxia 3 (SCA3)

- SCA3, also known as Machado–Joseph disease (MJD) is the most common autosomal dominant ataxia worldwide
- Characterized by progressive cerebellar ataxia, which results in lack of muscle control and coordination as well as a slow progression to an early death
- To date no disease-modifying therapy is available
- The primary cause of SCA3 is the abnormal expansion of CAG repeats in the *ATXN3* gene



U.S. National Library of Medicine

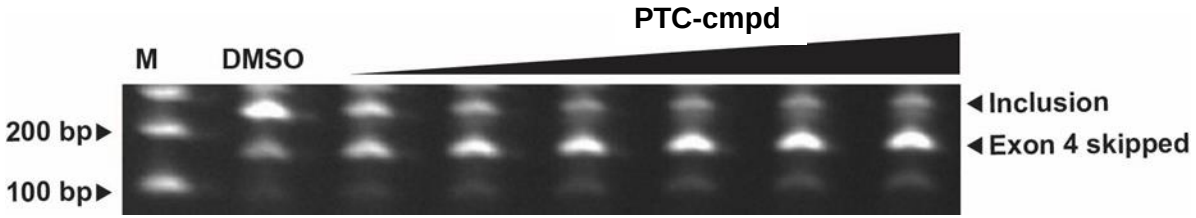
Targeting Alternative Splicing of *ATXN3*



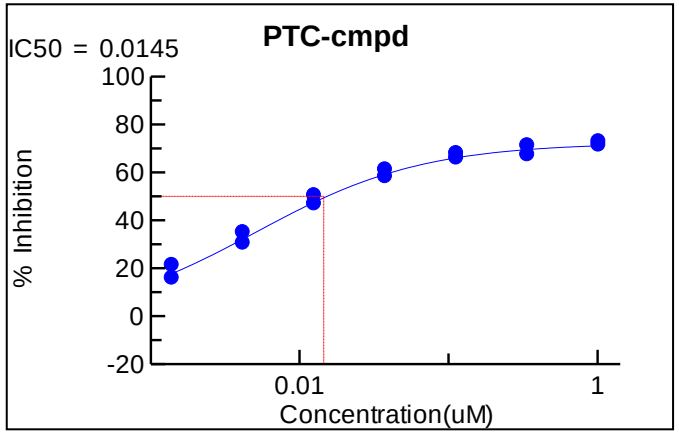
Compound-Mediated ATXN3 Exon Skipping and Protein Lowering *In Vitro*

ATXN3 exon skipping

End-point PCR

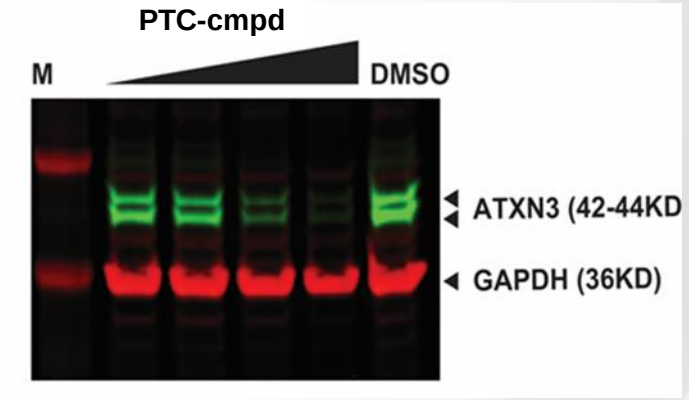


RT-qPCR

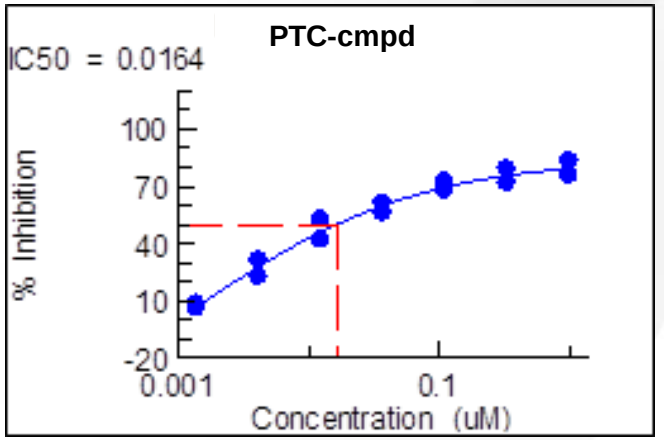


ATXN3 protein lowering

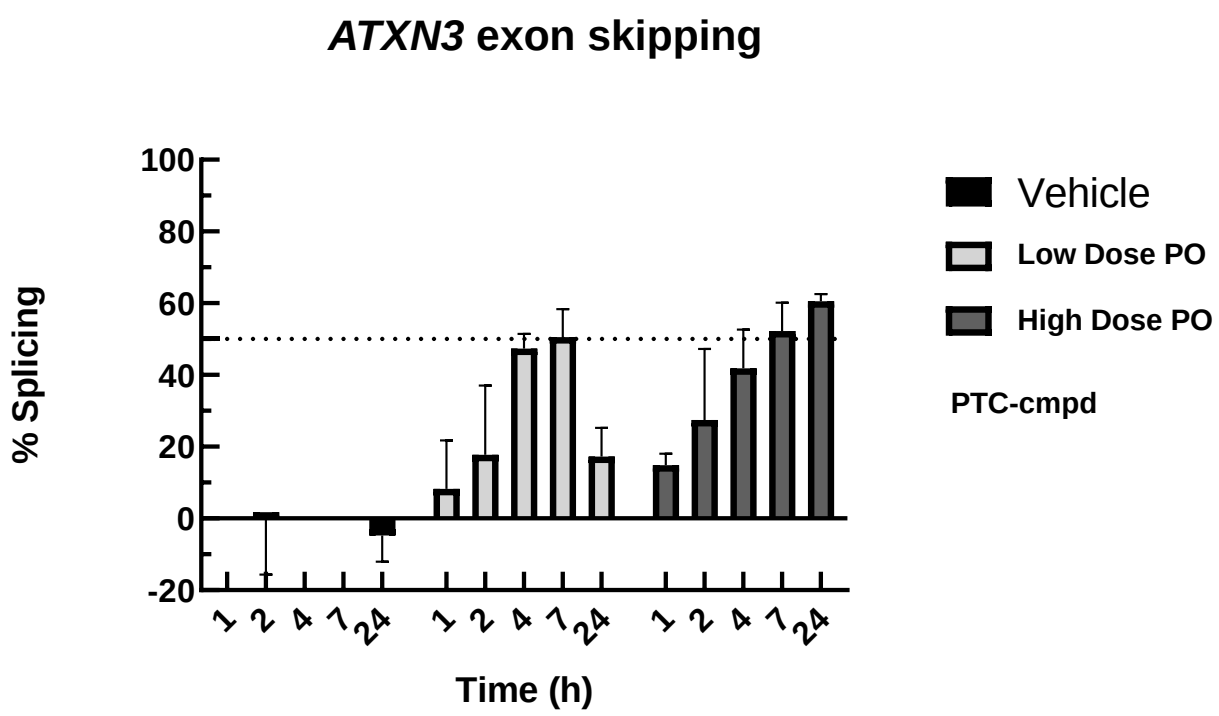
Western blot

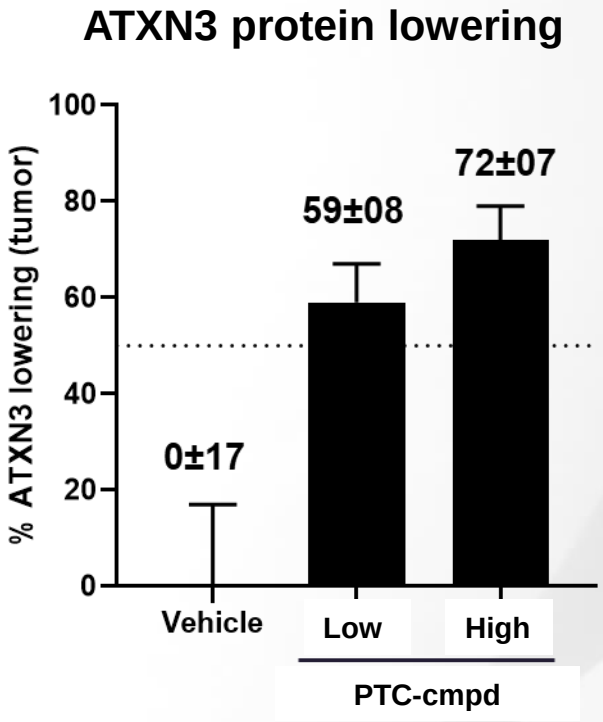


MSD



Compound-Mediated ATXN3 Exon Skipping and Protein Lowering *In Vivo*

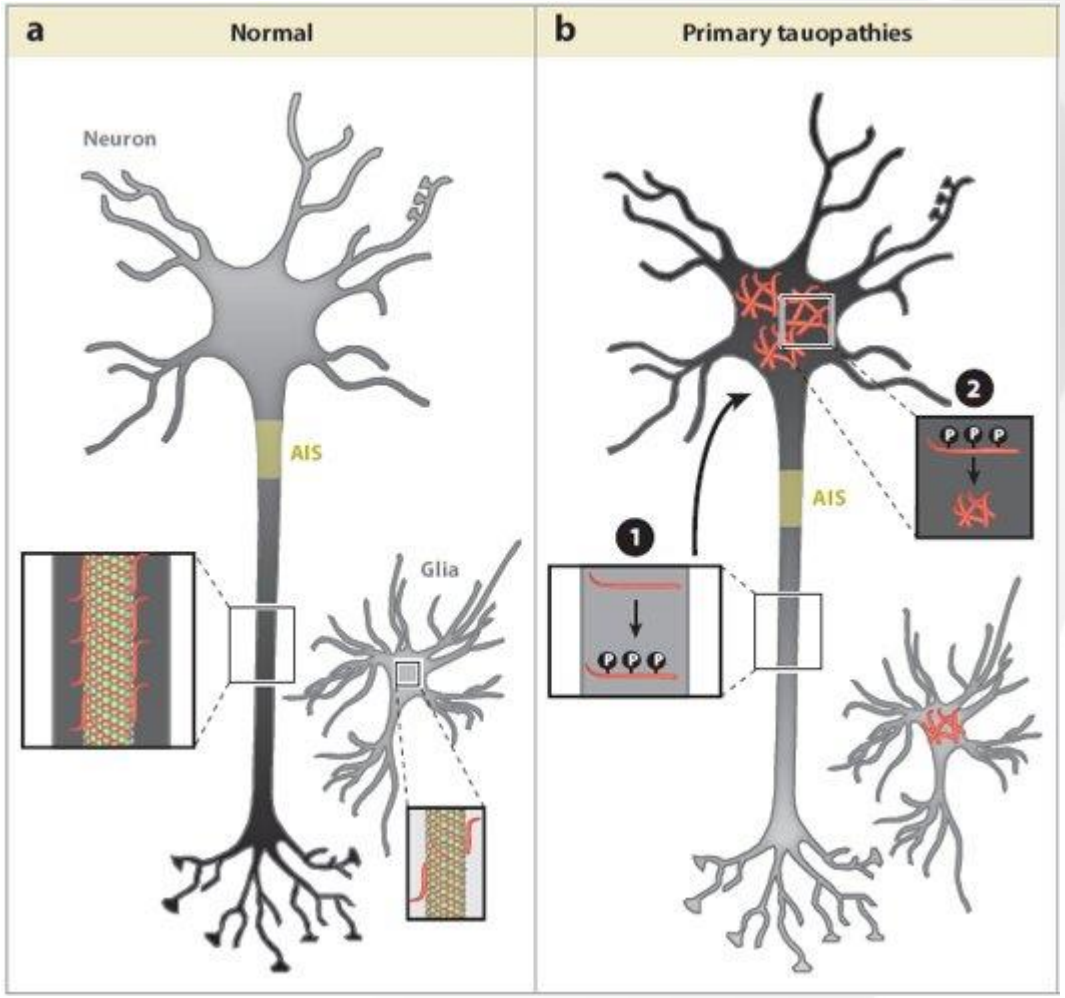




PD effect on *ATXN3* exon skipping and protein lowering was demonstrated in mouse xenograft models

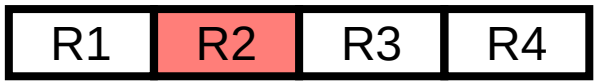
Targeting Splicing of MAPT to Correct Tauopathies

- MAPT, microtubule-associated protein tau, enriches in neuronal axons and regulates microtubule dynamics, axonal transport, and neurite outgrowth
- Accumulations of phosphorylated tau aggregates are the hallmark of several neurodegenerative diseases, referred to as tauopathies, such as FTDP-17 (MAPT mutation-driven)
- No disease-modifying therapy to treat tauopathies is available

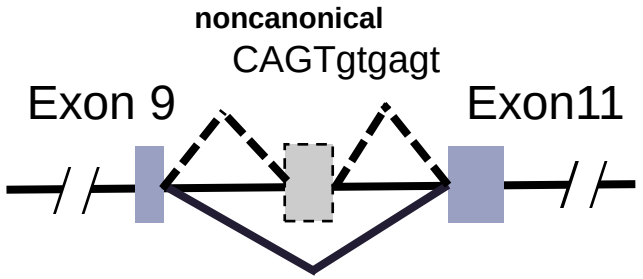


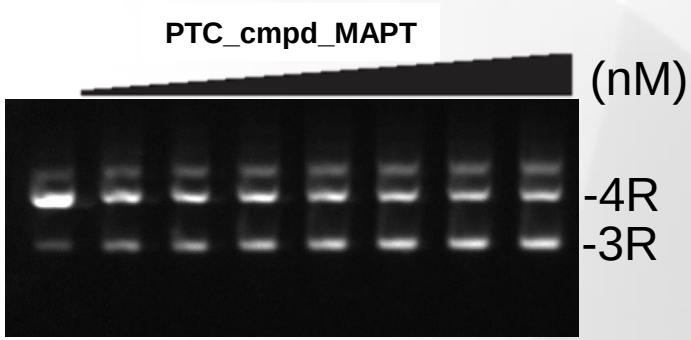
PTC Small Molecule Compounds Modulate MAPT Pre-mRNA Splicing

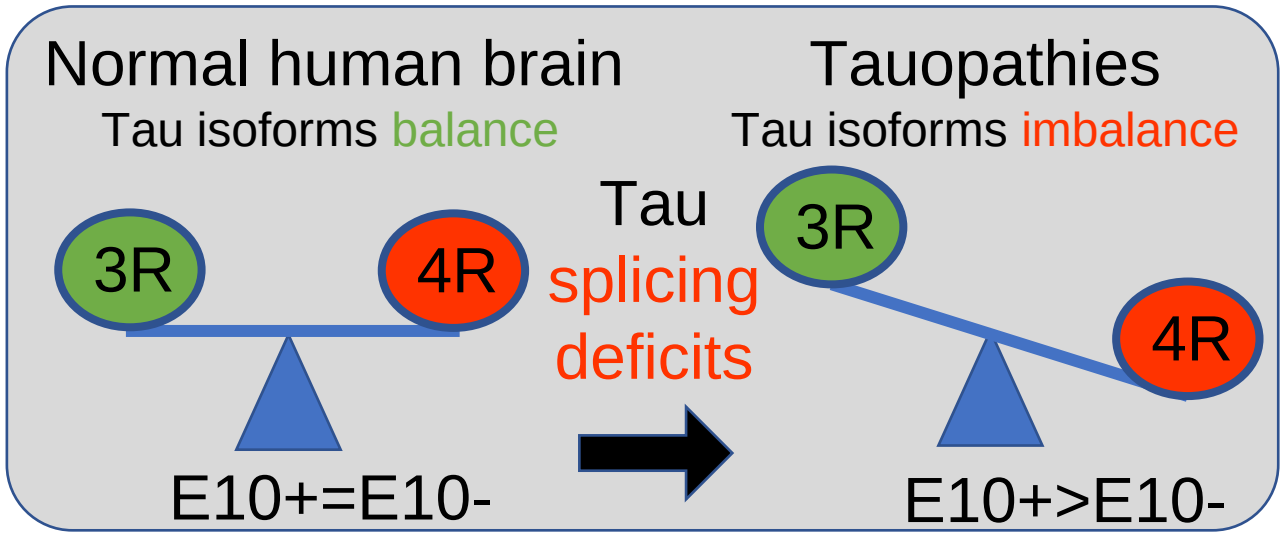
4R-Tau E10+



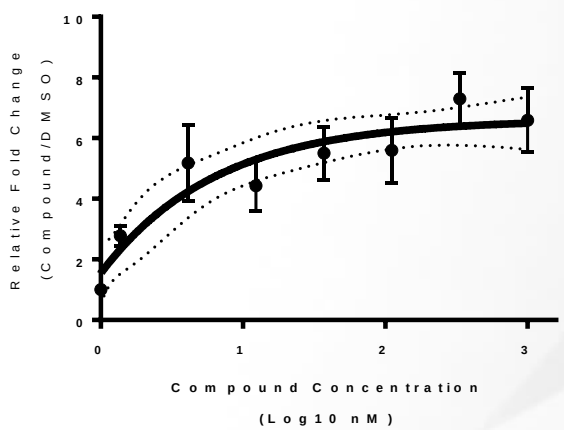
3R-Tau E10-



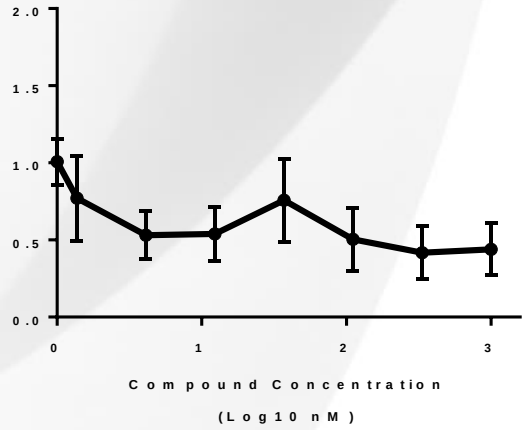




FTDP17 | AD | PSP | ALS

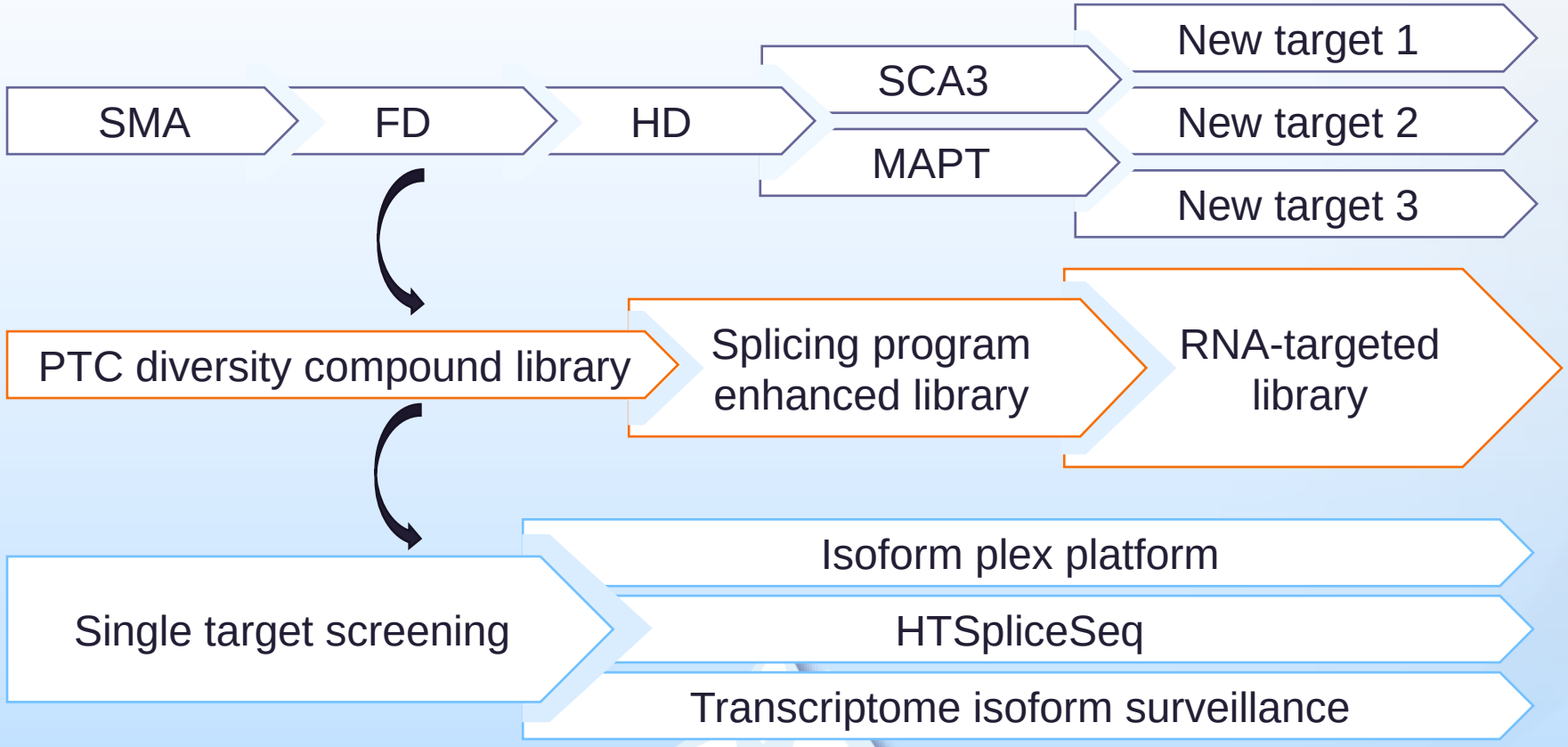


3R

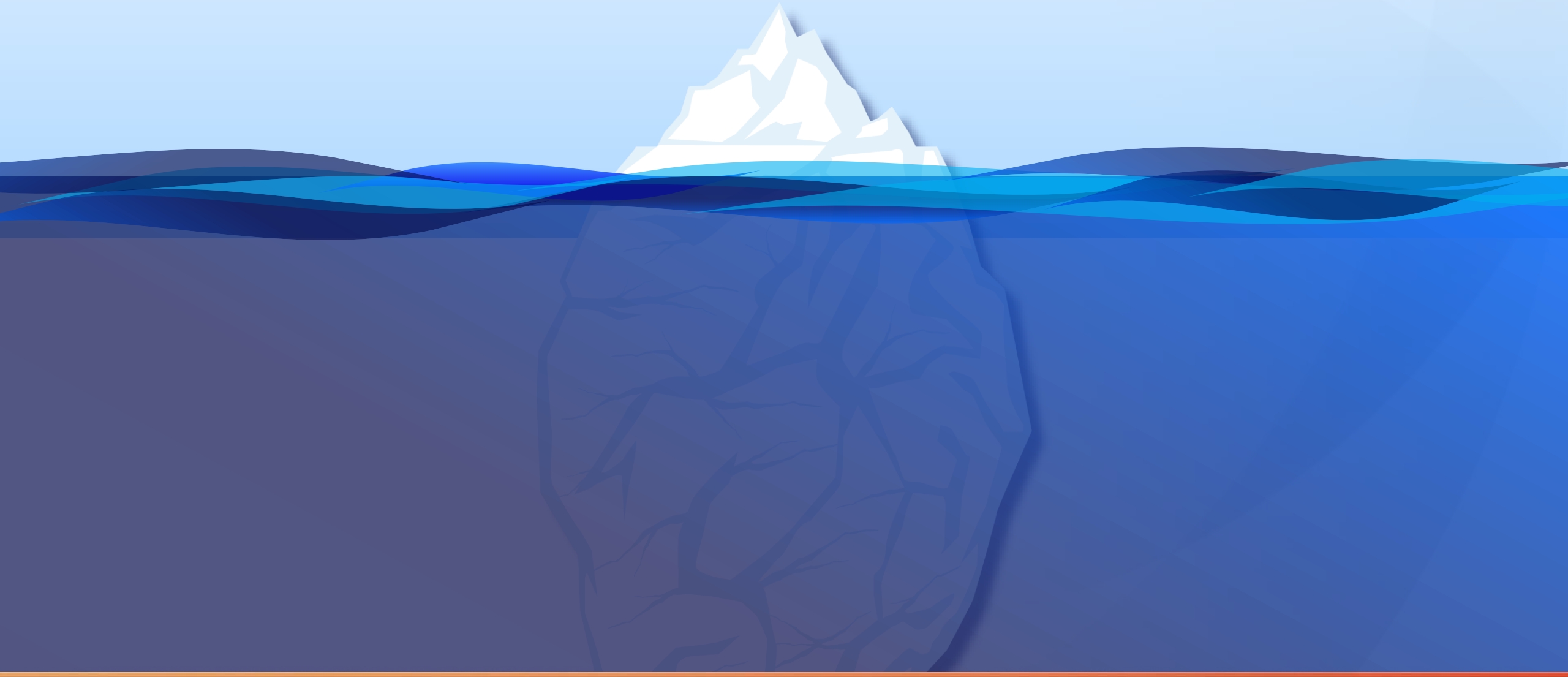


4R

Building the PTC Splicing Platform



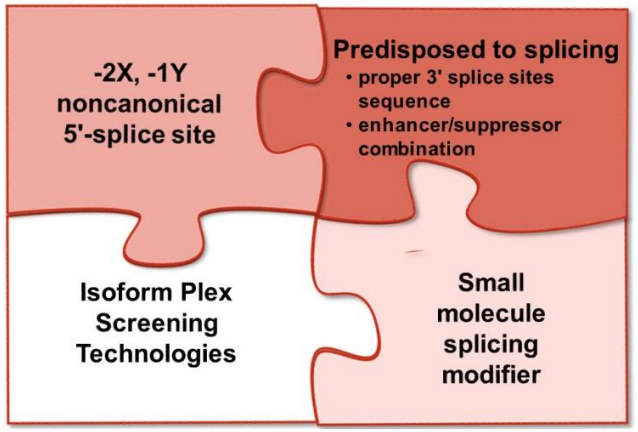
Building the PTC Splicing Platform



Closing Remarks

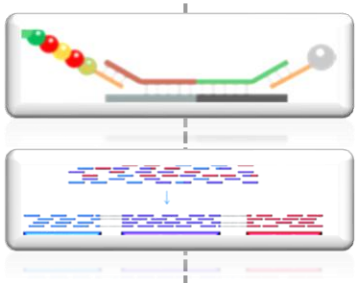
Stuart W. Peltz, Ph.D., CEO

PTC has Built a Fully Integrated, Validated, Innovative Splicing Platform with Broad Applicability



Exploiting U1-noncanonical exons

- Alternative splicing
- Decay exon inclusion
- Exon skipping



Isoform plex

HTSpliceseq

Transcriptome mRNA isoform detection platforms

2019

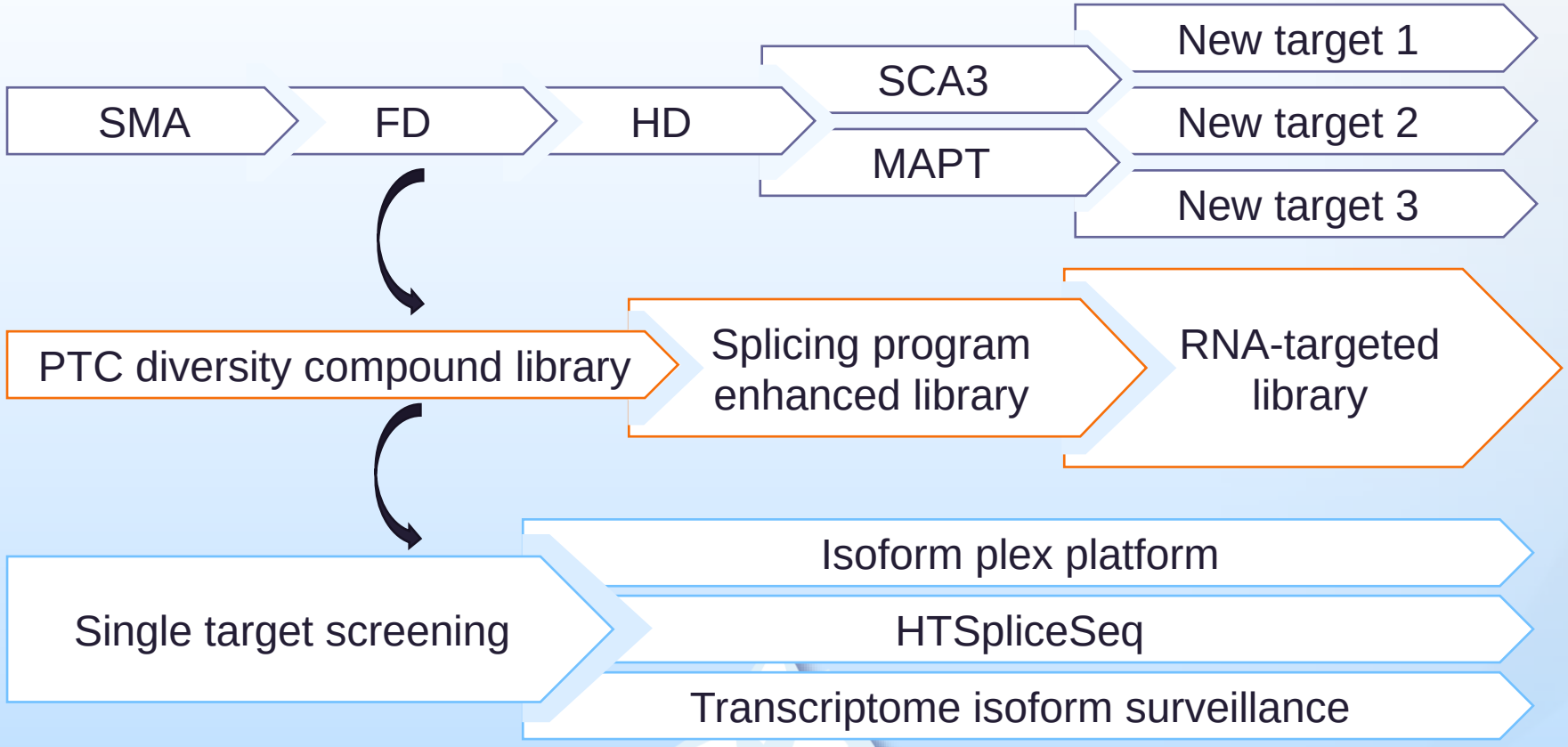
- **Risdiplam** *SMN2 exon 7 inclusion*
- **Familial dysautonomia** *ELP1 exon 20 inclusion*
- **Huntington disease** *Decay exon inclusion*

2020 and beyond

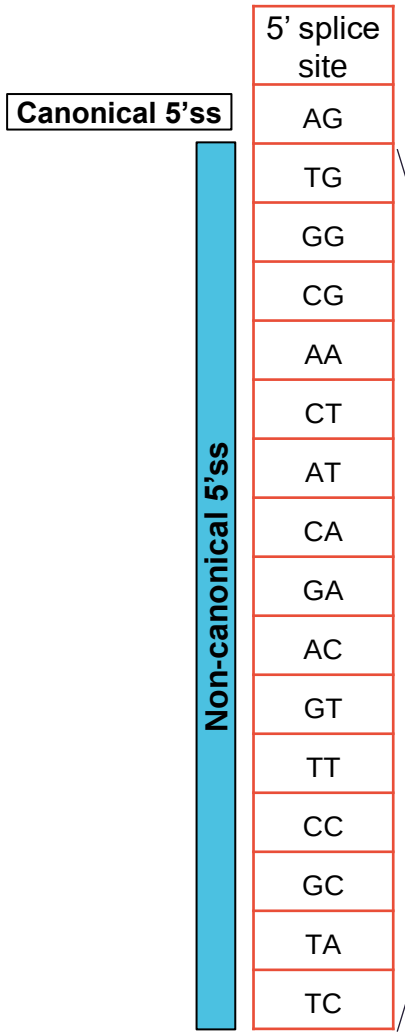
Proprietary RNA-targeted small molecule library

Many additional targets

Building the PTC Splicing Platform



Building a Database of Druggable Splicing Targets



Gene	splicing change caused by mutation?	Mutation_code	Desired Splicing	target disease	Affected tissue	Disease prevalence category
SMN2	no	AS -4A>C|AS +2G>A	inclusion	Spinal muscular atrophy (SMA)	Nervous system	>1/100k
IKBKAP	yes, 5'ss+6T>C	DS +6T>C	inclusion	Familial dysautonomia	Nervous system	<1/1M
HTT	no	WT	inclusion	Huntington's disease	Nervous system	>1/100k
ATXN3	no	WT	skipping	Spinocerebellar ataxia type 3	Muscle	>1/100k
MAPT	yes and no	WT	skipping	FTDP-17	Nervous system	>1/100k
Undisclosed	no	WT	skipping	Undisclosed	Muscle	>1/100k
Undisclosed	no	WT	skipping	Undisclosed	Nervous system	>1/100k
Undisclosed	no	WT	inclusion	Undisclosed	Nervous system	>1/100k
Undisclosed	no	WT	inclusion	Undisclosed	Muscle	>1/100k
Undisclosed	no	WT	inclusion	Undisclosed	Nervous system	
Undisclosed	no	WT	skipping	Undisclosed	Nervous system	
Undisclosed	no	WT	inclusion	Undisclosed	Nervous system	
Undisclosed	c.964-1G>C	AS -1G>C	AS	Undisclosed	Development	>1/100k
Undisclosed	no	WT	inclusion	Undisclosed	Nervous system	>1/1k
Undisclosed	no	WT	inclusion	Undisclosed	Nervous system	>1/1k
Undisclosed	c.815-27T>C	AS -27T>C	inclusion	Undisclosed	Metabolic	>1/100k
Undisclosed	c.-32-13T>G	AS -13T>G	inclusion	Undisclosed	Metabolic	>1/100k
Undisclosed	no	WT	skipping	Undisclosed	Kidney	>1/100k
Undisclosed	no	WT	skipping	Undisclosed	Muscle	>1/10k
Undisclosed	c.5714+5G>A	DS +5G>A	inclusion	Undisclosed	Eye	>1/10k
Undisclosed	c.1092+5G>A	DS +5G>A	inclusion	Undisclosed	Eye	<1/1M
Undisclosed	no	WT	inclusion	Undisclosed	Nervous system	>1/10k
Undisclosed	no	WT	inclusion	Undisclosed	Muscle	>1/100k
Undisclosed	c.2588G>C	AS +1G>C	inclusion	Undisclosed	Eye	>1/10k
Undisclosed	c.1909+22G>A	DS +22G>A	DS	Undisclosed	Nervous system	>1/100k
Undisclosed	c.4253+43G>A	DS +43G>A	inclusion	Undisclosed	Eye	>1/10k
Undisclosed	c.4539+2001G>A	AS +111G>A	skipping	Undisclosed	Eye	>1/10k
Undisclosed	no	WT	skipping	Undisclosed	Nervous system	>1/100k
Undisclosed	no	WT	skipping	Undisclosed	systemic	>1/10k

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