
# PTC 2018 R&D Analyst Day

Stuart Peltz, Founder & CEO | April 2018

# Forward-looking statements within the meaning of The Private Securities Litigation Reform Act of 1995

All statements, other than those of historical fact, contained in this presentation, are forward-looking statements, including statements regarding: the future expectations, plans and prospects for PTC; PTC's plans for, and the likelihood of success of, its research and development programs; the timing of and likelihood of success of its regulatory path forward in the U.S., including as it relates to any clinical trials and non-clinical studies to generate data on dystrophin production in ataluren, a re-submission of an NDA for ataluren to the FDA, and any further interactions between PTC and the FDA; expansion of Translarna; advancement of PTC's joint collaboration program in SMA; the clinical utility and potential advantages of Translarna (ataluren) and Emflaza™ (deflazacort); PTC's strategy, future operations, future financial position, future revenues or projected costs; and the objectives of management. Other forward-looking statements may be identified by the words "plan," "anticipate," "believe," "estimate," "expect," "intend," "may," "target," "potential," "will," "would," "could," "should," "continue," 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 Emflaza and Translarna; whether, and to what extent, third party payors impose additional requirements before approving Emflaza prescription reimbursement; PTC's ability to resolve the matters set forth in the denial to the Complete Response letter it received from the FDA in connection with its NDA for Translarna for the treatment of nonsense mutation Duchenne muscular dystrophy (nmDMD), and PTC's ability to perform additional clinical trials, non-clinical studies, and CMC assessments or analyses at significant cost; PTC's ability to maintain its marketing authorization of Translarna for the treatment of nmDMD in the European Economic Area (EEA), including whether the European Medicines Agency (EMA) determines in future annual renewal cycles that the benefit-risk balance of Translarna authorization supports renewal of such authorization; PTC's ability to enroll, fund, complete and timely submit to the EMA the results of Study 041, a randomized, 18-month, placebo-controlled clinical trial of Translarna for the treatment of nmDMD followed by an 18-month open-label extension, which is a specific obligation to continued marketing authorization in the EEA; PTC's ability to realize the anticipated benefits of the acquisition of Emflaza, including the possibility that the expected benefits from the acquisition will not be realized or will not be realized within the expected time period; significant transaction costs, unknown liabilities, the risk of litigation and/or regulatory actions related to the acquisition of Emflaza, as well as other 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 Translarna, Emflaza and PTC's other product candidates; the enrollment and conduct of studies under the SMA collaboration and events during, or as a result of, the studies that could delay or prevent further development under the program; PTC's scientific approach and general development progress; PTC's ability to satisfy its obligations under the terms of the senior secured term loan facility with MidCap Financial; the sufficiency of PTC's cash resources and its ability to obtain adequate financing in the future for its foreseeable and unforeseeable operating expenses and capital expenditures; the use of proceeds of any offering of securities or other financing and the factors discussed in the "Risk Factors" section of PTC's most recent 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, including Translarna or Emflaza.

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.



PTC THERAPEUTICS™ 20 YEARS OF COMMITMENT

# Completing our 20th anniversary and thinking about what's next: Our strategic roadmap for the next 3 to 5 years

**Vision**

**PTC is a fully integrated, innovative rare disease company leveraging research capabilities and core technology platforms, building out world-class commercial capabilities, and being an ideal partner for late-stage, ultra-orphan diseases for which there is high unmet medical need.**

## STRATEGY

### *Fully Integrated Orphan Franchise*

- Prioritize development based on targeted rare disease parameters
- Leverage and strengthen commercial capability to bring treatments to patients with high unmet need
- Become an attractive in-licensing partner for ultra-orphan assets

### *Niche Oncology Development*

- Prioritize indications and focus the development of PTC299 and PTC596
- Flexible for late-stage development/ commercialization

## PHILOSOPHY

### *Flexible and Opportunistic*

- Remain adaptive to exploring emerging opportunities
- Foster discovery and development leadership with current and future technology platforms

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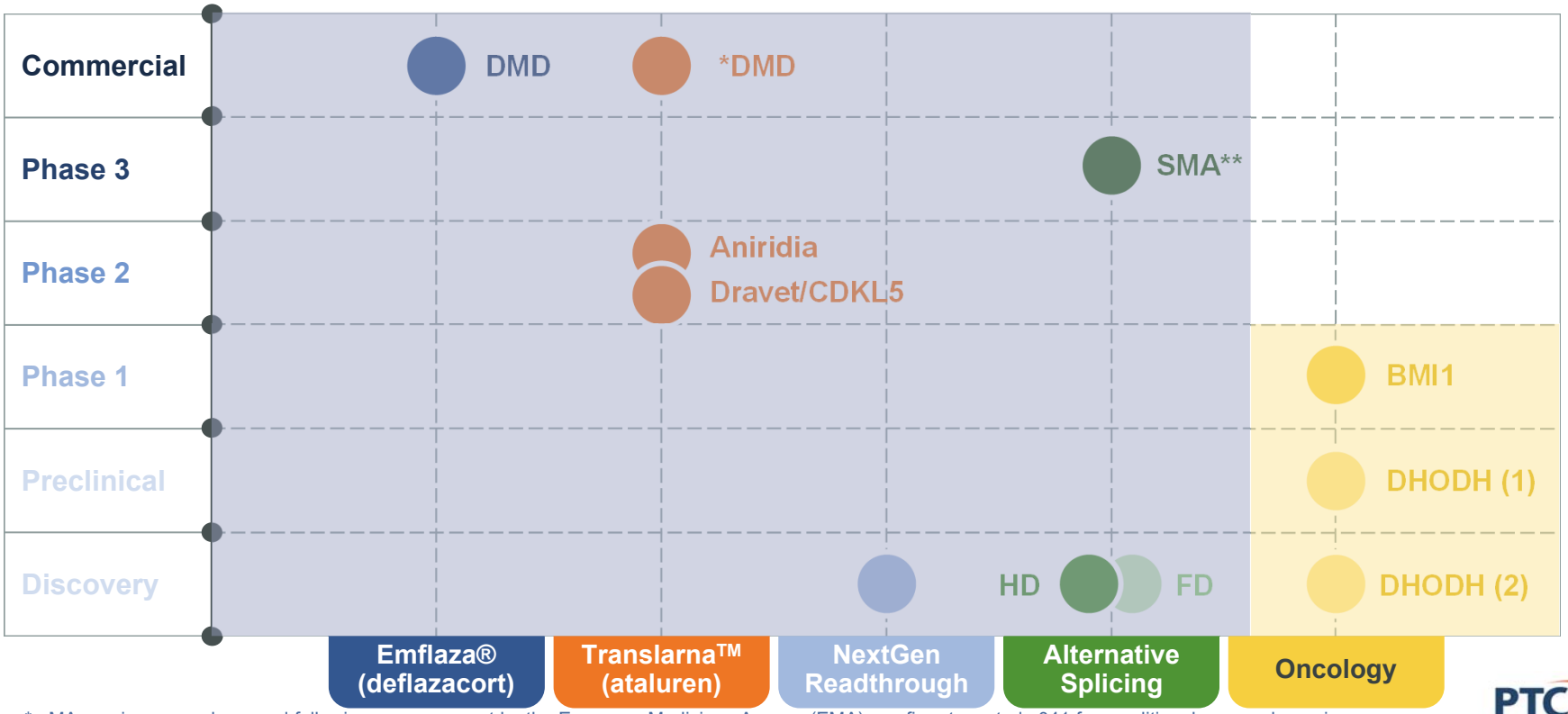
# Internal expanding pipeline through in-house innovation




* MA requires annual renewal following reassessment by the European Medicines Agency (EMA), confirmatory study 041 for conditional approval ongoing.

** Sunfish clinical study of RG7916 in SMA type 2/3 patients transitioned to its phase 3 second stage in Oct 2017, Firefish in SMA type 1 patients transitioned to its phase 3 second stage in March 2018.

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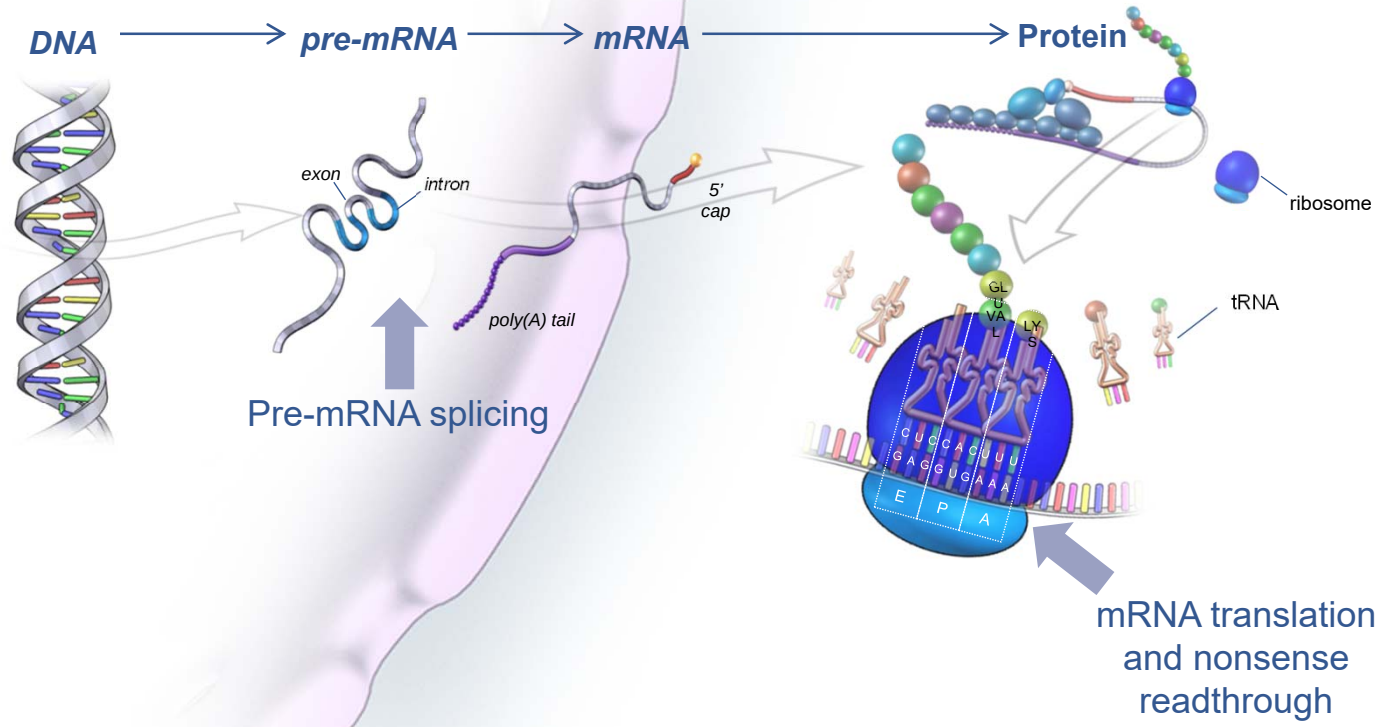
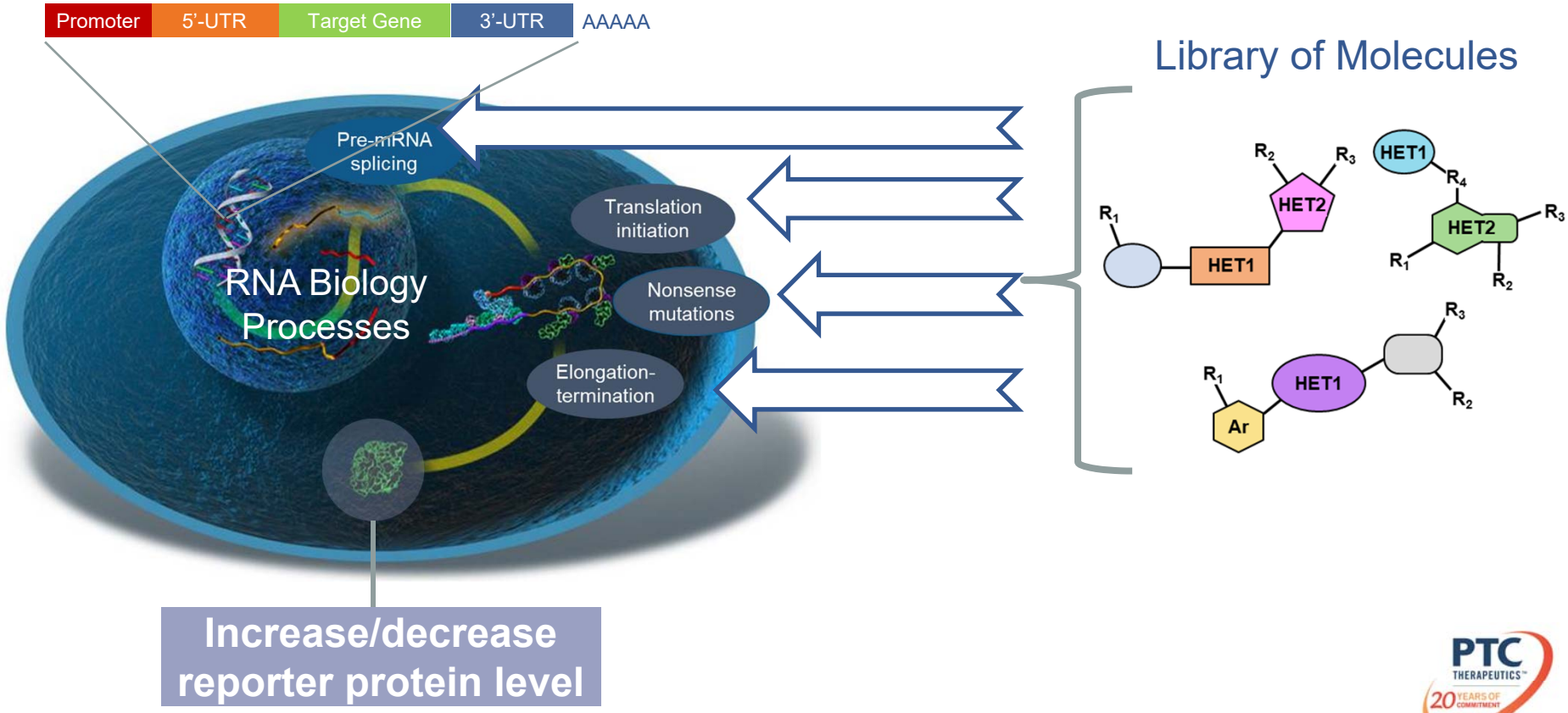
# PTC discovery is focused on the development of small molecules that target RNA biology




PTC uses small molecules to target RNA processes to treat challenging diseases

# Chemical genetics to discover therapeutics targeting RNA biology

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# An integrated orphan biotech: Multiple platforms discovering, developing, delivering differentiated therapies

## 1) Growing global DMD franchise 2018 revenue guidance of $260- $295 million

- Strong Translarna™ year-over-year growth reflects continued global patient uptake
- Emflaza® successful launch; opportunity to establish standard of care
- Translarna lifecycle management: US approval opportunity, ongoing clinical studies

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Guidance provided Jan 8, 2018.



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# An integrated orphan biotech: Multiple platforms discovering, developing, delivering differentiated therapies

## 2) Leveraging internal splicing technology platform

- Splicing platform: approach, optimization process, goals: Huntington's Disease & familial dysautonomia
- Spinal Muscular Atrophy (SMA) program in pivotal stage, potential to be best-in-class SMA therapy
  - Dr. Baranello: RG7916 clinical data, the evolving treatment landscape
  - SMA Foundation: The remaining unmet need, challenges with current treatment options





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# An integrated orphan biotech: Multiple platforms discovering, developing, delivering differentiated therapies

## 3) Niche rare oncology pipeline: Value creation opportunity

- PTC596: targeting pediatric brain tumors and sarcomas
- PTC299: DHODH inhibitor in hematological malignancies (AML)


# DMD: Translarna™ & Emflaza® Growing a Global Franchise

Marcio Souza, COO

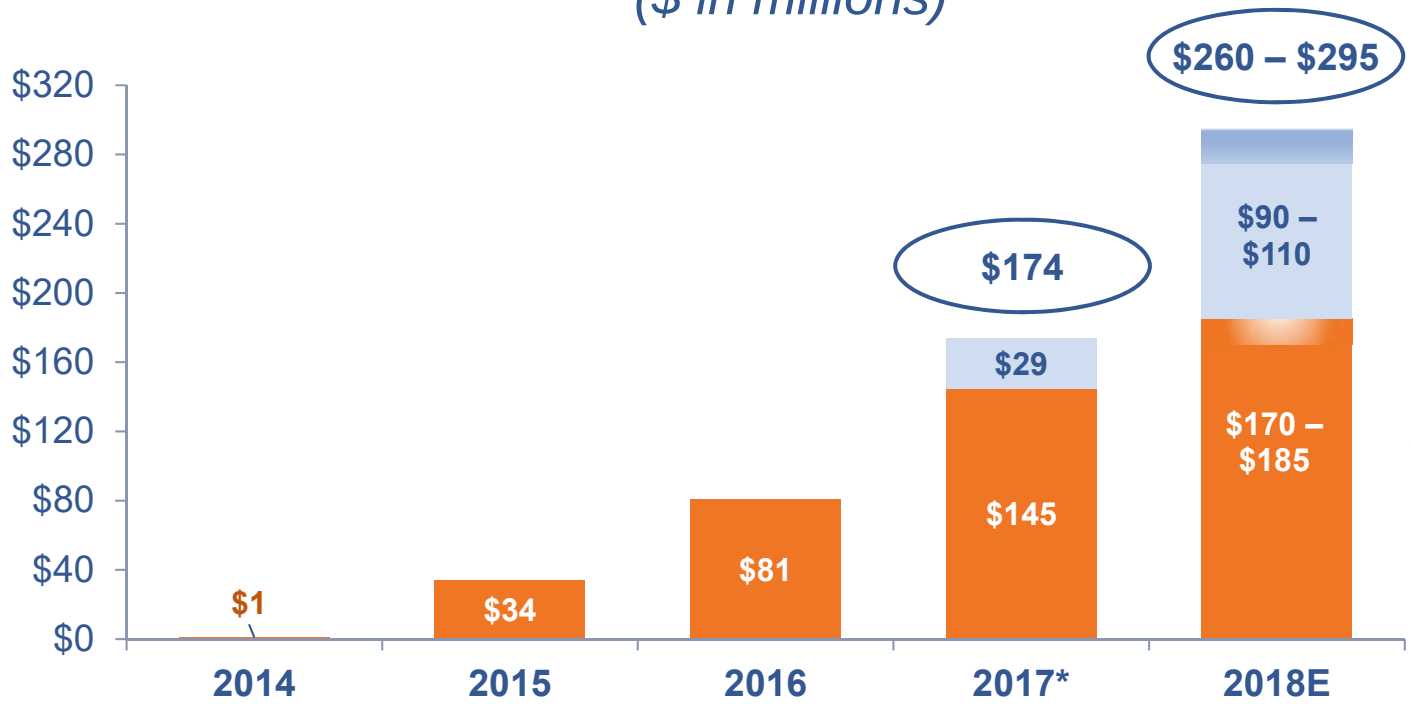
# Global leadership in Duchenne muscular dystrophy (DMD) ~20 years

- Largest genotyping program globally supported by PTC Therapeutics
- First-ever approved drug globally with Translarna™
  - Penetration in key markets has been very high
- DMD franchise gives access to largest body of information on disorder in the world
- First company to complete a clinical trial in patients younger than 5 years of age in DMD
- Relationships with >150 patient advocacy groups

# Growing global DMD franchise

## Translarna™ & Emflaza® DMD Net Sales

*($ in millions)*




Emflaza® (deflazacort)

translarna™ ataluren

- Guidance provided Jan 8, 2018.



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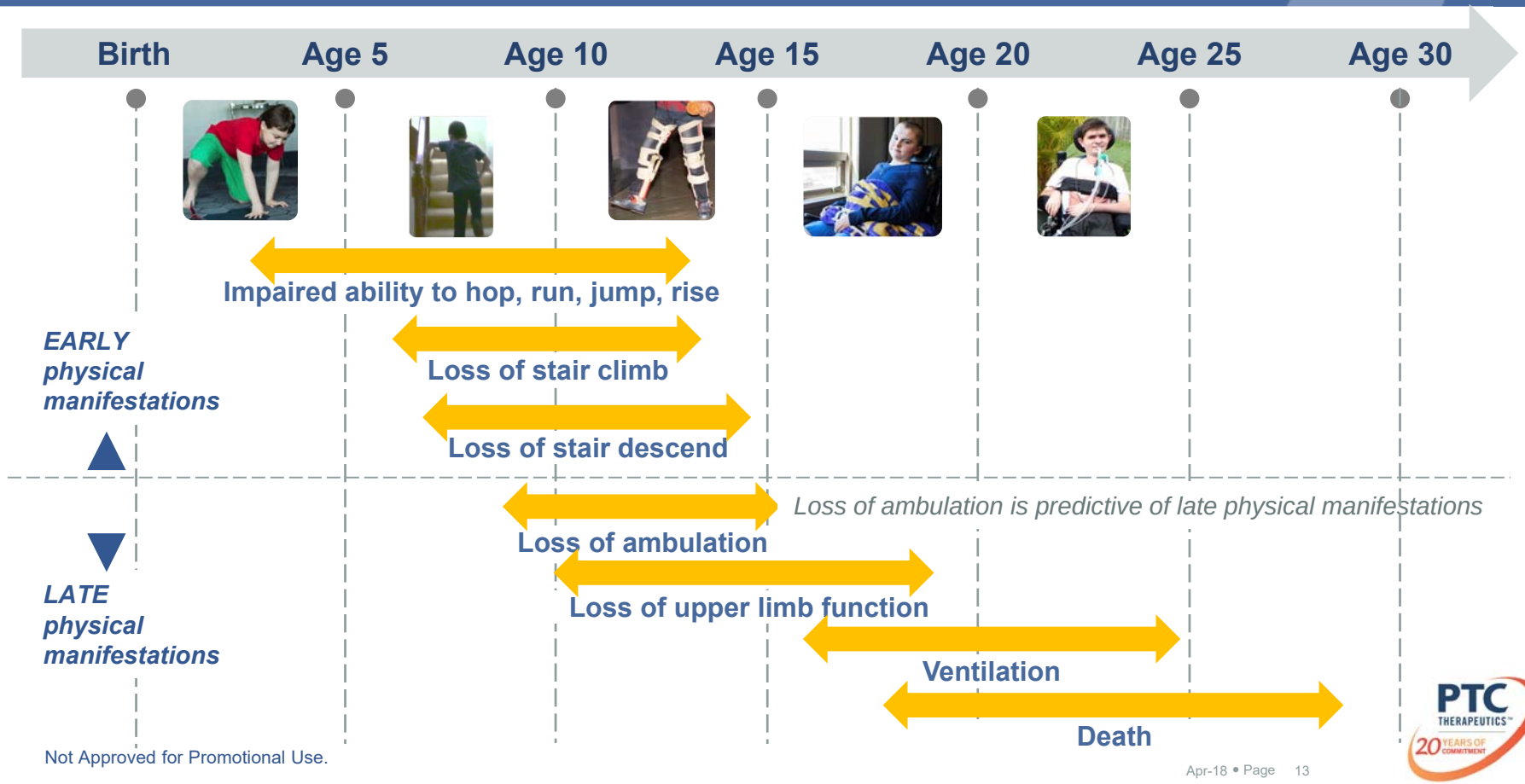
# DMD progression is sequential, non-linear, and irreversible

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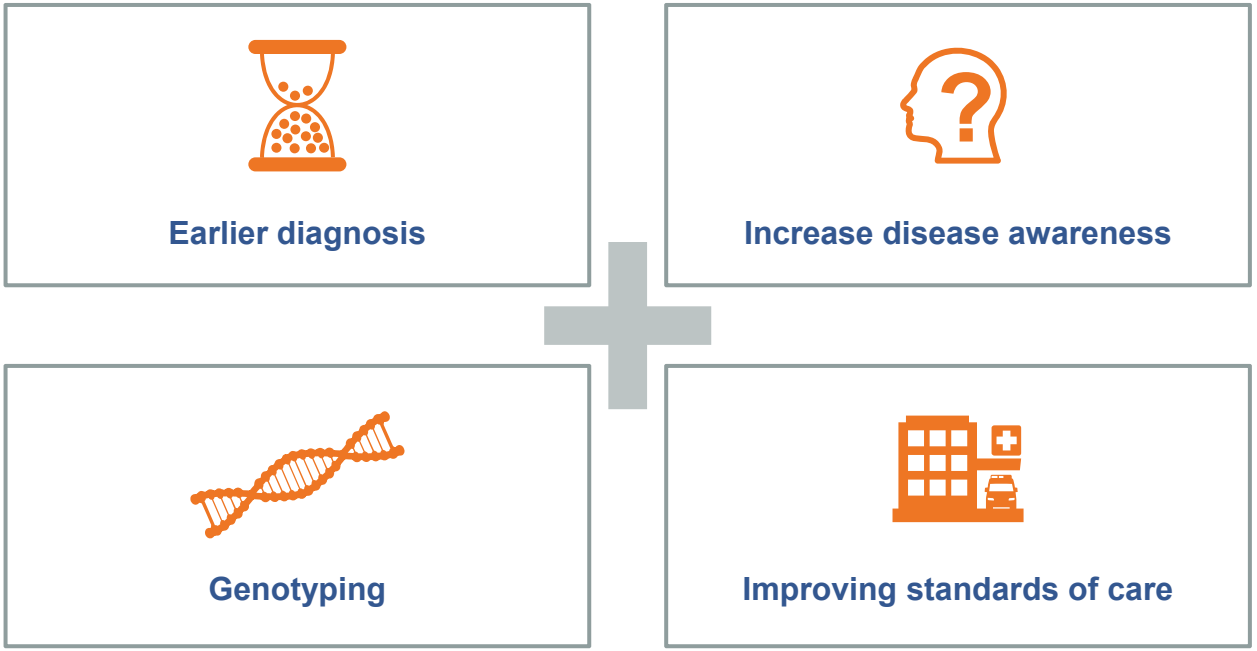
# Improving patient outcome by delivering best-in-class therapies earlier to preserve function




**Pursuing label expansions to bring Emflaza® & Translarna™ to younger patients to ultimately improve patient outcome**

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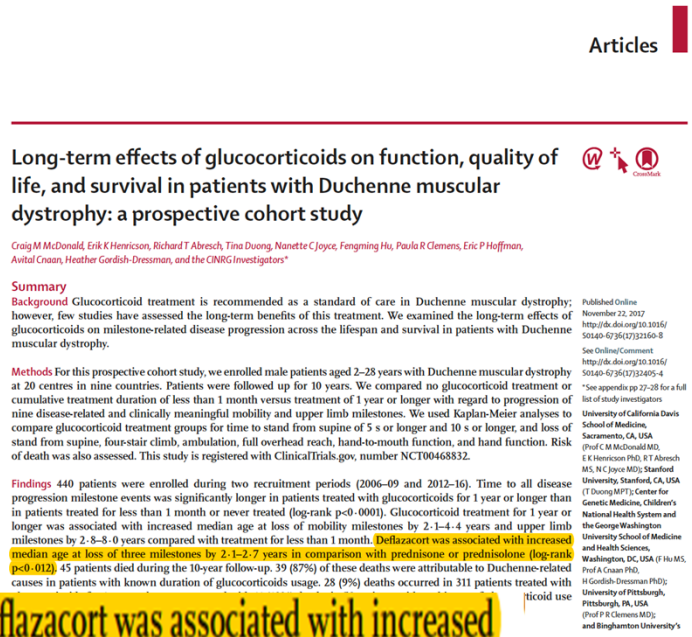
# Emflaza®: Establishing standard of care for all DMD patients in the US

Emflaza®
(deflazacort)

- 2017 Emflaza net sales of $29 M
- Guidance for 2018 of $90 - $110 M
- Results from Lancet publication reinforce Emflaza efficacy differentiation



Articles

Long-term effects of glucocorticoids on function, quality of life, and survival in patients with Duchenne muscular dystrophy: a prospective cohort study

Craig M McDonald, Erik K Henricson, Richard T Abresch, Tina Duong, Nanette C Joyce, Fengming Hu, Paula R Clemens, Eric P Hoffman, Avital Cnaan, Heather Gordish-Dressman, and the CINRG Investigators*

Summary

Background Glucocorticoid treatment is recommended as a standard of care in Duchenne muscular dystrophy; however, few studies have assessed the long-term benefits of this treatment. We examined the long-term effects of glucocorticoids on milestone-related disease progression across the lifespan and survival in patients with Duchenne muscular dystrophy.

Methods For this prospective cohort study, we enrolled male patients aged 2–28 years with Duchenne muscular dystrophy at 20 centres in nine countries. Patients were followed up for 10 years. We compared no glucocorticoid treatment or cumulative treatment duration of less than 1 month versus treatment of 1 year or longer with regard to progression of nine disease-related and clinically meaningful mobility and upper limb milestones. We used Kaplan-Meier analyses to compare glucocorticoid treatment groups for time to stand from supine of 5 s or longer and 10 s or longer, and loss of stand from supine, four-stair climb, ambulation, full overhead reach, hand-to-mouth function, and hand function. Risk of death was also assessed. This study is registered with ClinicalTrials.gov, number NCT00468832.

Findings 440 patients were enrolled during two recruitment periods (2006–09 and 2012–16). Time to all disease progression milestone events was significantly longer in patients treated with glucocorticoids for 1 year or longer than in patients treated for less than 1 month or never treated (log-rank p<0·0001). Glucocorticoid treatment for 1 year or longer was associated with increased median age at loss of mobility milestones by 2·1–4·4 years and upper limb milestones by 2·8–8·0 years compared with treatment for less than 1 month. Deflazacort was associated with increased median age at loss of three milestones by 2·1–2·7 years in comparison with prednisone or prednisolone (log-rank p<0·012). 45 patients died during the 10-year follow-up. 39 (87%) of these deaths were attributable to Duchenne-related causes in patients with known duration of glucocorticoids usage. 28 (9%) deaths occurred in 311 patients treated with

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See Online/Comment http://dx.doi.org/10.1016/S0140-6736(17)32405-4

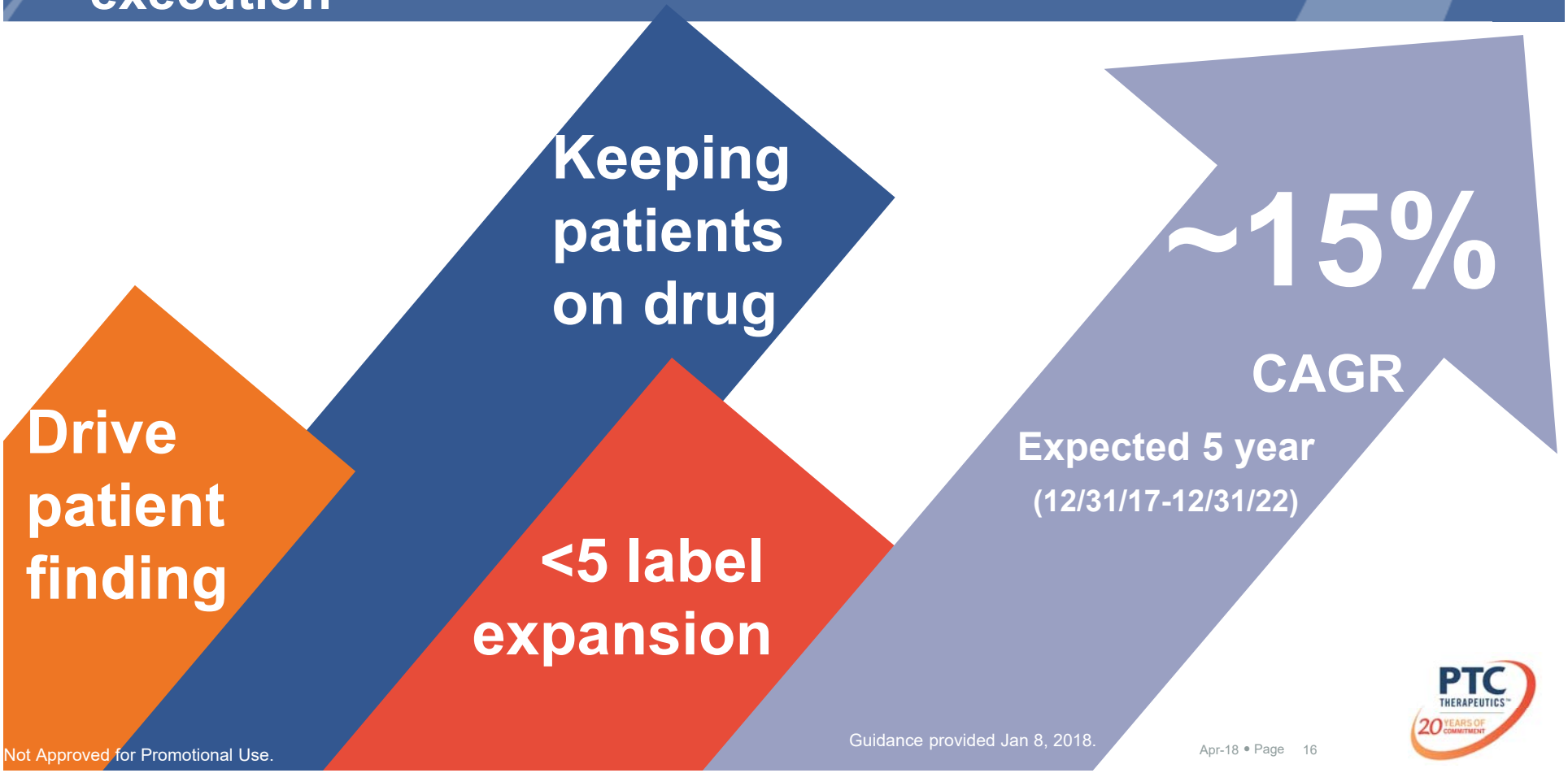
*See appendix pp 27–28 for a full list of study investigators

University of California Davis School of Medicine, Sacramento, CA, USA (Prof C M McDonald MD, E K Henricson PhD, R T Abresch MS, N C Joyce MD); Stanford University, Stanford, CA, USA (T Duong MPT); Center for Genetic Medicine, Children's National Health System and the George Washington University School of Medicine and Health Sciences, Washington, DC, USA (F Hu MS, Prof A Cnaan PhD, H Gordish-Dressman PhD); University of Pittsburgh, Pittsburgh, PA, USA (Prof P R Clemens MD); and Binghamton University's

milestones by 2·8–8·0 years compared with treatment for less than 1 month. Deflazacort was associated with increased median age at loss of three milestones by 2·1–2·7 years in comparison with prednisone or prednisolone (log-rank p<0·012). 45 patients died during the 10-year follow-up. 39 (87%) of these deaths were attributable to Duchenne-related

PTC THERAPEUTICS 20 YEARS OF COMMITMENT

# Translarna™: Proven track record of successful global execution




Guidance provided Jan 8, 2018.

# Aggressively seeking in-licensing opportunities

- Prepared to execute as orphan disease partner
- Established footprint in ~45 countries worldwide
- Experienced commercial team in orphan disease
- Fully integrated global commercial infrastructure


**South Plainfield, New Jersey US Headquarters**

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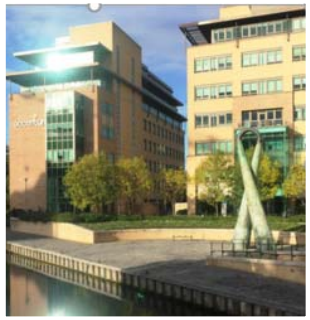
**Zug Switzerland, Marketing, Medical, and Regulatory Hub**



**Dublin, Ireland International HQ**

**Latam Regional Office, Sao Paulo, Brazil**



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# Emflaza® - Establishing Standard of Care

Eric Pauwels, SVP General Manager- Americas

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# Strategic rationale behind Emflaza® acquisition

- Leverage our 20 years of global experience with key DMD stakeholders
- ACT DMD demonstrated Emflaza® (deflazacort) is the “best-in-class” anti-inflammatory therapy
- Diversification of product portfolio, revenues, and geography
- Establish a global footprint, with 2 of 3 DMD approved assets
- Leverage PTC’s leadership team experience in US rare-disease launches
- Position ourselves favorably for future BD collaborations

# Extensive rare-disease experience launching products in challenging therapeutic areas

Natpara® (parathyroid hormone)
Hypoparathyroidism

REPLAGAL® agalsidase alfa
Fabry Disease

firazyr® icatibant
HAE

Revlimid® (lenalidomide) capsules
Multiple Myeloma

Emflaza® (deflazacort)
Duchenne Muscular Dystrophy

elaprase® (idursulfase)
Hunters Syndrome

VPRIV®
Gaucher Diseases

translarna™ ataluren
Duchenne Muscular Dystrophy

ISTODAX® (romidepsin) for injection 10-MG SINGLE-USE VIAL
CTCL/PTCL

Gattex® (Teduglutide [rDNA origin]) for Injection
Short Bowel Syndrome

Vidaza® azacitidine for injection
Myelodysplastic Syndrome

THALOMID® (thalidomide) Capsules
Multiple Myeloma

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# Launched Emflaza® and achieved rapid uptake before emerging data published

**Feb 9**
FDA approval

**May 15**
Emflaza 1st commercial shipment

**Nov**
1,500 pts commercial/bridge

**2017**

1Q | 2Q | 3Q | 4Q | 1Q18

**Mar 16**
Agreement to acquire Emflaza announced

**Apr 20**
Completes acquisition of Emflaza

**Nov 17**
*Lancet* publishes CINGR 10 year Natural History Study in DMD

**Jan 23**
*Lancet* publishes DMD Standard of Care Guidelines

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# Market research results show that physicians highly recognize Emflaza® and expect to increase utilization

- Unaided awareness doubled to ~80% *(vs prelaunch measurements)*
- Stated market share increased by ~40%
- 70% of HCPs expect their use to grow

PTC U.S. Market Research Report, 2018.
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# 2017 focus: Transitioning patients to commercial Emflaza

**Phase I: Deflazacort patients transition to commercial drug**

## Major initiatives:

- Hire and deploy expert field sales team
- Establish exclusive specialty pharmacy
- Build high-touch patient services program

# Deployed ~25-person orphan disease commercial team

**Sales Team Experience**

*By the Numbers (Averages)*

- Years in industry = 19
- Drug launches = 7
- Orphan drugs sold = 6
- Start-ups worked at = 3
- Years selling in neurology = 3

- Strong existing relationships in many key centers of excellence facilitated greater access and collaboration during the critical initial phase of launch
- A commercial team, well-versed in orphan drug business models, was able to educate key centers on navigating complexities of rare disease reimbursement

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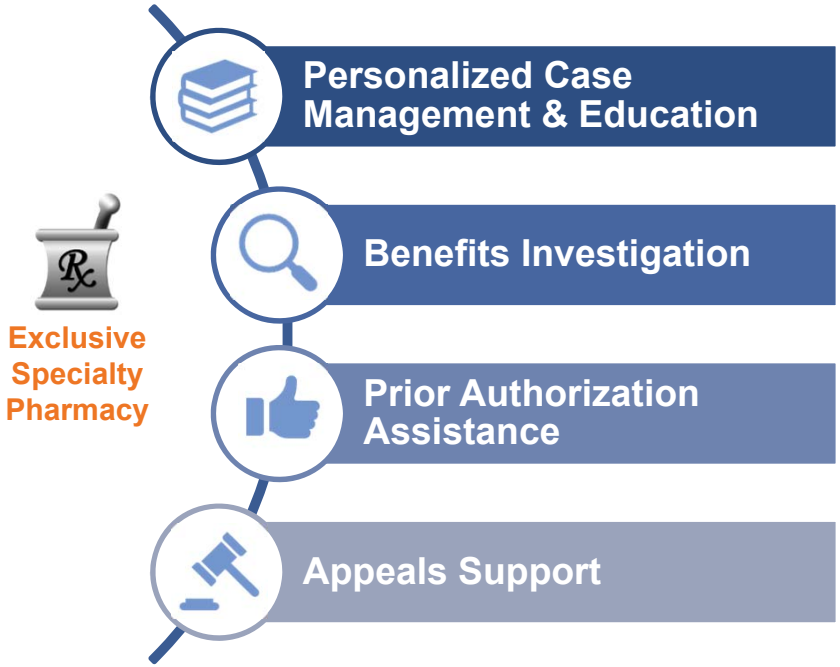
# A single site specialty pharmacy allows for broad patient access with low out-of-pocket costs




- Access to >200 million US lives (>85%)
- 48 states are covering Emflaza®
- Favorable gross to net (mid teens)

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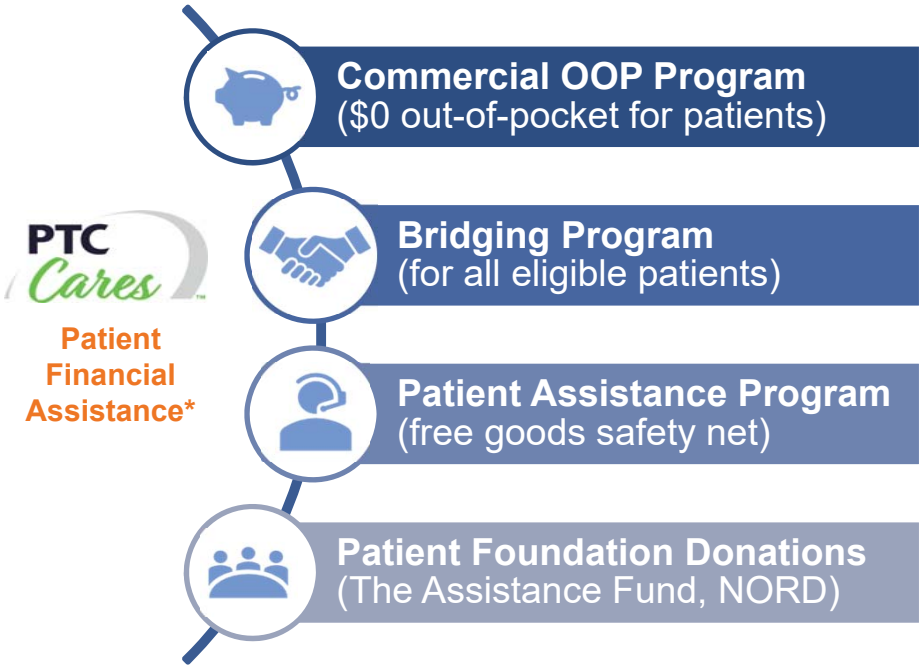
# The PTC patient support programs minimize patients' average monthly out-of-pocket (OOP) expenses




## Commercial Insurance Patients

- All commercial patients have qualified for OOP assistance

## Public Insurance Patients

- Public patients have a $0 or nominal monthly OOP expense
- Patients can also be referred to charitable foundations for additional support

***For eligible participants***
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# Number of key initiatives underway to achieve success in phase II of launch

**Phase II: Active or exposed steroid patients establish Emflaza as standard of care**


## Healthcare Professional Initiatives

- Published emerging data
- Medical education initiatives
- Conference presentations
- Emflaza Start Program

## Patient and Caregiver Initiatives

- Patient and caregiver local meetings
- New Emflaza education campaign
- Digital and social media
- Public relations

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# Substantial evidence of Emflaza®'s differentiation

**McDonald, et al (*Lancet*)**
*10-Year Natural History Study (CINRG)*

**ACT DMD SOC (publication under review)**
*Placebo arm of PTC trial*

**Collaborative Trajectory Analysis Project**
*Meta analysis of PTC and Eli Lilly trials*

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# Published evidence of Emflaza®'s benefits

Emflaza® (deflazacort)

| | |
|---|---|
| Preserve muscle function (through reduced change in 6MWD and TFTs)[1,2] | Reduce the risk of developing scoliosis and delay the need for spinal surgery[2] |
| Delay loss of ambulation[1,3,4] | Preserve pulmonary function and delay need for nocturnal ventilation[2] |
| Result in significantly less weight gain compared to prednisone[5] | Prolong survival in the second decade of life[2] |

6MWD = 6-minute walk distance; TFT = timed function test.

**1.** Narayanan S, et al. Disease burden and treatment landscape in Duchenne muscular dystrophy in the United States. Poster presented at: ISPOR 22nd Annual International Conference; May 23, 2017; Boston, MA. **2.** Biggar WD, et al. *Neuromuscul Disord*. 2006;16(4):249-255. **3.** Bello L, et al. *Neurology*. 2015;85(12):1048-1055. **4.** Wang RT, et al. *PLoS Curr*. 2014;6. **5.** Bonifati MD, et al. *Muscle Nerve.* 2000;23(9):1344-1347.

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# Strategy to penetrate the segment of untreated DMD patients

**Phase III: Corticosteroid-naïve patients ensure all Duchenne patients receive SOC**

## Major Emflaza® initiatives:

- Expand label for pediatric 2- to 5-year-olds
- Continued analysis of clinical data
- Additional medical education initiatives
- Expanded education to payers and patient advocacy groups
- Lifecycle initiatives

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# Potential brand expansion & post-marketing commitments

| | |
|---|---|
| **Pediatric Trial (≥2 to <5 years old)** | **Potential Formulation(s)** |
| **New Therapeutic Areas/ Indications** | **Post-Marketing Requirements** |

Leadership strategic direction on potential value creation opportunities for the brand.

# PTC is the leader in DMD treatment
# 2 of 3 approved products

- Translarna is the first-ever targeted therapeutic approved for DMD anywhere in the world (EMA, 2014)
- Translarna is now available in >40 countries worldwide
- Emflaza is the first-and-only corticosteroid approved specifically for DMD anywhere in the world (US, 2017)
- PTC DMD franchise is now helping many thousands of families living with Duchenne around the world

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# Execution of key initiatives will result in US market leadership

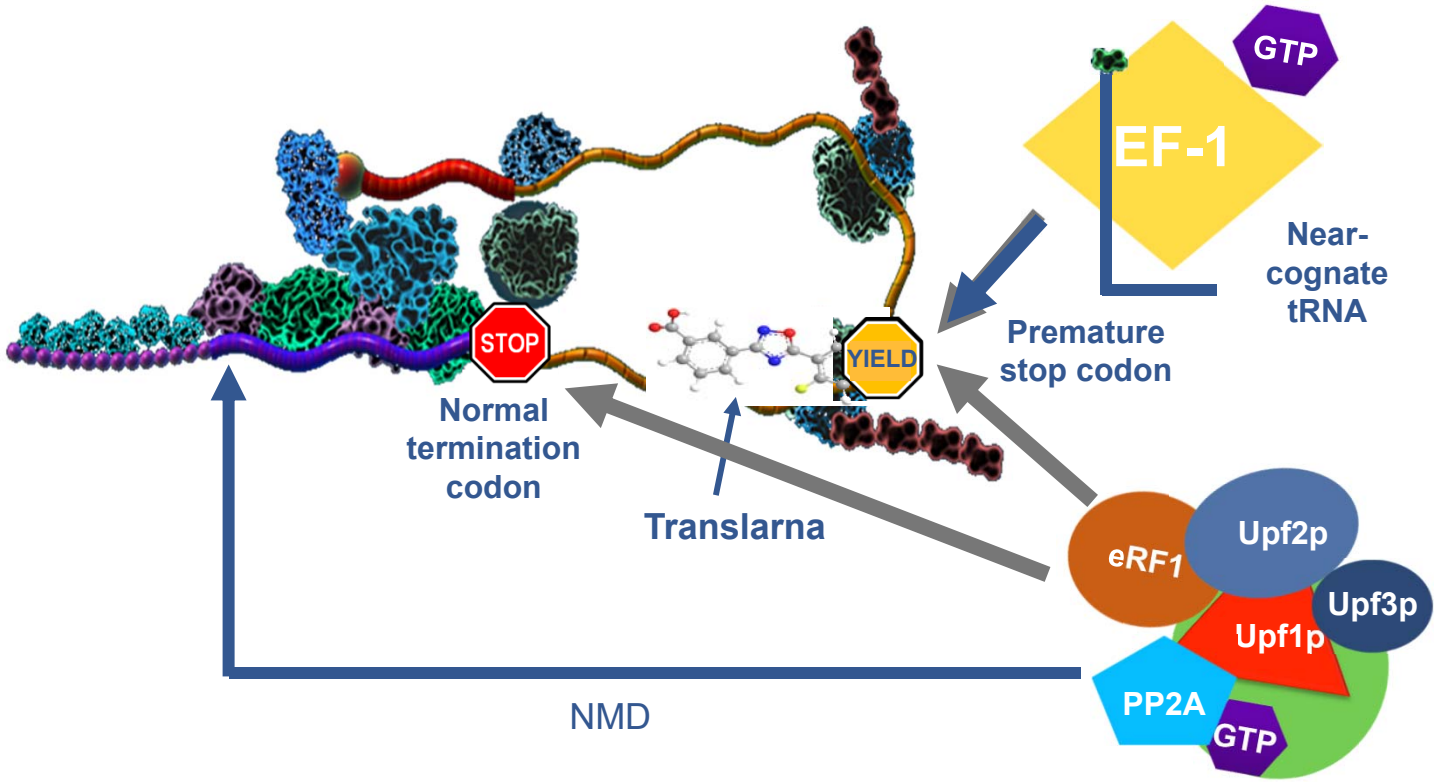
## Market Leadership

- Emflaza® is the leading **prescribed brand** for DMD
- Emflaza is on the path to become the new standard of care
- US market will be a significant growth engine for PTC

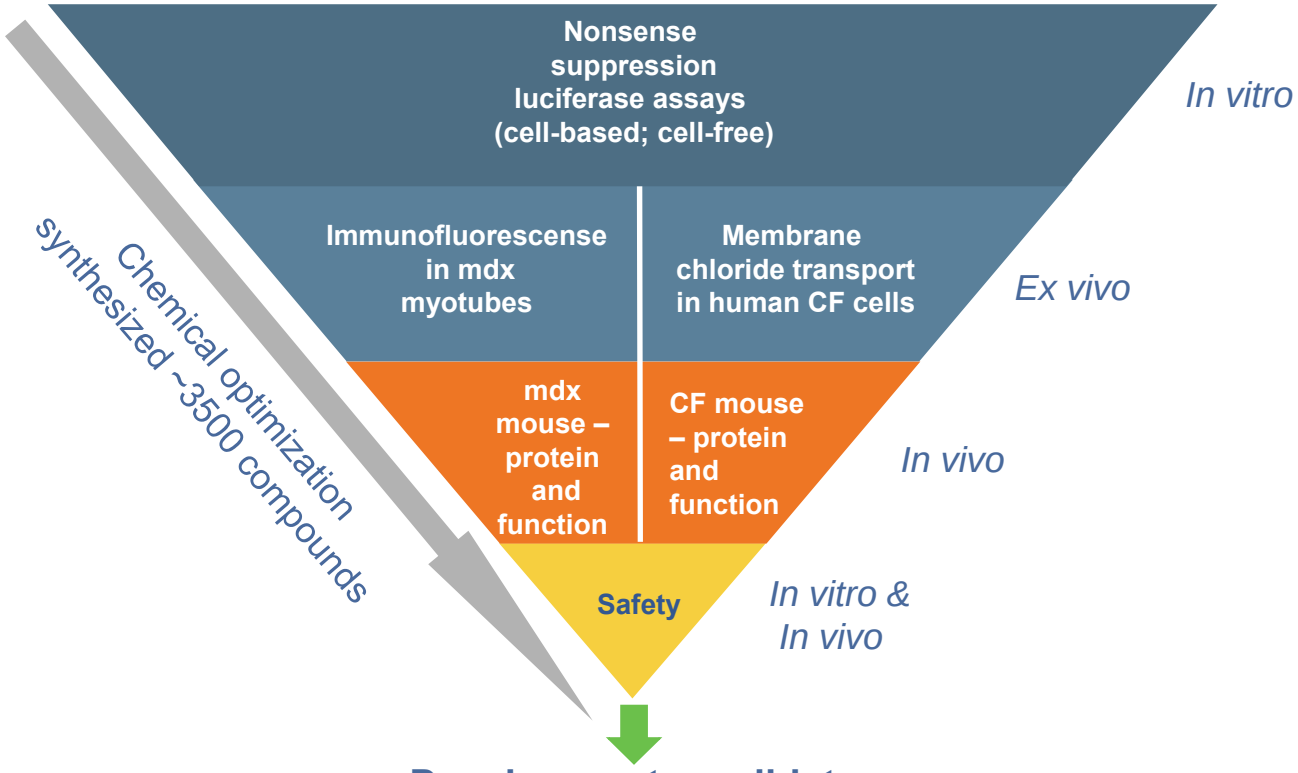

# Translarna MOA and beyond

Ellen Welch, SVP Genetic Disorders & Translational Medicine

# Premature termination differs from normal termination



# Path to discover Translarna



# Translarna-mediated readthrough in the literature

**Muscle disease**
- DMD (Welch 2007; *Kayali 2012;* Finkel 2013; *Li 2014;* Bushby 2014; McDonald 2017)
- Miyoshi Myopathy (Wang 2010)

**Neurological disorders**
- Infantile Neuronal Ceroid Lipofuscinoses (INCL) (*Sarkar 2011; Miller 2013; Miller 2015*)
- Late Infantile Ceroid Lipofuscinoses (LINCL) (*Miller 2013; Yu 2013*)
- Ataxia telangiectasia (*Du 2013*)
- Usher Syndrome (USCH1C) (*Goldmann 2011; Goldmann 2012*)
- Krabbe (GALC) (*Lubbi 2016*)

**Pulmonary disease**
- Cystic fibrosis (CF) (Du 2008; Kerem 2008; Sermet-Gaudelus 2010; Wilshanski 2011; *Gonzalez-Hilarion 2012; Johansonn 2014*; Kerem 2014; *Pibiri 2015; Caldrer 2015*)
- Heritable pulmonary arterial hypertension (HPAH) (*Drake 2013*)

**Skin disease**
- Pseudoxanthoma Elasticum (*Zhou 2013*)
- Xeroderma Pigmentosum (*Kuschal 2013*)

**Premature aging**
- Werner Syndrome (*Argrelo 2015*)

**Oncology**
- p53 (Roy 2016)

*Light blue = Independent investigators*

**Eye disorders**
- Choroideremia (*Moosajee 2016*)
- Aniridia (*Gregory-Evans 2014; Wang 2017*)
- Retinitis Pigmentosa (*Schwartz 2015; Schwarz 2017*)
- Retinal dystrophies (*Ramsden 2017*)
- Usher syndrome (*Neuhaus 2017*)

**Ion channel disease**
- Long QT syndrome (*Yu 2014*)

**Metabolic disorders**
- Metabolic acidosis (*Fang 2015*)
- Carnitine Palmitoyltransferase 1A Deficiency (*Tan 2011*)
- Methylmalonic Aciduria (MMA) (*Buck 2010*)
- Propionic Acidemia (PA) (*Sanchez-Alcudia 2012*)
- Maroteaux-Lamy syndrome (MPS VI) (*Bartolomeo 2013; Gómez-Grau 2015*)
- Hurler's syndromes (MPS I) (Keeling, unpublished)
- MPS II (*Matalonga 2015*)
- MPS IIIB (Sanfilipo B) (*Matalonga 2015*)
- Niemman–Pick A/B (*Matalonga 2015*)
- San Filippo C (*Gómez-Grau 2015*)

**Reporter assays**
- GFP (*Lentini 2013; Shen 2014; Pibiri 2014; Pibiri 2015,* Roy 2016)
- FireflyLuciferase (*Lentini 2013; Pibiri 2014; Pibiri 2015*)
- NanoLuc (Roy 2016)



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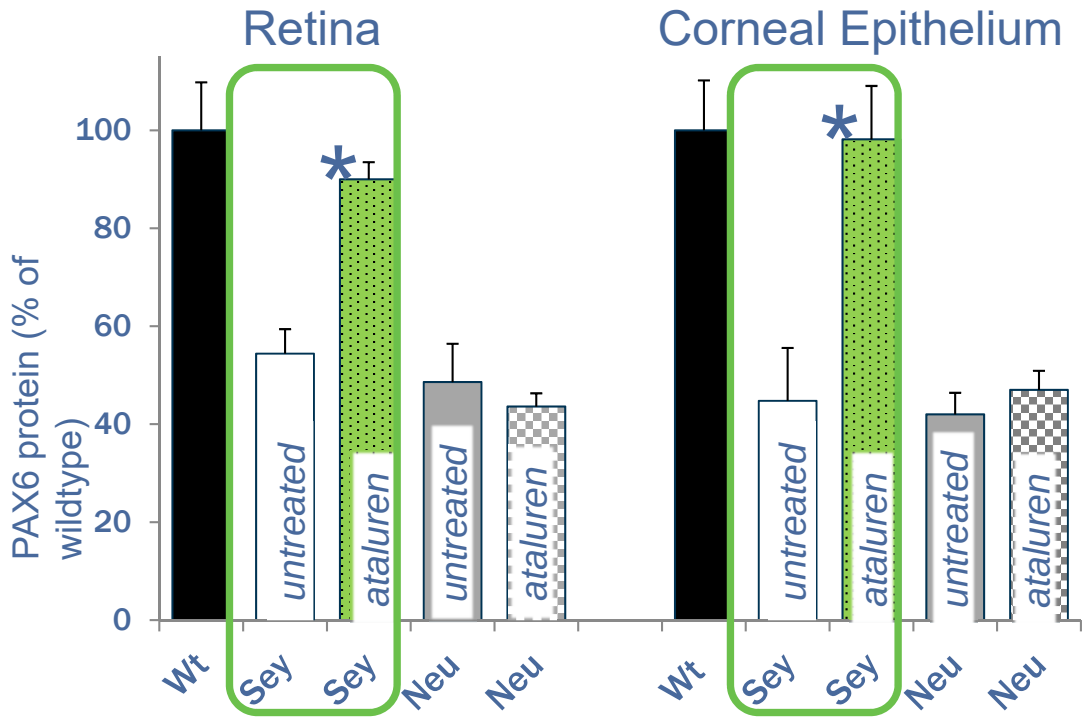
# Translarna treatment increases PAX6 protein in retina and cornea in the Sey nonsense mutation aniridia mouse model

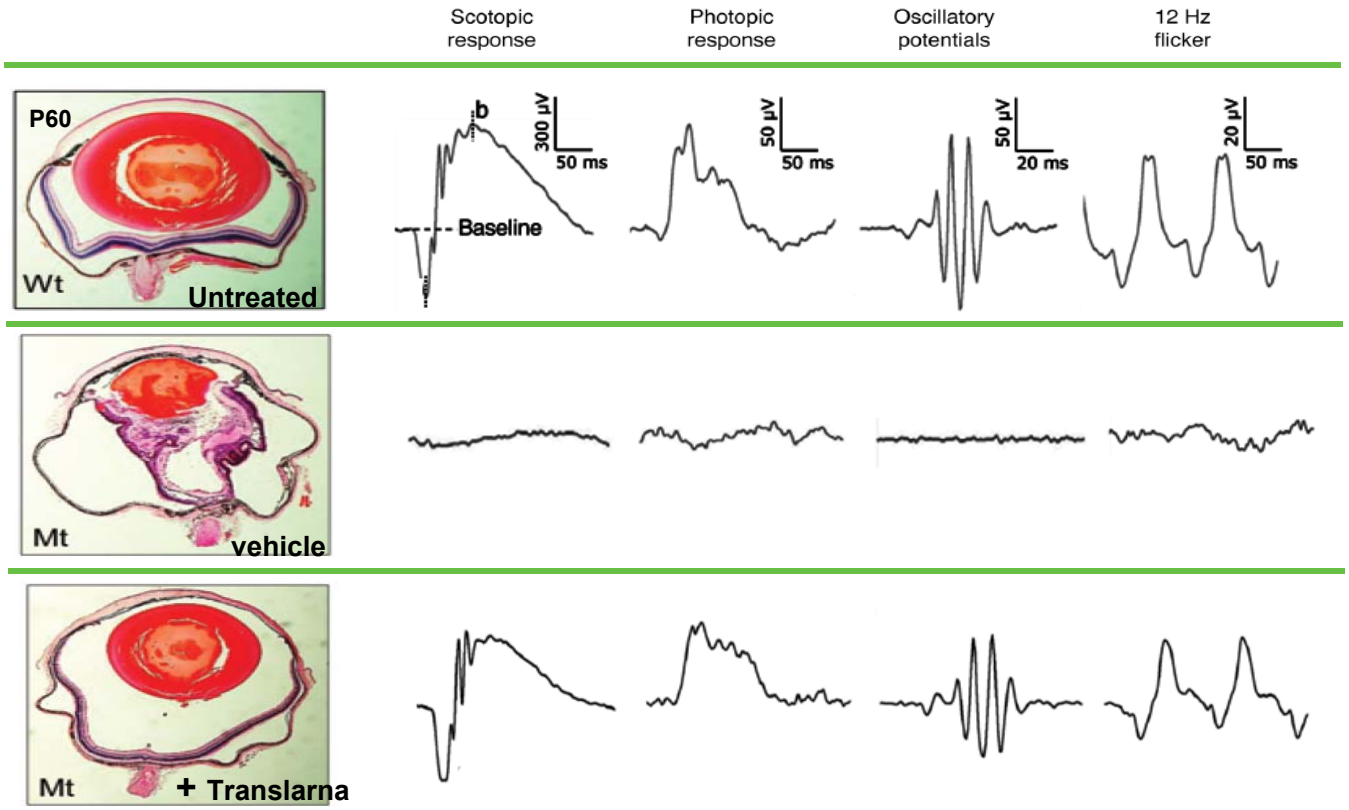



* $p<0.001$ (n=6)

No effect of Translarna on the *Neu* splice-site mutant

Gregory-Evans CY, et al. *J Clin Invest*. 2014;124(1):111-116.

# Translarna treatment restores morphology and sight in a nonsense mutation mouse model of aniridia

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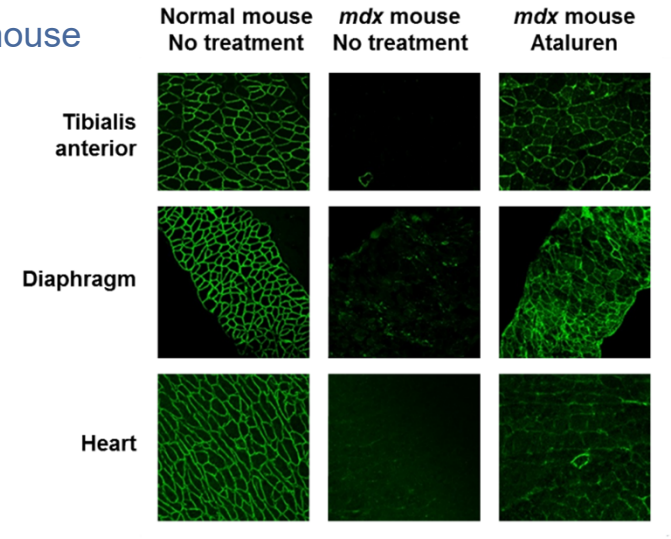
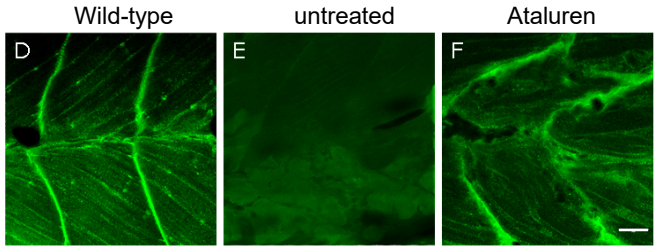
Gregory-Evans CY, et al. *J Clin Invest*. 2014;124(1):111-116.

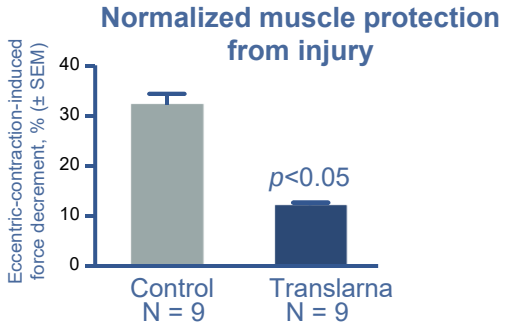
# Translarna treatment results in full-length functional dystrophin protein production in DMD animal models

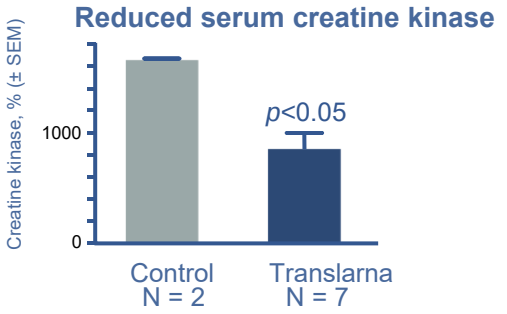
*mdx* mouse




nmDMD zebrafish



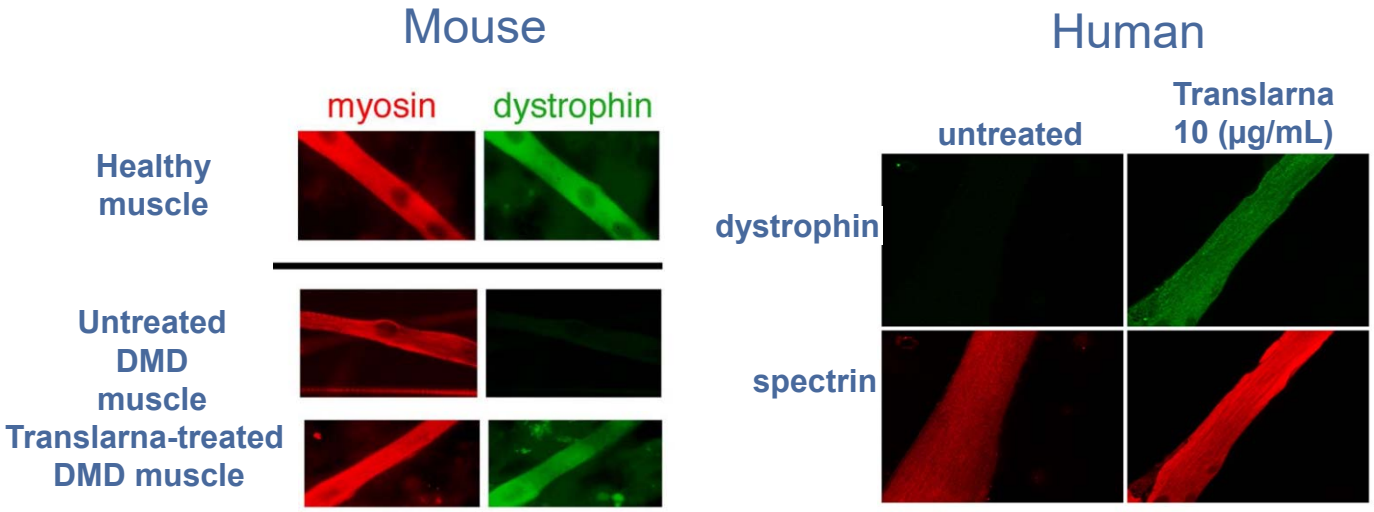





Kayali R, et al. *Hum Mol Genet.* 2012;21(18):4007-4020.
Welch RM, et al. *Nature*. 2007;447(7140):87-91.
Li *et al. FASAB J.* 2014

# Translarna increases dystrophin protein levels in mouse and human myotube cultures




Kayali R, et al. *Hum Mol Genet*. 2012;21(18):4007-4020.
Welch RM, et al. *Nature*. 2007;447(7140):87-91.

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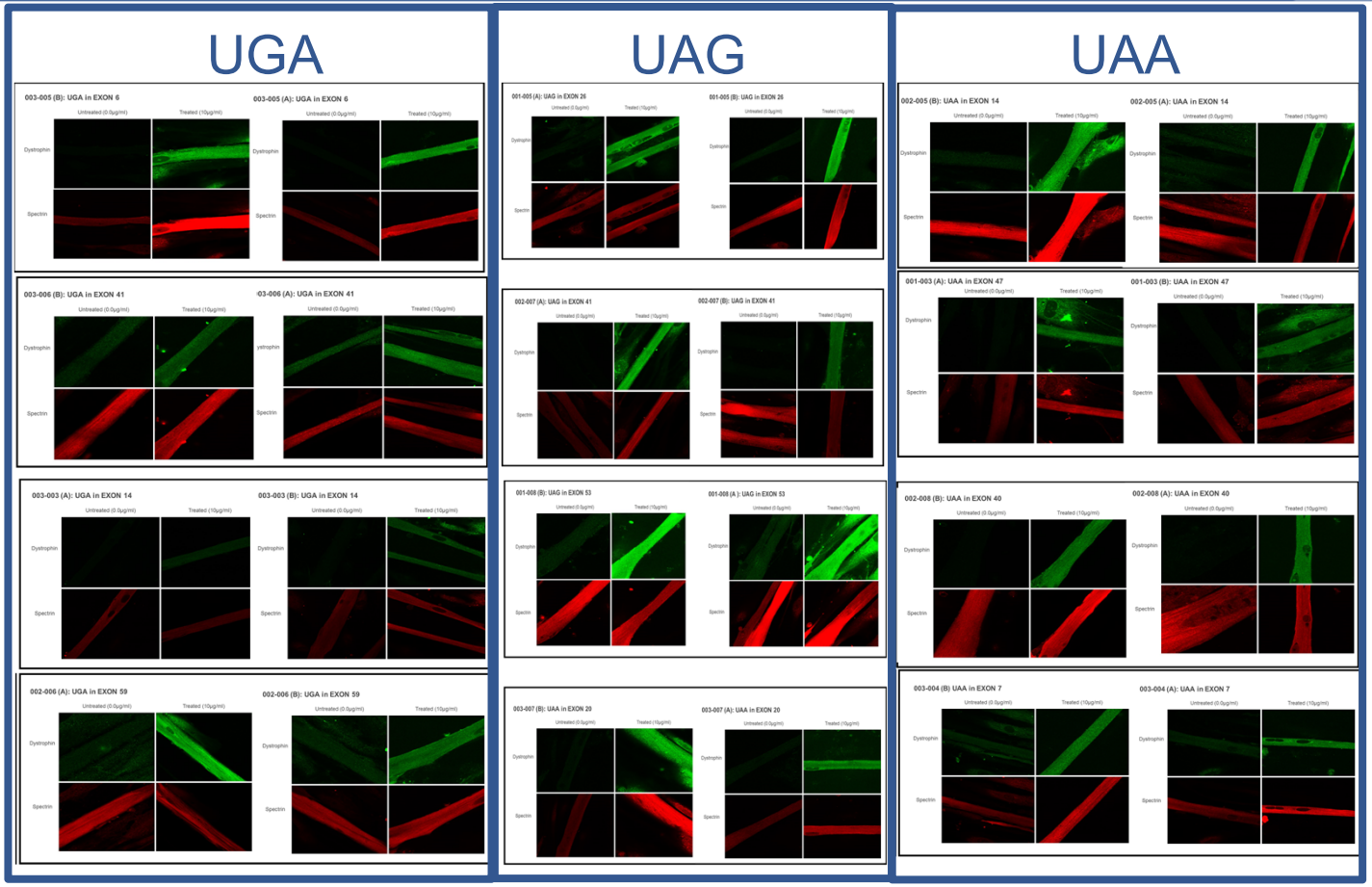
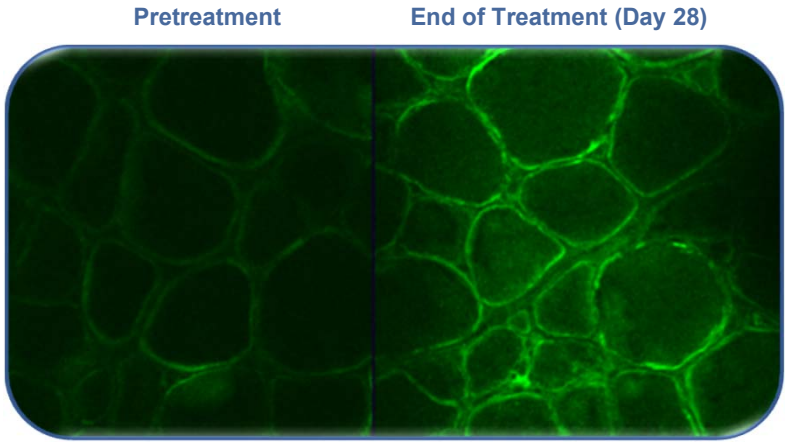
# Dystrophin is produced in all nonsense codon (UGA, UAG, UAA) myotube cultures treated with Translarna



# Increased dystrophin production in humans

## Phase 2a study

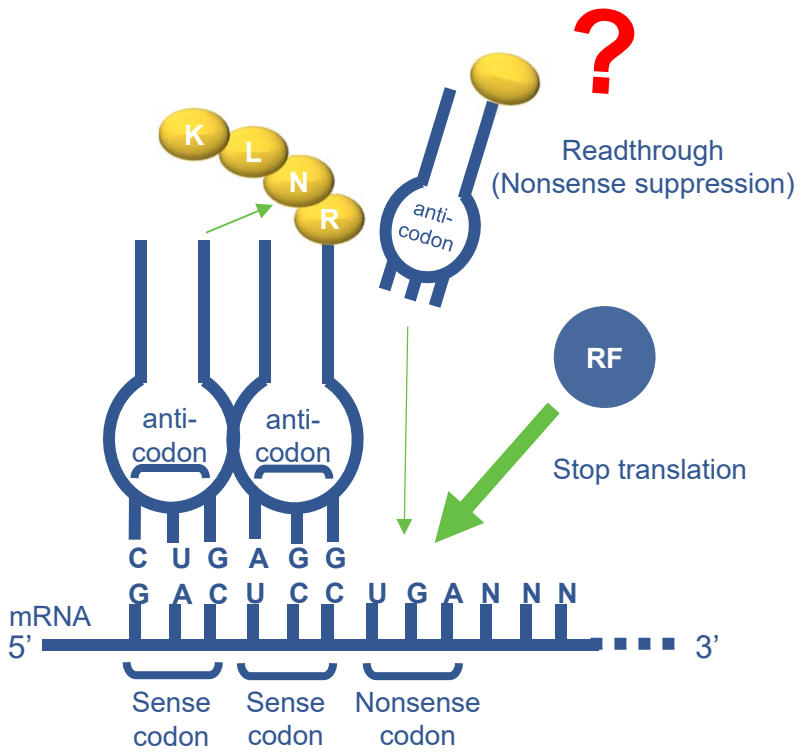
- Proof-of-concept study in patients with nonsense-mutation DMD
- Extensor digitorum brevis muscle biopsy from patients pre- and post-treatment
- Key finding: 61% of patients showed an increase in dystrophin staining after 28 days of treatment; the mean increase in dystrophin was 11%



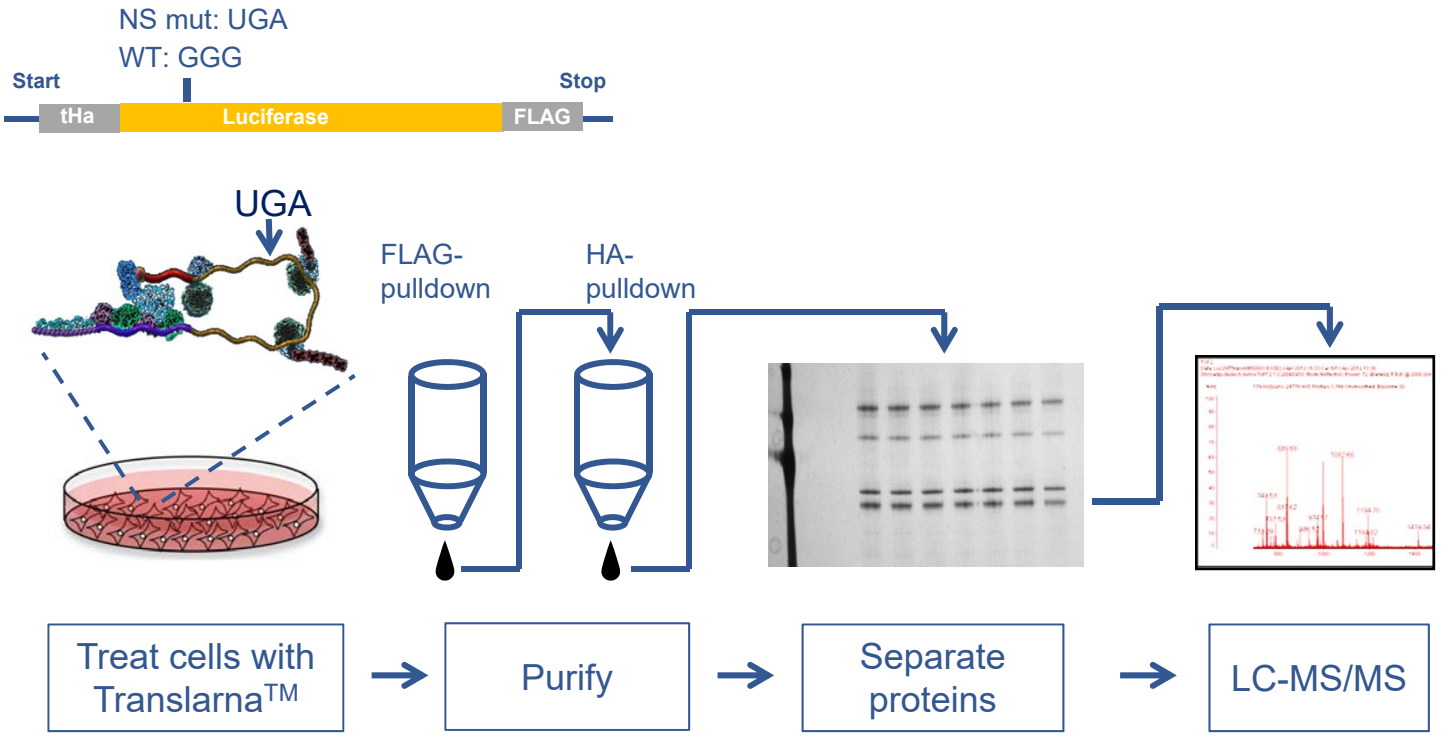

*P*= 0.008

Finkel 2013

# Determining which amino acid is inserted at a PTC by Translarna treatment



# Developed a method to purify the full-length protein produced by treatment with Translarna



# Amino acids incorporated at the site of each premature stop codon

| UGA | UAA | UAG |
|---|---|---|
| Arginine | Tyrosine | Tyrosine |
| Tryptophan | Glutamine | Glutamine |
| Cysteine[T] | Lysine[T] | Tryptophan[T] |

[T]<2% incorporation

The identities of the amino acids and the frequencies of the amino acid insertions are very similar to those observed from endogenous readthrough

# Amino acid incorporation summary

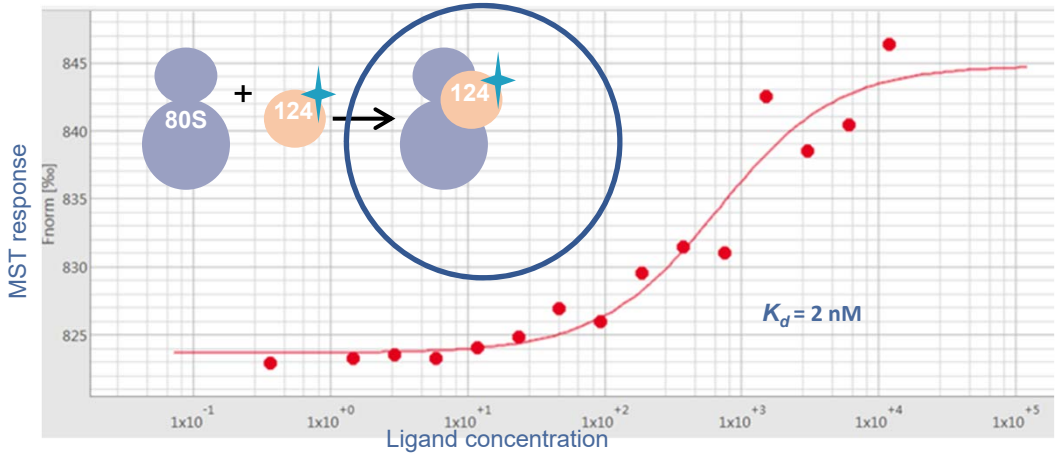
- Natural readthrough predominantly occurs through mispairing at the first or third codon positions
- Translarna alters the frequency of mispairing at the first or third codon positions
- Readthrough-induced proteins are functional

# MicroScale Thermophoresis (MST) to assay ribosome binding of readthrough compounds

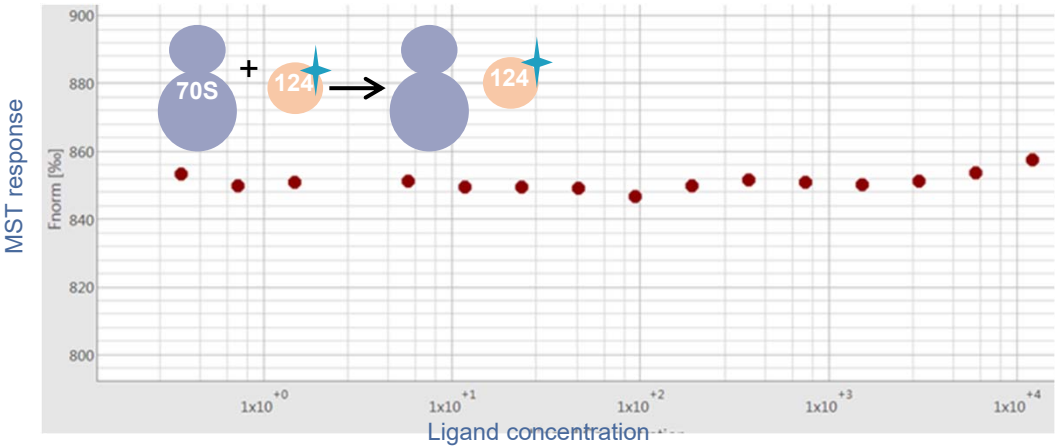
## Series of control experiments performed

| Control | Interaction |
|---|---|
| Gentamicin + prokaryotic ribosome | Yes |
| Gentamicin + eukaryotic ribosome | Yes |
| Gentamicin + small ribosomal subunit | Yes |
| Gentamicin + RNA binding site RNA fragment | Yes |
| Gentamicin + random RNA fragment | No |
| Compound that does not bind ribosome | No |

# Translarna binds to eukaryotic ribosome




**Human ribosomes**

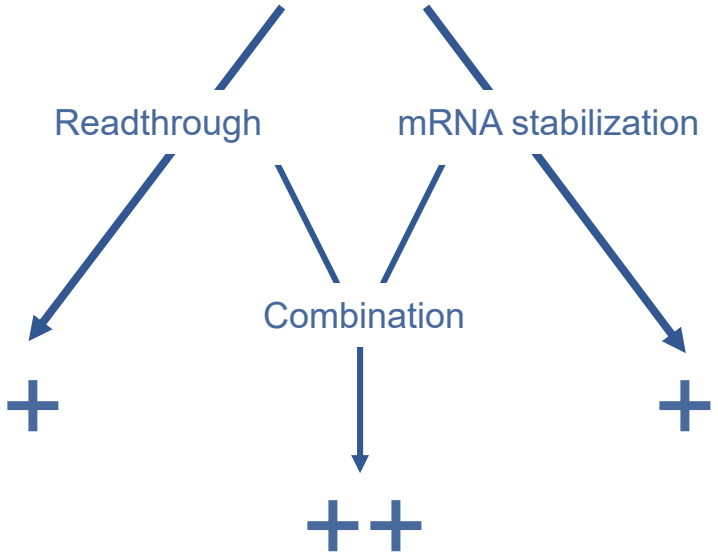



***E. coli* ribosomes**

# The fate of an mRNA that harbors a premature termination codon

UGA

- No full-length protein produced
- Reduced mRNA abundance due to mRNA decay




**Next gen development underway**

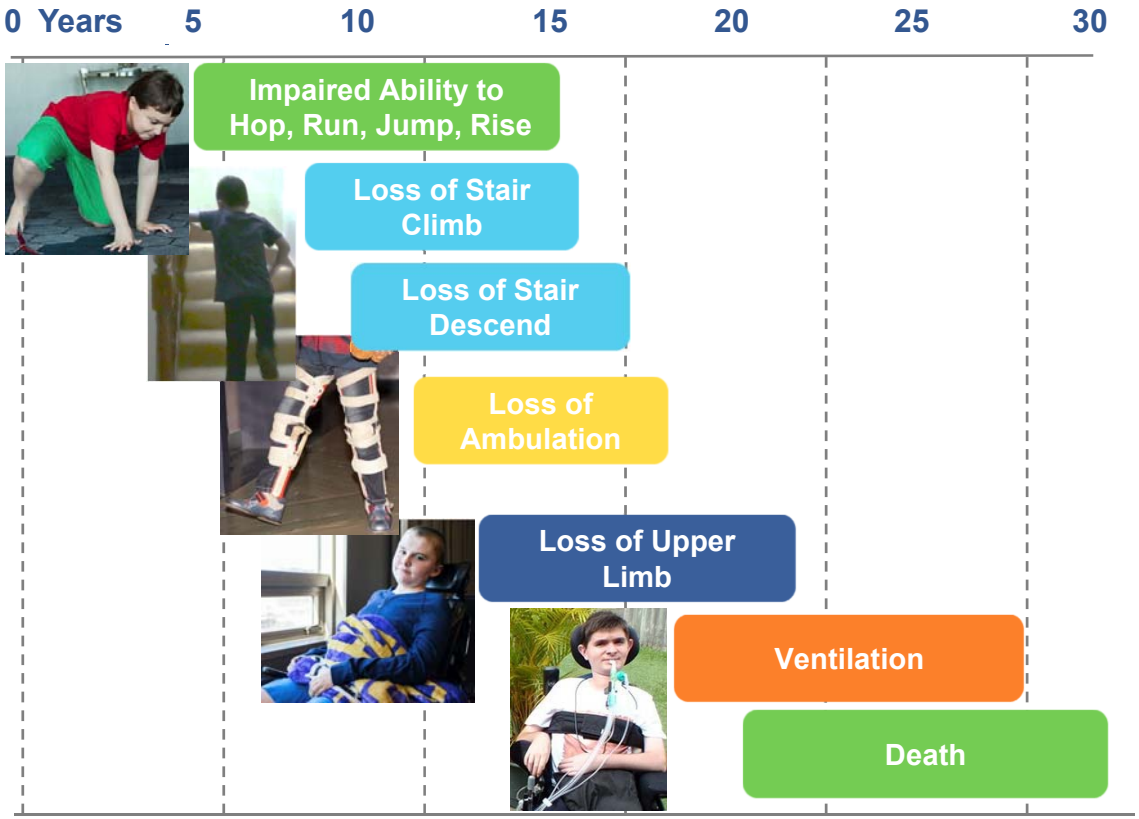
# Summary of non-sense program

- Translarna treatment promotes readthrough at nonsense codons in many disease models
- Allows insertion of a defined set of amino acids at the site of the nonsense codon
- Interacts with the ribosome
- New chemical matter identified
  - Enhanced activity with Translarna
  - Stabilization of nonsense containing mRNAs


# DMD Franchise Development & Lifecycle Management

Joe McIntosh, SVP Head of Clinical Development

# DMD progression is sequential, non-linear, and irreversible




Early Physical Manifestations

*Loss of ambulation is predictive of late physical manifestations*

Late Physical Manifestations

# A large body of clinical evidence supports Translarna™'s benefit in nmDMD

## Past

2008-2009

**Study 007**
**(RCT)**
**48 weeks**
**N=174**

2013-2015

**Study 020**
**(RCT)**
**48 weeks**
**N=228**

2012-2018

**Study 016/19**
**(Long-term study)**
**~3.5 years***
**N=94**

**Study 30**
**Pediatric**
**(2-5 yrs old)**
**N=14**

## Future

**Study 025**
**STRIDE registry**
**N=200**

**Preservation of function**

**Study 041**
**(RCT)**
**144 weeks**
**N=250**

**Provide additional pivotal data**

**Pioneering the understanding of the DMD natural history**

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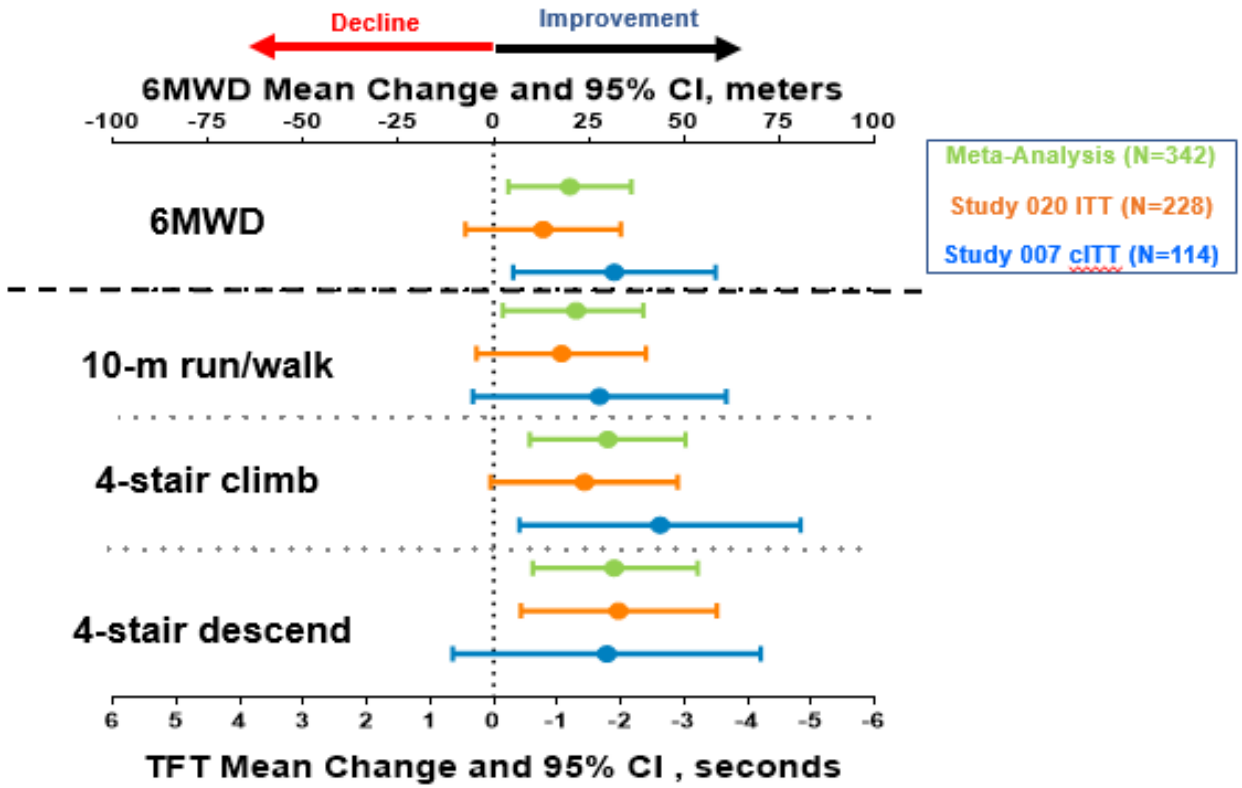
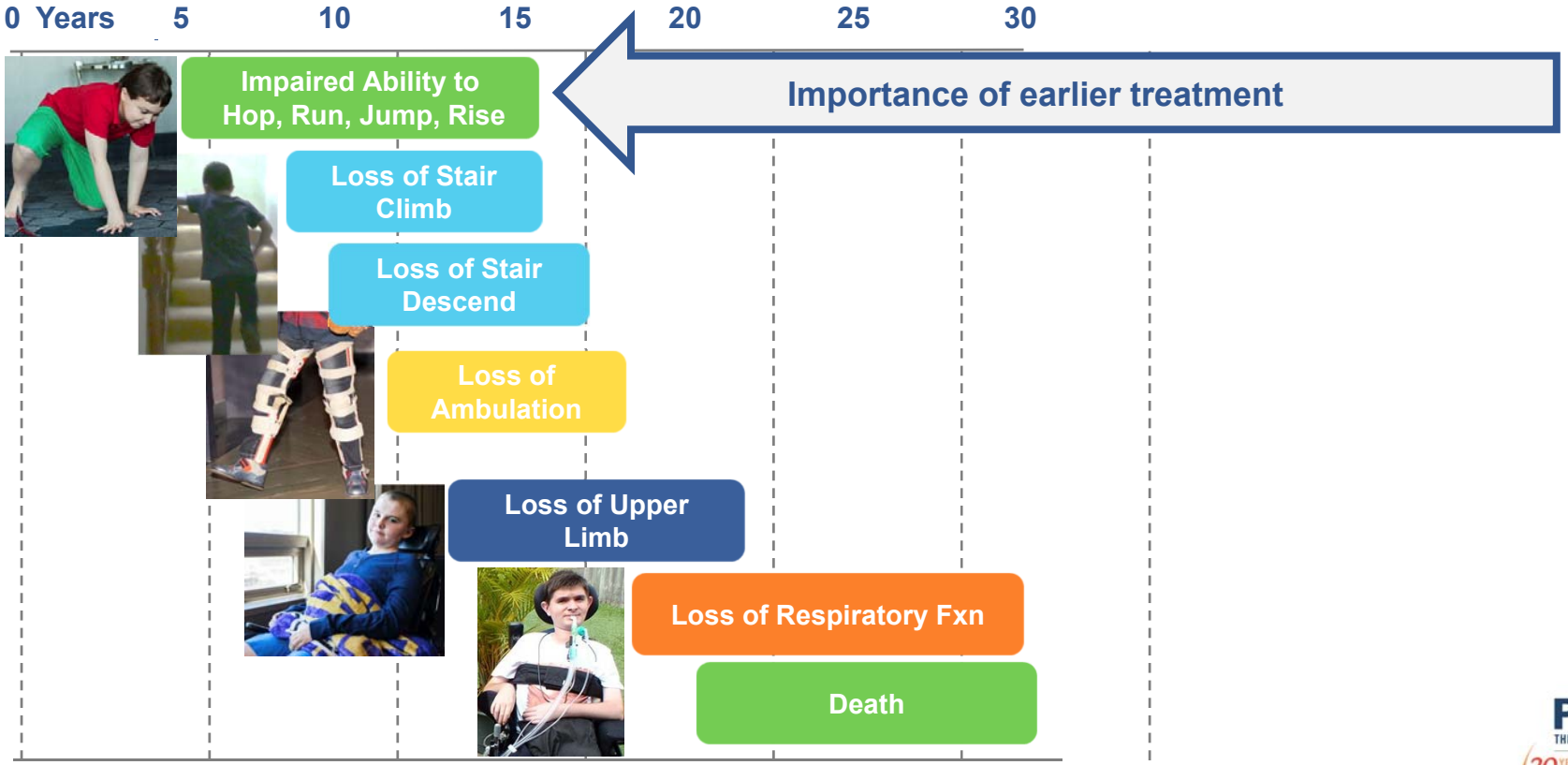
*Median exposure

# Positive benefit seen in Translarna™- treated patients across muscle function outcomes



# ~20 years studying DMD highlights importance of early treatment in patients

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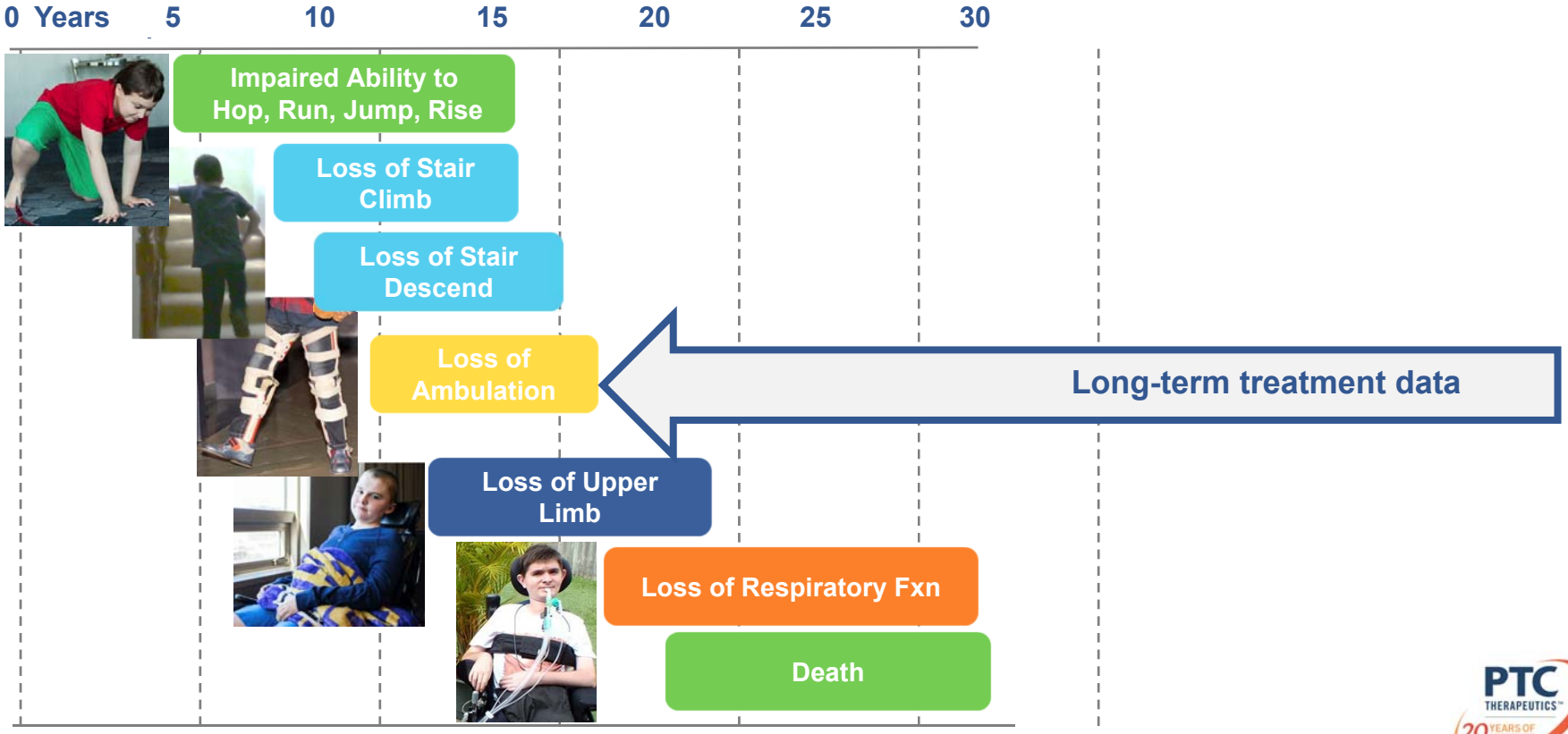
# Exposures in 2-5 year olds were comparable with those seen in nmDMD patients >5 years of age

- Concentration/time profiles of 2-5 year of age are within the range associated with efficacy in older children
- Extrapolation for efficacy and safety to patients >5 years can be performed on PK
- EU filing under review to expand from current-label children to nmDMD >2 years of age

**Addressed EMEA review questions**
**Expect CHMP decision mid-2018**

# Long-term benefits are observed when measuring DMD functional milestones

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# Long-term studies required to fully demonstrate the benefit in DMD

## Long-term effects of glucocorticoids on function, quality of life, and survival in patients with Duchenne muscular dystrophy: a prospective cohort study

Craig M McDonald, Erik K Henricson, Richard T Abresch, Tina Duong, Nanette C Joyce, Fengming Hu, Paula R Clemens, Eric P Hoffman, Avital Cnaan, Heather Gordish-Dressman, and the CINRG Investigators*

**Summary**

**Background** Glucocorticoid treatment is recommended as a standard of care in Duchenne muscular dystrophy; however, few studies have assessed the long-term benefits of this treatment. We examined the long-term effects of glucocorticoids on milestone-related disease progression across the lifespan and survival in patients with Duchenne muscular dystrophy.

Published Online
November 22, 2017
http://dx.doi.org/10.1016/S0140-6736(17)32160-8

See Online/Comment

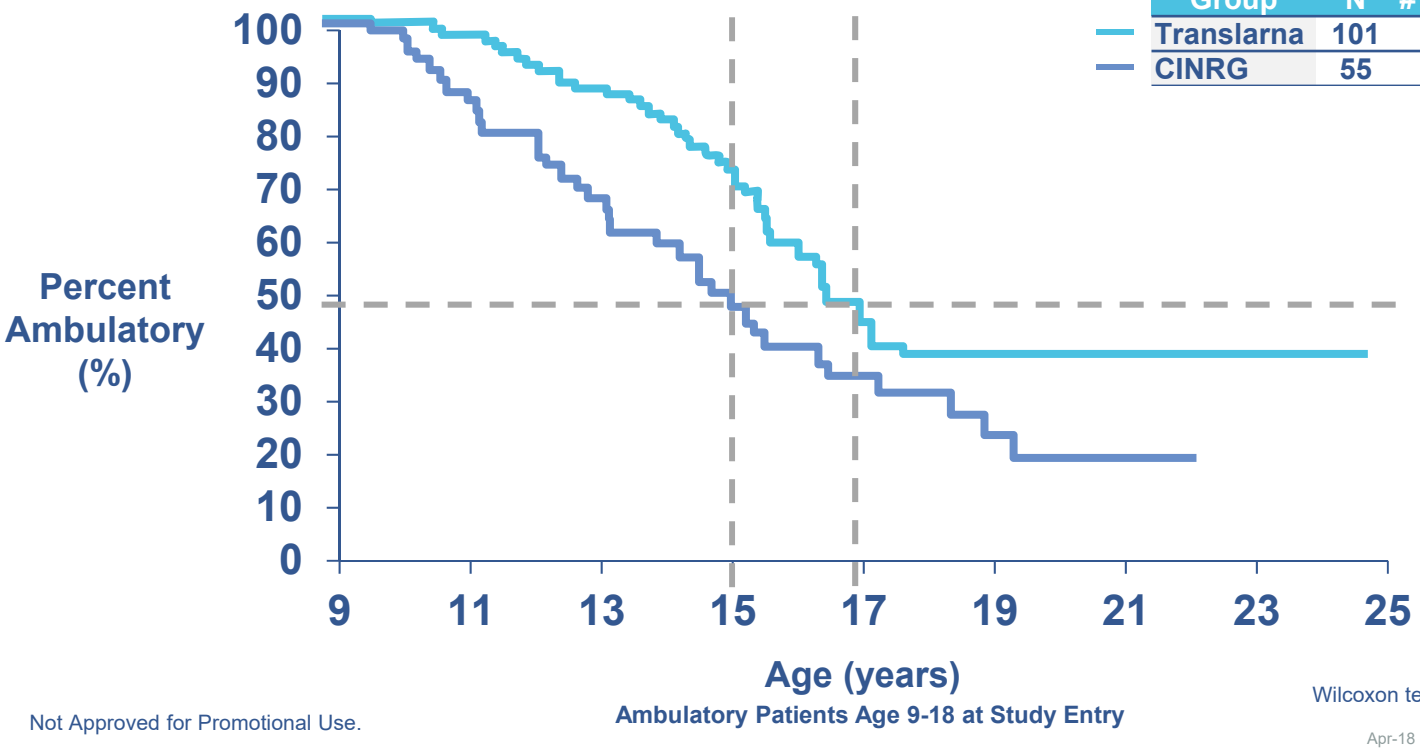
# Long-term, open-label studies allow assessment of benefit on ambulatory and respiratory milestones

**Patients from other Translarna trials continued into:**

- **Study 16**
  - US
  - N=144
  - Measured loss of ambulation
- **Study 19**
  - Ex-US
  - N=94
  - Measured loss of ambulation and pulmonary function

# Consistent benefit in preservation of ambulation in preliminary ongoing 019-016 Translarna vs CINRG

| Group | N | # LOA | % LOA | Median Age at LOA |
|---|---|---|---|---|
| Translarna | 101 | 45 | 44.6 | 16.8 |
| CINRG | 55 | 35 | 63.6 | 15.0 |




Ambulatory Patients Age 9-18 at Study Entry

Wilcoxon test $P = 0.0029$

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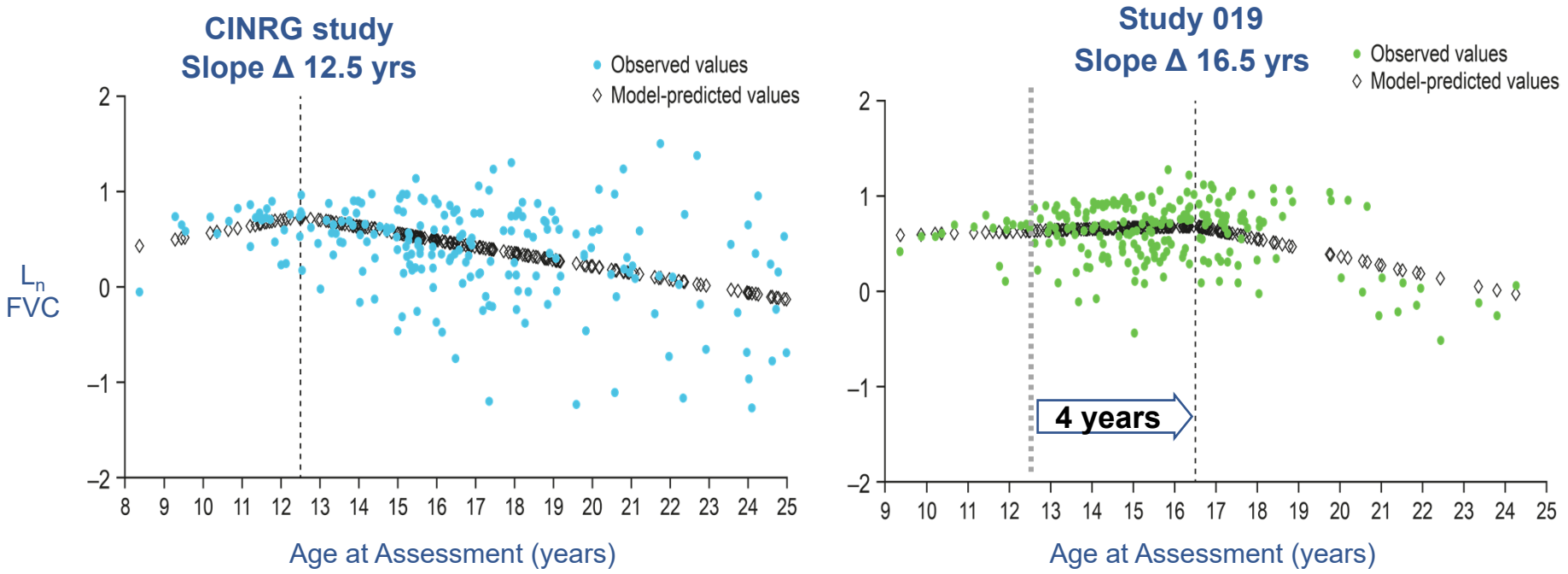
# Study 019: Extension data support preservation in pulmonary function by 4 years with Translarna™



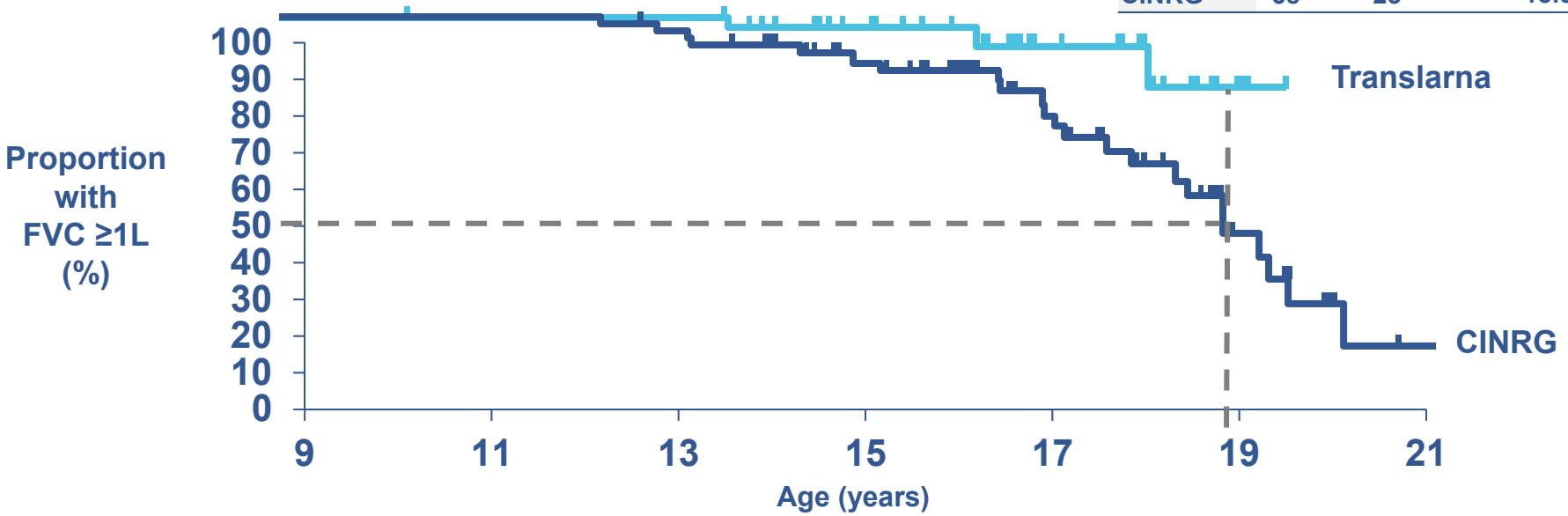

**Absolute FVC Change = 13.8%* compared to matched CINRG patients**

Breakpoints in slope with regard to age are indicated. 238 assessments from 114 patients included from the CINRG study; 259 assessments from 54 patients included from study 019. Matched based on age and steroid use. **P*=0.005

Not Approved for Promotional Use.

# Study 019: Age at transition to FVC <1L in Translarna vs CINRG non-ambulatory patients

| Group | N | # FVC <1L | Median age at FVC <1 L |
|---|---|---|---|
| Study 019 | 38 | 3 | Not reached |
| CINRG | 58 | 23 | 18.8 |




**Lung vital capacity (FVC) <1L predictive of mortality in 1 year**

Not Approved for Promotional Use.

Log-rank *P*=0.0317
CINRG study matched based on age and steroid use.

PTC THERAPEUTICS 20 YEARS OF COMMITMENT

# STRIDE registry (Study 025)

- Long-term follow up of patients receiving Translarna™ commercially
- Goal to enroll 200 patients, achieved March 2018
- Preliminary results show continuous benefit for patients receiving Translarna with a reduction in decline when compared to natural history
- Data expected to be presented in future scientific meetings

# Continue to study benefit of Translarna™ to expand patient access

- PK data submitted for potential label expansion in 2-5 years of age
  - Potential to expand treatable population by 20%
- Long-term data collected for potential non-ambulatory application label expansion (~60% DMD patients non-ambulatory)
- STRIDE registry provides real-world data, and preliminary data suggest delaying of disease progression

# Additional Studies Required to Secure US Approval

# Path for potential US DMD approval

- The aim of this study is to demonstrate dystrophin expression with Translarna therapy using newer quantifications techniques
- The projected study would have pre-treated and untreated cohorts
- Final design, biopsy methodology, and dystrophin assessment methodology are being finalized
- We expect to start the study before YE:18
- Once these data are available we intend to submit with the current NDA to pursue accelerated approval in the US

# Study 041: Placebo-controlled study underway

- Leverages our deep understanding of DMD natural history to maximize success
- Primary analysis focuses on an enriched patient population (i.e. the transition phase)
- Targets enrollment of N=250 patients with enriched sub-population of N=160
- Designed post-market study to support potential full approval of Translarna in nmDMD
- Study is open and enrolling, expected to fully enroll before YE:18

# Translarna-mediated readthrough in the literature

## Muscle disease

- DMD (Welch 2007, *Kayali 2012*, Finkel 2013, *Li 2014*; Bushby 2014)
- Miyoshi Myopathy (Wang 2010)
- Cardiomyopathy *(Lee 2017)*

## Neurological disorders

- Infantile Neuronal Ceroid Lipofuscinoses (INCL) (*Sarkar 2011; Miller 2013; Miller 2015*)
- Late Infantile Ceroid Lipofuscinoses (LINCL) (*Miller 2013, Yu 2013*)
- Ataxia telangiectasia (*Du 2013*)
- Usher Syndrome (USCH1C) (*Goldmann 2011; Goldmann 2012*)
- Krabbe (GALC) (*Lubbi 2016*)

## Pulmonary disease

- Cystic fibrosis (CF) (Du 2008, Kerem 2008, Sermet-Gaudelus 2010, Wilshanski 2011, *Gonzalez-Hilarion 2012; Johansonn 2014*; Kerem 2014; *Pibiri 2015; Caldrer 2015*)
- Heritable pulmonary arterial hypertension (HPAH) (*Drake 2013*)

## Skin disease

- Pseudoxanthoma Elasticum (*Zhou 2013*)
- Xeroderma Pigmentosum (*Kuschal 2013*)

## Premature aging

- Werner Syndrome (*Argrelo 2015*)

## Eye disorders

- Choroideremia (*Moosajee 2016*)
- Aniridia (*Gregory-Evans 2014; Wang 2017*)
- Retinitis Pigmentosa (*Schwartz 2015;Schwarz 2017*)
- Retinal dystrophies (*Ramsden 2017*)
- Usher syndrome (*Neuhaus 2017*)

## Ion channel disease

- Long QT syndrome (*Yu 2014*)

## Metabolic disorders

- Metabolic acidosis (*Fang 2015*)
- Carnitine Palmitoyltransferase 1A Deficiency (*Tan 2011*)
- Methylmalonic Aciduria (MMA) (*Buck 2010*)
- Propionic Acidemia (PA) (*Sanchez-Alcudia 2012*)
- Maroteaux-Lamy syndrome (MPS VI) (*Bartolomeo, 2013; Gómez-Grau 2015*)
- Hurler's syndromes (MPS I) (Keeling, unpublished)
- MPS II (*Matalonga 2015*)
- MPS IIIB (Sanfilipo B) (*Matalonga 2015*)
- Niemman–Pick A/B (*Matalonga 2015*)
- San Filippo C (*Gómez-Grau 2015*)

## Oncology

- p53 (Roy 2016)

## Reporter assays;

- GFP (*Lentini 2013; Shen 2014; Pibiri 2014; Pibiri 2015;* Roy 2016)
- FireflyLuciferase (*Lentini 2013; Pibiri 2014; Pibiri 2015*)
- NanoLuc (Roy 2016)

Not Approved for Promotional Use.

*Light blue = Independent investigators*



PTC THERAPEUTICS 20 YEARS OF COMMITMENT

# Progressing proof of concept studies
# Aniridia and Dravet/CDKL5

**20-40%**
**Aniridia**
nonsense mutation

**50% Dravet**
**10% CDKL5**
nonsense mutation

## Aniridia

- 12-month placebo-controlled trial
- Additional 12-month therapy added to account for rate of disease progression
- Primary endpoint: PAX6 levels, eye function
- Enrollment is complete, with 36 enrolled patients

## Dravet/CDKL5: Genetic epilepsy

- 32-weeks placebo-controlled cross-over trials
- Primary endpoint number of monthly seizures
- Still enrolling to get a target of 12 patients

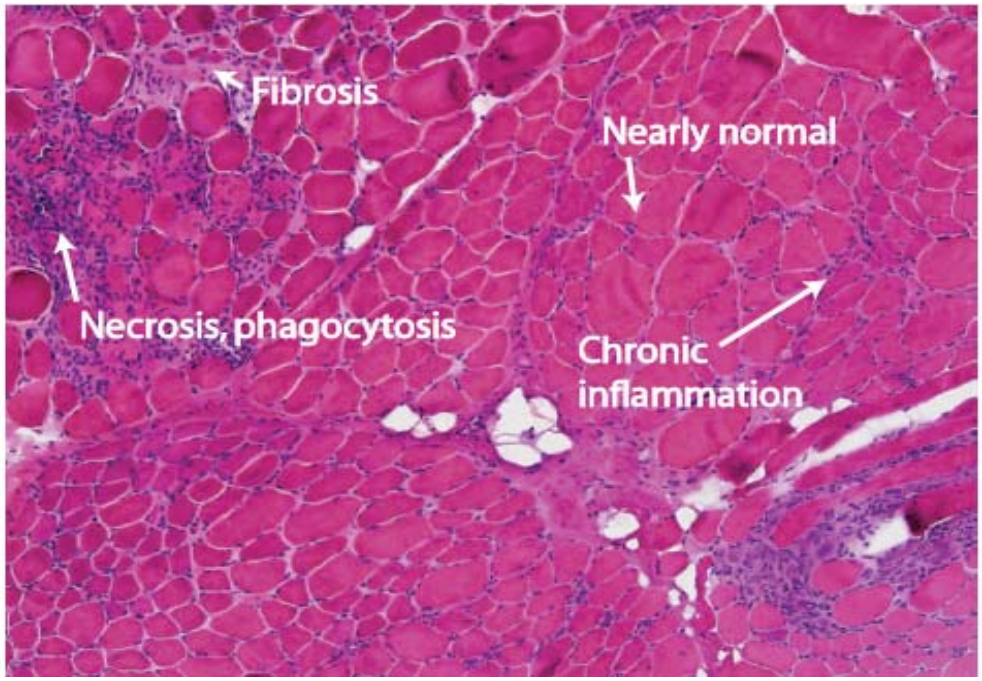
**Data from both studies expected in 2019**

# Translarna market expansion plan includes a label expansion and new country submissions

- Addressed EMA review questions for label expansion to include children 2-5 years of age
  - Expect CHMP decision in mid-2018
- Global market expansion with regulatory submissions
- Non-ambulatory expansion strategy being finalized in mid-2018

# Emflaza®: Differentiated Corticosteroid with Improved Outcomes

# Absence of dystrophin leads to muscle degeneration through inflammatory process

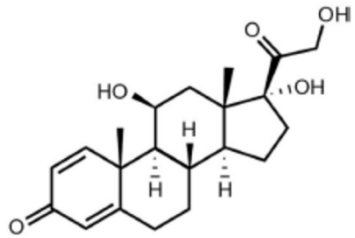



- **Muscle biopsy from a patient with DMD demonstrates:**
  - Chronic inflammation between myofibers
  - Phagocytosis by neutrophils and macrophages
  - Necrosis and fibrosis

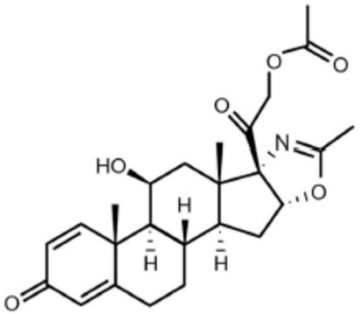
Rosenberg AS, et al. *Sci Transl Med.* 2015;7(299):299rv4.

# Pharmacologic differences between Emflaza® and other corticosteroids

- Emflaza is a synthetic corticosteroid with structural differences from prednisone:
  - Higher anti-inflammatory effect
  - Lower mineral corticoid effect
  - Longer duration of action than other glucocorticoids



Prednisolone



Deflazacort



Parente L. *BMC Pharmacol Toxicol*. 2017;18(1):1 doi:10.1186/s40360-016-0111-8..

# Data Differentiating the Efficacy Benefit of Emflaza® in DMD

# Recent publication of long-term natural history data that support the benefit of Emflaza®



## Long-term effects of glucocorticoids on function, quality of life, and survival in patients with Duchenne muscular dystrophy: a prospective cohort study

*Craig M McDonald, Erik K Henricson, Richard T Abresch, Tina Duong, Nanette C Joyce, Fengming Hu, Paula R Clemens, Eric P Hoffman, Avital Cnaan, Heather Gordish-Dressman, and the CINRG Investigators**

### Summary

**Background** Glucocorticoid treatment is recommended as a standard of care in Duchenne muscular dystrophy; however, few studies have assessed the long-term benefits of this treatment. We examined the long-term effects of glucocorticoids on milestone-related disease progression across the lifespan and survival in patients with Duchenne muscular dystrophy.

**Methods** For this prospective cohort study, we enrolled male patients aged 2–28 years with Duchenne muscular dystrophy at 20 centres in nine countries. Patients were followed up for 10 years. We compared no glucocorticoid treatment or cumulative treatment duration of less than 1 month versus treatment of 1 year or longer with regard to progression of nine disease-related and clinically meaningful mobility and upper limb milestones. We used Kaplan-Meier analyses to compare glucocorticoid treatment groups for time to stand from supine of 5 s or longer and 10 s or longer, and loss of stand from supine, four-stair climb, ambulation, full overhead reach, hand-to-mouth function, and hand function. Risk of death was also assessed. This study is registered with ClinicalTrials.gov, number NCT00468832.

**Findings** 440 patients were enrolled during two recruitment periods (2006–09 and 2012–16). Time to all disease progression milestone events was significantly longer in patients treated with glucocorticoids for 1 year or longer than in patients treated for less than 1 month or never treated (log-rank p<0·0001). Glucocorticoid treatment for 1 year or longer was associated with increased median age at loss of mobility milestones by 2·1–4·4 years and upper limb milestones by 2·8–8·0 years compared with treatment for less than 1 month. Deflazacort was associated with increased median age at loss of three milestones by 2·1–2·7 years in comparison with prednisone or prednisolone (log-rank p<0·012). 45 patients died during the 10-year follow-up. 39 (87%) of these deaths were attributable to Duchenne-related causes in patients with known duration of glucocorticoids usage. 28 (9%) deaths occurred in 311 patients treated with glucocorticoids for 1 year or longer compared with 11 (19%) deaths in 58 patients with no history of glucocorticoid use (odds ratio 0·47, 95% CI 0·22–1·00; p=0·0501).

Published Online November 22, 2017 http://dx.doi.org/10.1016/S0140-6736(17)32160-8

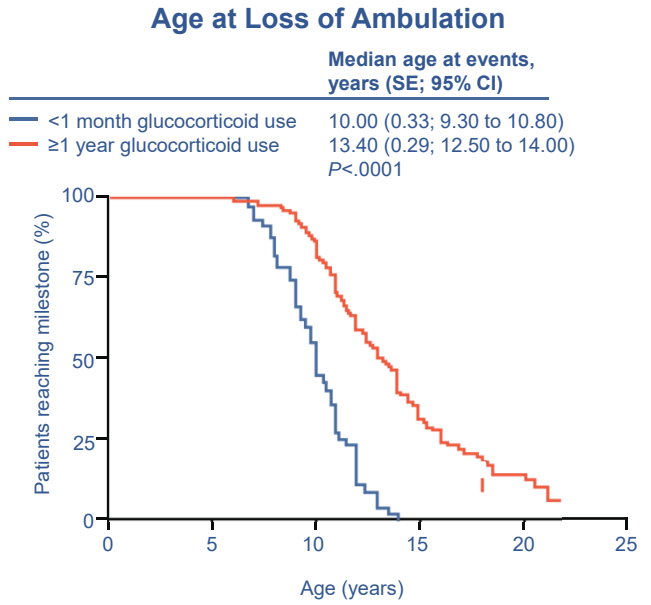
See Online/Comment http://dx.doi.org/10.1016/S0140-6736(17)32405-4

*See appendix pp 27–28 for a full list of study investigators

**University of California Davis School of Medicine, Sacramento, CA, USA** (Prof C M McDonald MD, E K Henricson PhD, R T Abresch MS, N C Joyce MD); **Stanford University, Stanford, CA, USA** (T Duong MPT); **Center for Genetic Medicine, Children's National Health System and the George Washington University School of Medicine and Health Sciences, Washington, DC, USA** (F Hu MS, Prof A Cnaan PhD, H Gordish-Dressman PhD); **University of Pittsburgh, Pittsburgh, PA, USA** (Prof P R Clemens MD); **and Binghamton University's**

# *Lancet* publication demonstrated delay in loss of ambulation in corticosteroid-treated DMD patients

## Glucocorticoids for ≥1 year; delay in loss of ambulation of 3.4 years




**Number at risk**

| | | | | | | |
|---|---|---|---|---|---|---|
| <1 month glucocorticoid use | 73 | 73 | 26 | 0 | 0 | 0 |
| ≥1 year glucocorticoid use | 330 | 329 | 223 | 52 | 9 | 0 |

*Reprinted from* The Lancet, *Vol. 391, McDonald CM, Henricson EK, Abresch RT, et al. Long-term effects of glucocorticoids on function, quality of life, and survival in patients with Duchenne muscular dystrophy: a prospective cohort study., 451-461, Copyright 2018, with permission from Elsevier.*

McDonald CM, et al. *Lancet.* 2018;391:451-461. Figure 1.

Not Approved for Promotional Use.

# *Lancet* publication demonstrated delay in loss of milestones in favor of Emflaza® compared to prednisone

- Compared to prednisone, deflazacort was associated with further delayed loss of function across 3 milestones by 2.1 to 2.7 years
- Of note, the following was observed:
  - Age at loss of ability to stand from supine ($p$=0.0114)
  - Age at loss of ambulation ($p$=0.0102)
  - Age at loss of hand-to-mouth function with retained hand function (Brooke score ≤5) ($p$=0.0110)



McDonald CM, et al. *Lancet.* 2018;391:451-461.

# Additional publications will continue to support the benefit of Emflaza® compared to other corticosteroids

- Expected additional publications of placebo-controlled data sets that included Emflaza and other corticosteroids:
  - ACT DMD Translarna placebo data
  - Tadalafil placebo data
- Our goal is to establish Emflaza as the standard-of-care for DMD



McDonald CM, et al. *Lancet.* 2018;391:451-461.

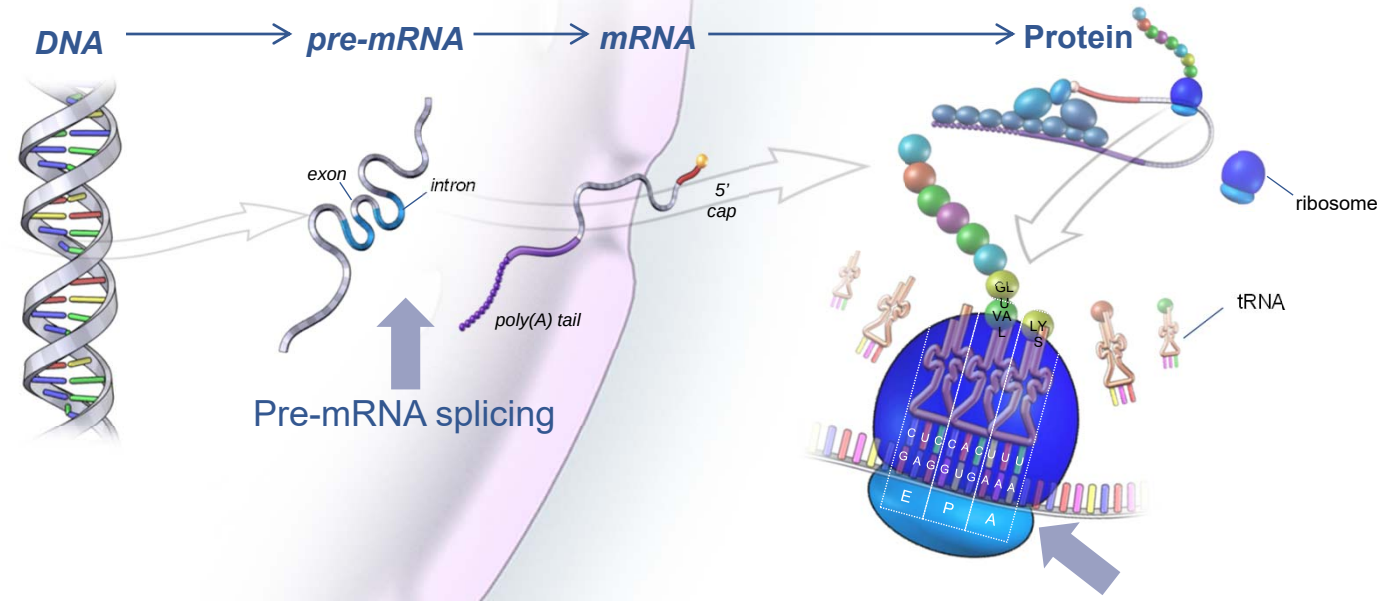
# DMD platform Q&A panel

- Marcio Souza, COO
- Eric Pauwels, General Manager - Americas
- Joe McIntosh, Head of Clinical Development
- Ellen Welch, Research Genetic Disorders & Translational Medicine


# Targeting Splicing to Discover and Develop Novel Small Molecule Therapeutics

Christopher Trotta, VP Biology

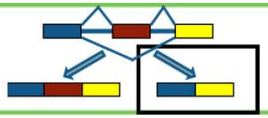
# PTC discovery is focused on development of small molecules that target RNA biology



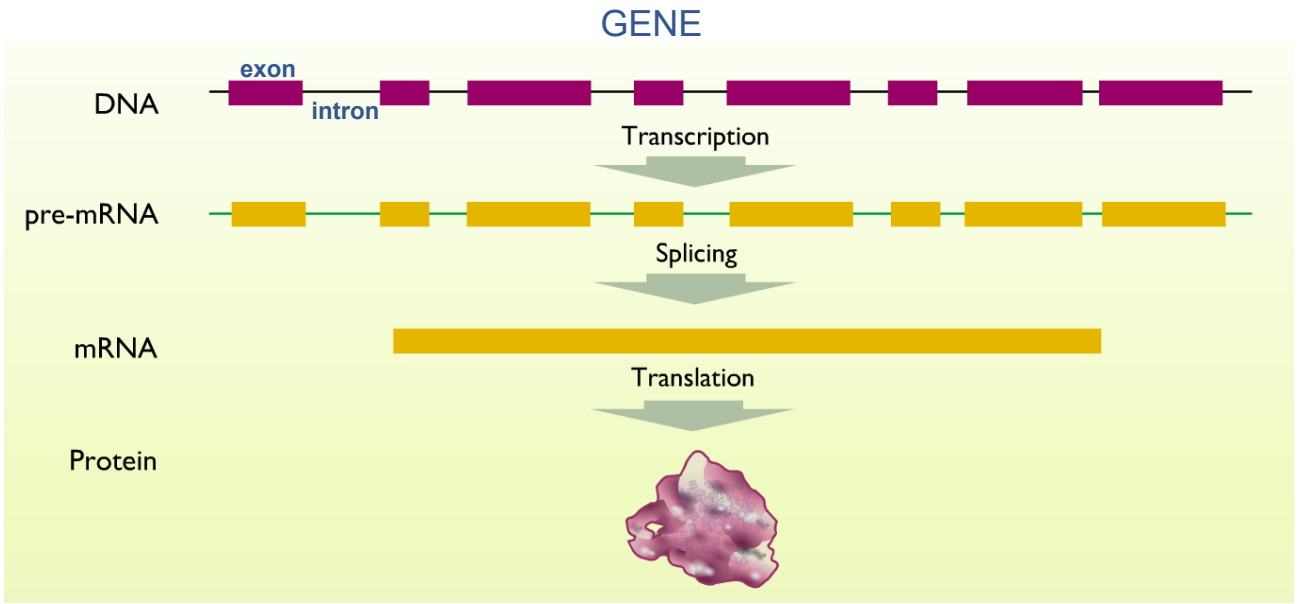

PTC uses small molecules to target RNA processes to treat challenging diseases

# PTC's platform technologies target RNA biology to modulate gene expression with small molecules

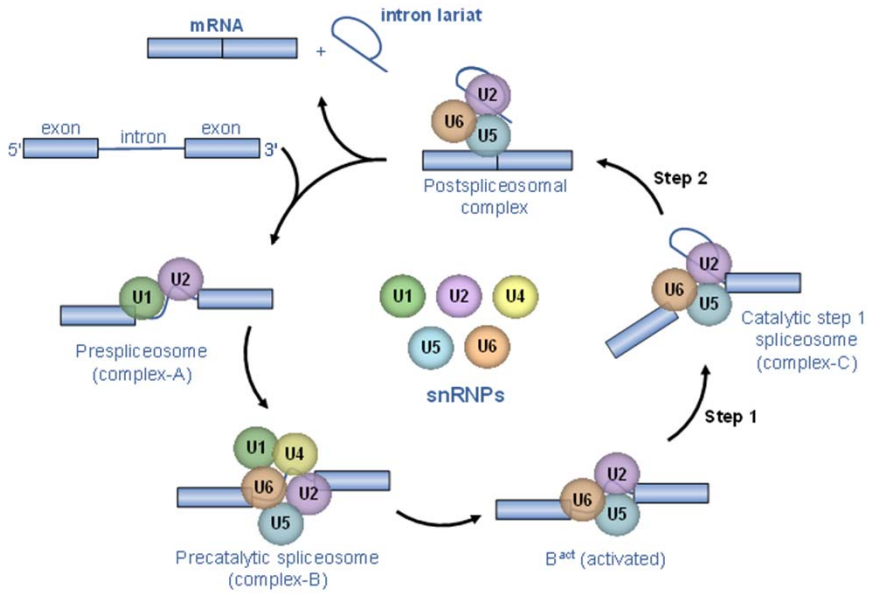
- 20 years of therapeutic targeting of RNA biology
- 13 years of discovering and developing drugs that target pre-mRNA splicing
- Cutting-edge platform technology discovered and developed by PTC
- Technology **validated** by the SMA program which is currently is in pivotal clinical trials
- Quickly expanding to other indications including Huntington's disease and Familial Dysautonomia

| Platform | Mechanism Targeted | Programs |
|---|---|---|
| Splicing |  Target-splicing events to restore or decrease protein levels | SMA – SMN2<br>FD – IKBKAP<br>HD – HTT<br>Others |

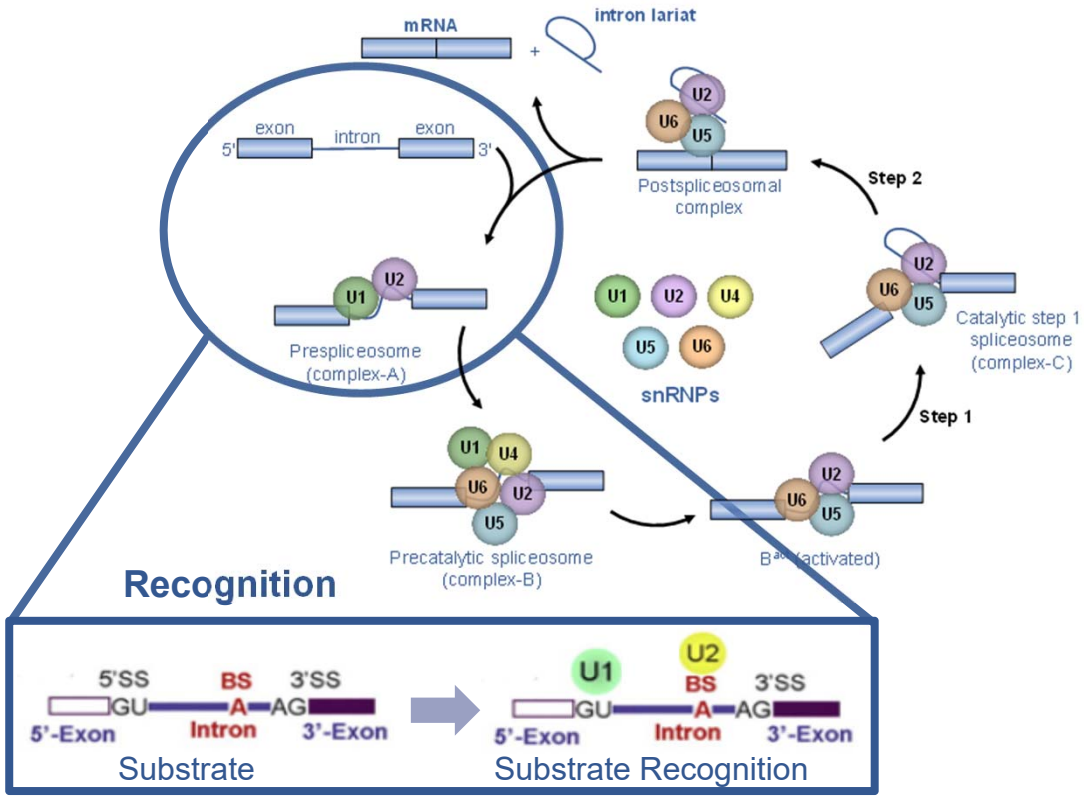
# Pre-mRNA splicing is required for gene expression



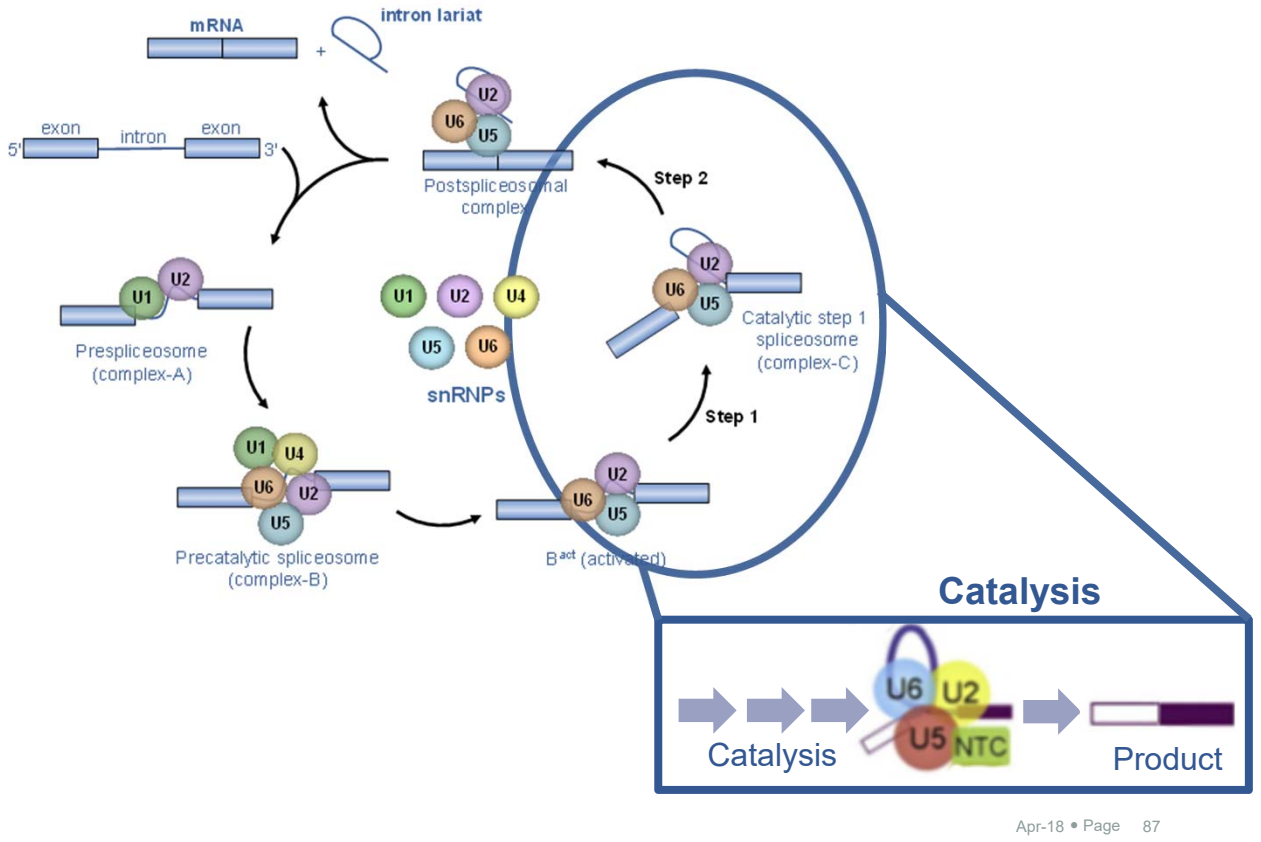
# Pre-mRNA splicing requires a complex machine-assembly of the spliceosome



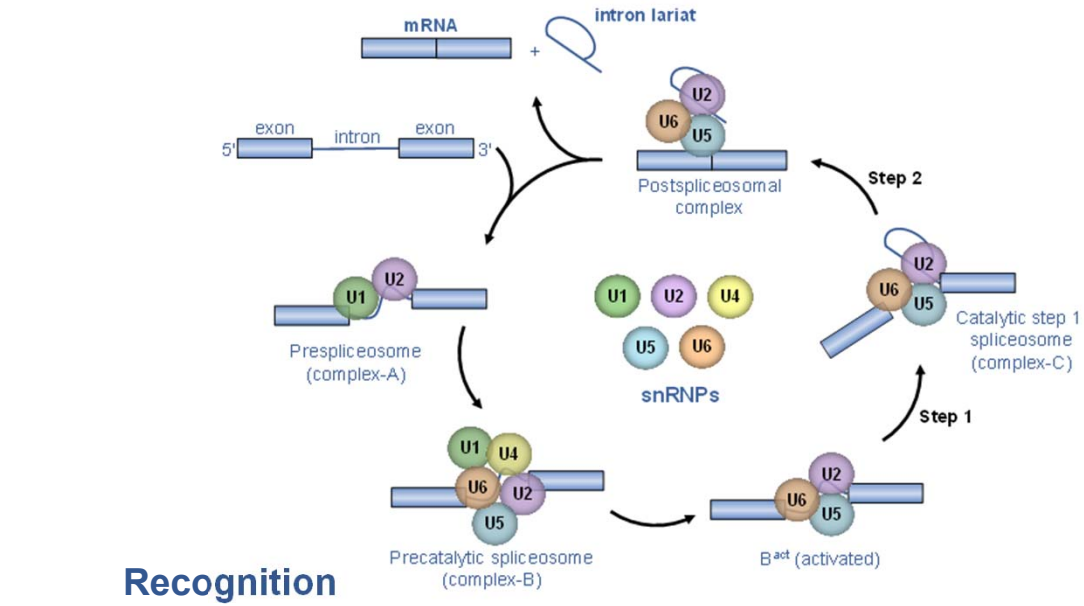
# There are 2 key steps in the splicing reaction: 1) Recognition

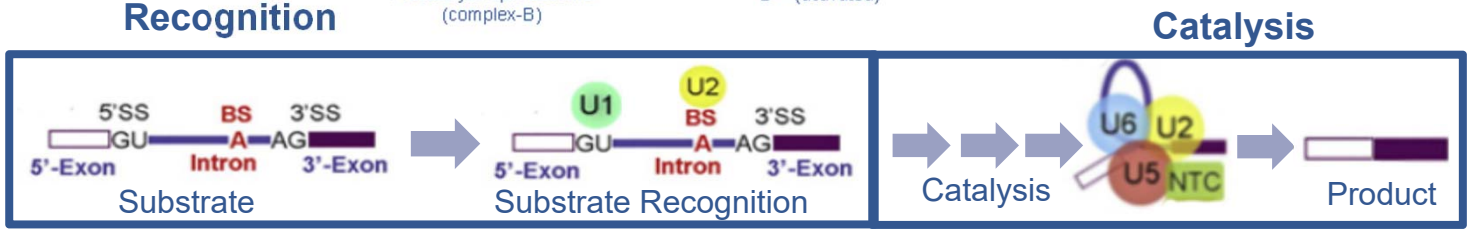


# There are 2 key steps in the splicing reaction: 1) Recognition followed by 2) Catalysis

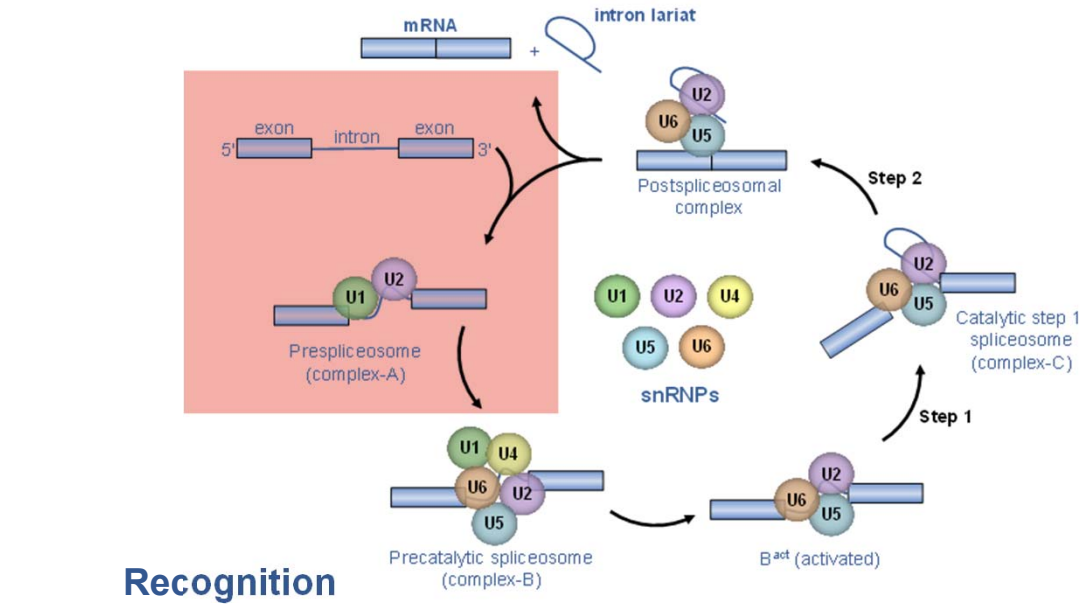


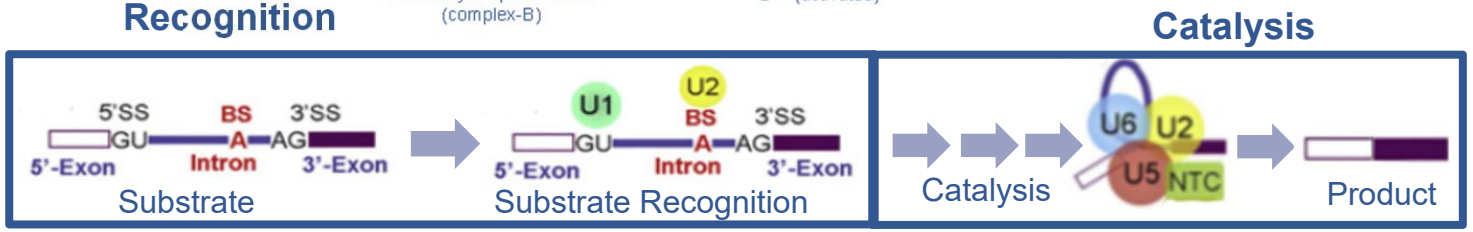
# PTC's splicing platform: Discovery of small molecule splicing modifiers



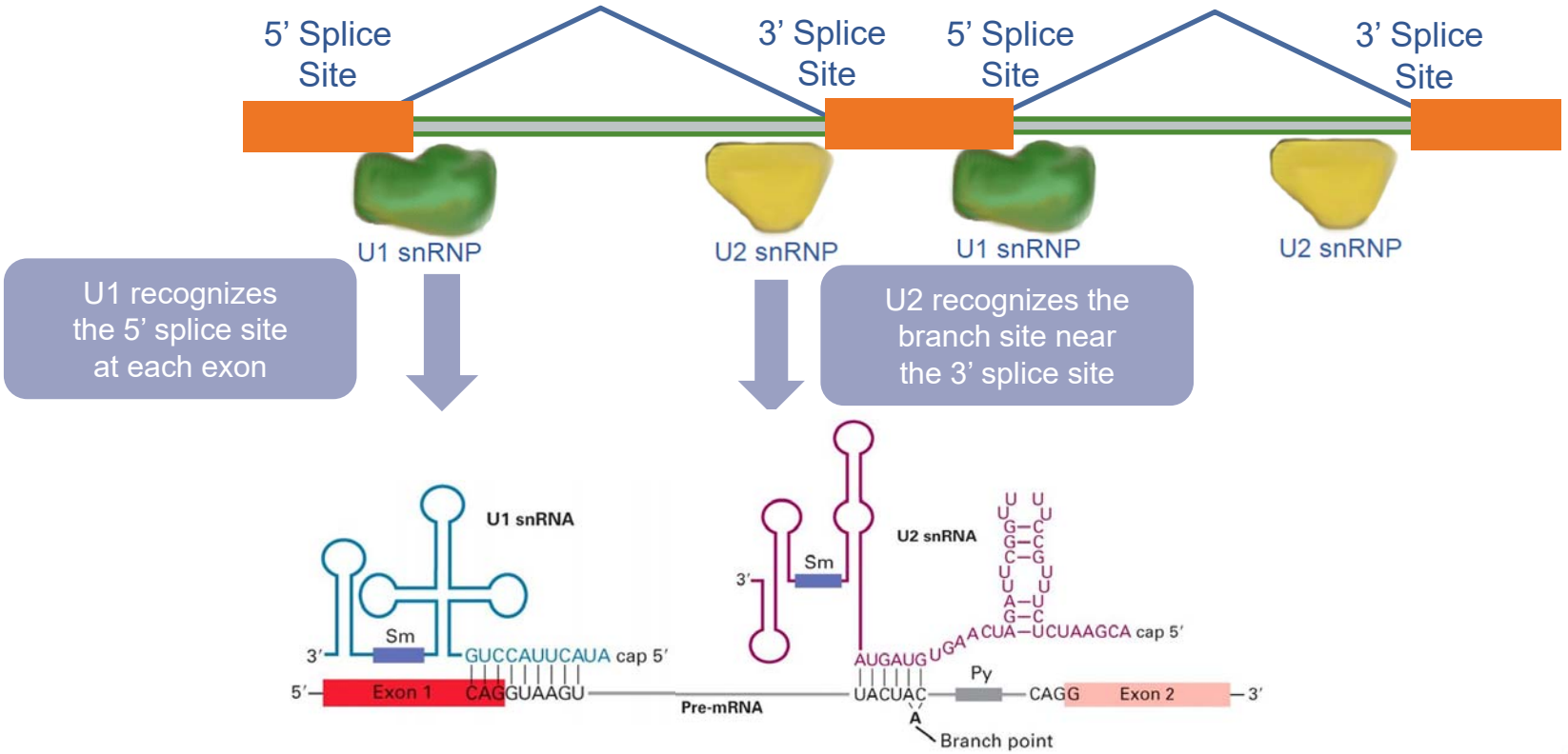



# Taking aim at the recognition step in pre-mRNA slicing

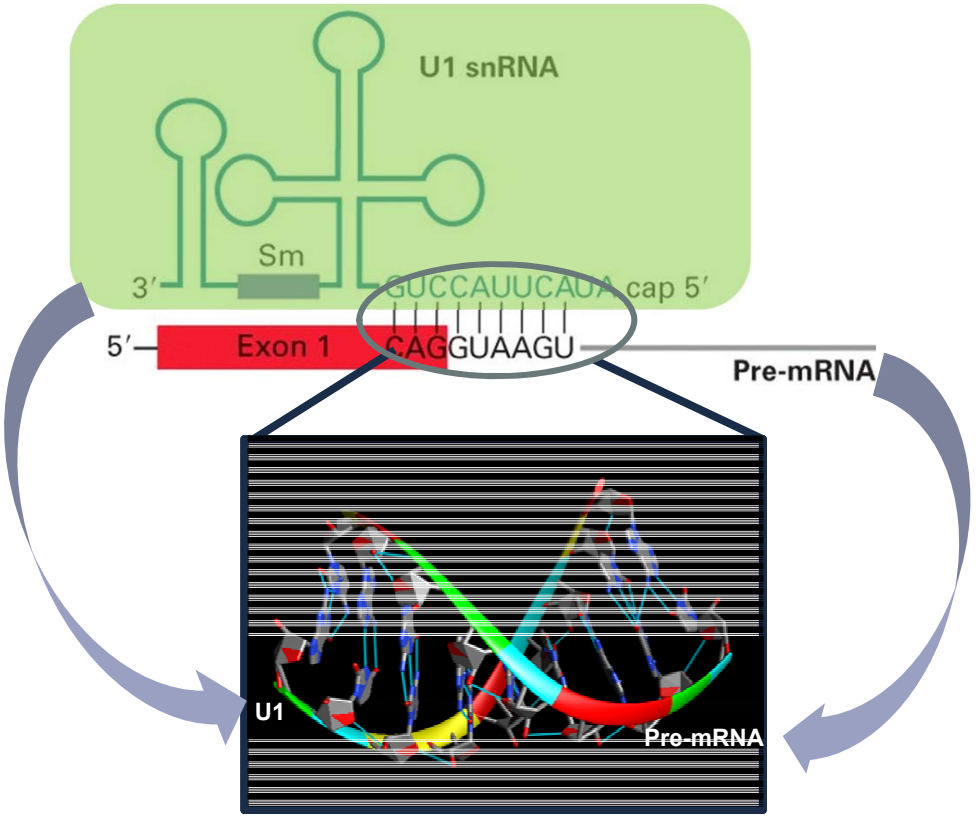


# Recognition of pre-mRNA is mediated by U-snRNP complexes U1 and U2



# The U1-pre-mRNA interaction is the most extensive and selective interaction in the splicing pathway



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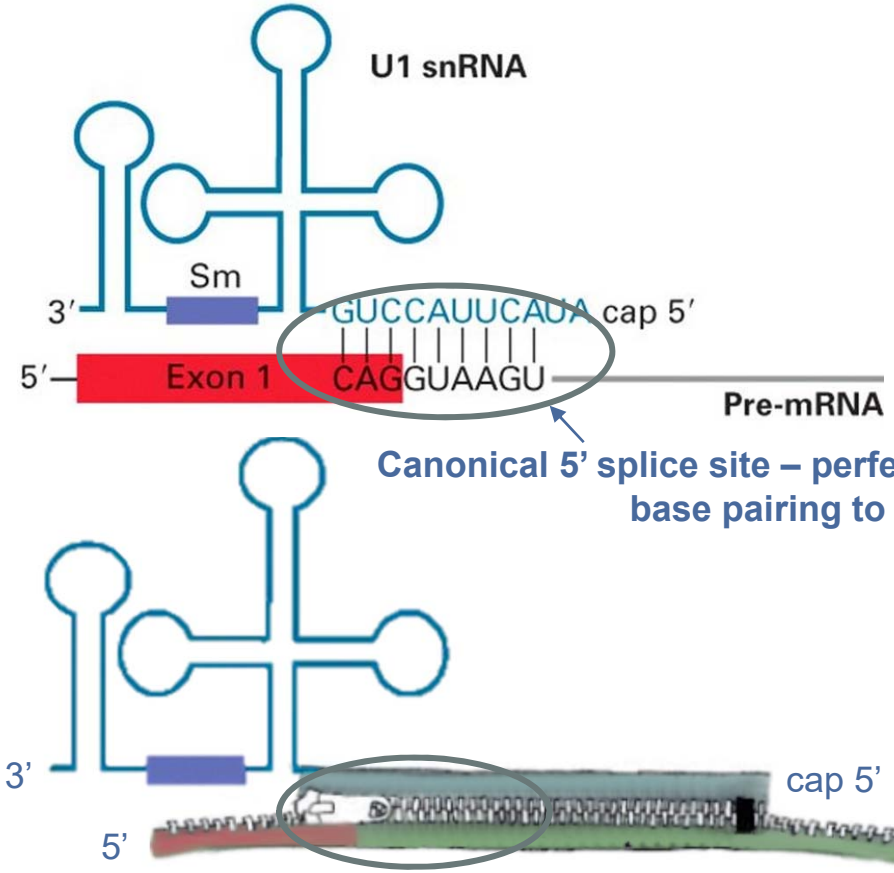
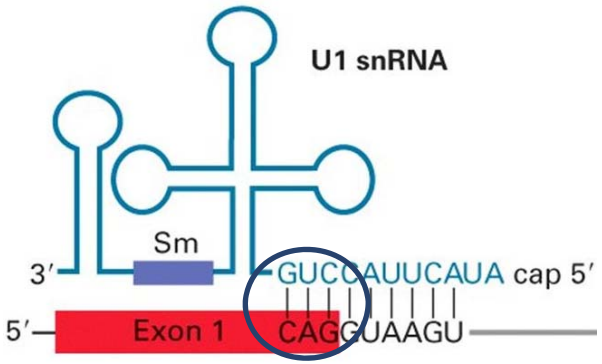
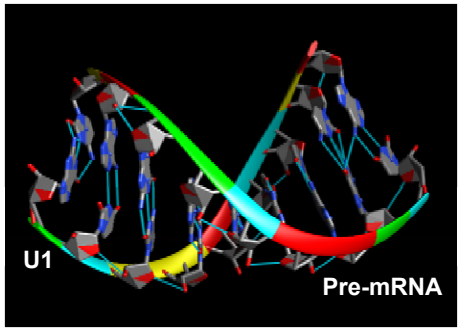


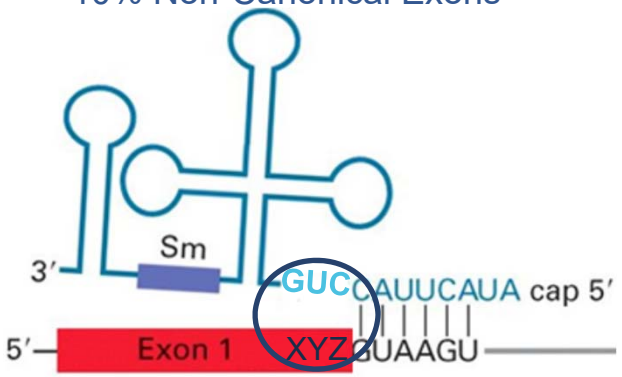
# Two classes of exons based on U1 binding potential– canonical and non-canonical exons

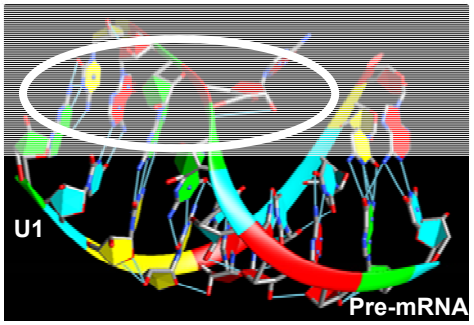
90% Canonical Exons




10% Non-Canonical Exons

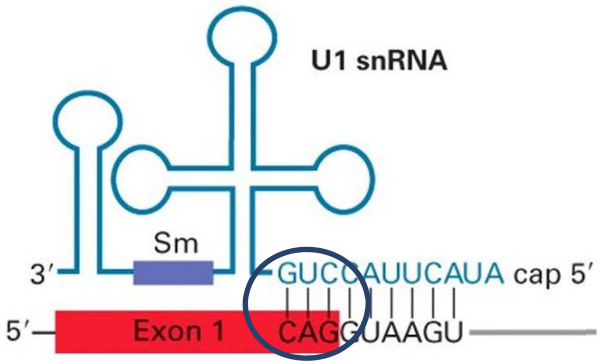


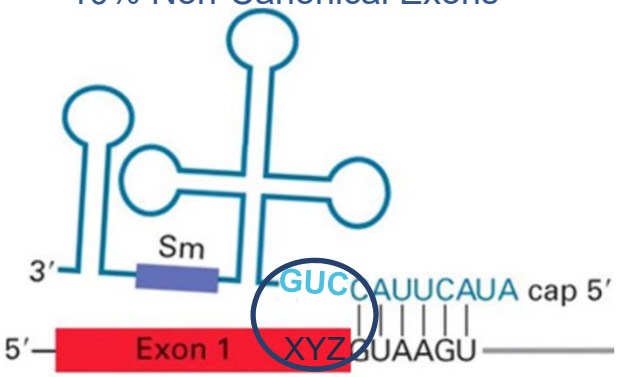

**Structural diversity at the 5’ splice site**

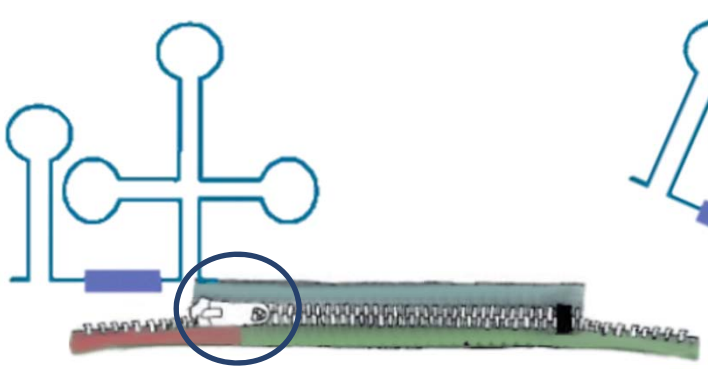
# Two classes of exons based on U1 binding potential– canonical and non-canonical exons

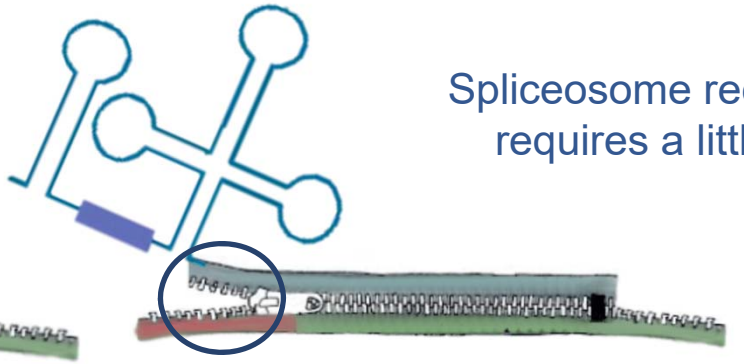
90% Canonical Exons




10% Non-Canonical Exons



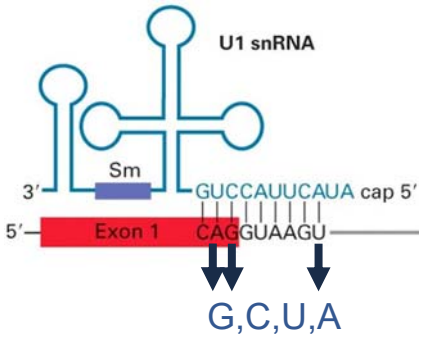





Spliceosome recognition requires a little help

# Three types of non-canonical exons in the human genome

1. Endogenous non-canonical exons–10% of exons in the human genome
2. Mutation of canonical exons–DNA mutation that creates an exon with a non-canonical 5’ splice site



# Three types of non-canonical exons in the human genome

1. Endogenous non-canonical exons–10% of exons in the human genome
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3. Pseudoexons—Non-canonical exons that are not recognized and spliced

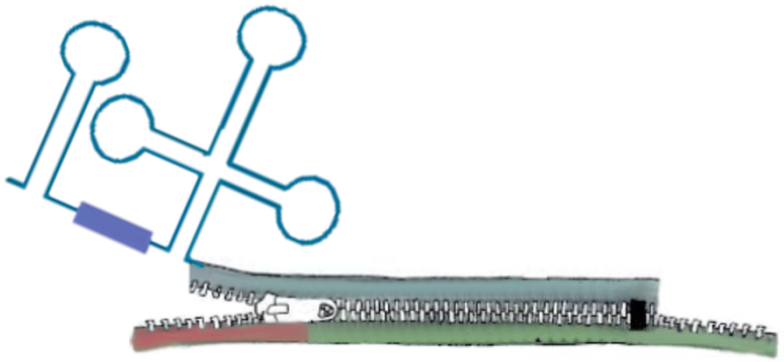
# PTC programs that target the recognition step of splicing

**Non-canonical exons involved in human disease:**

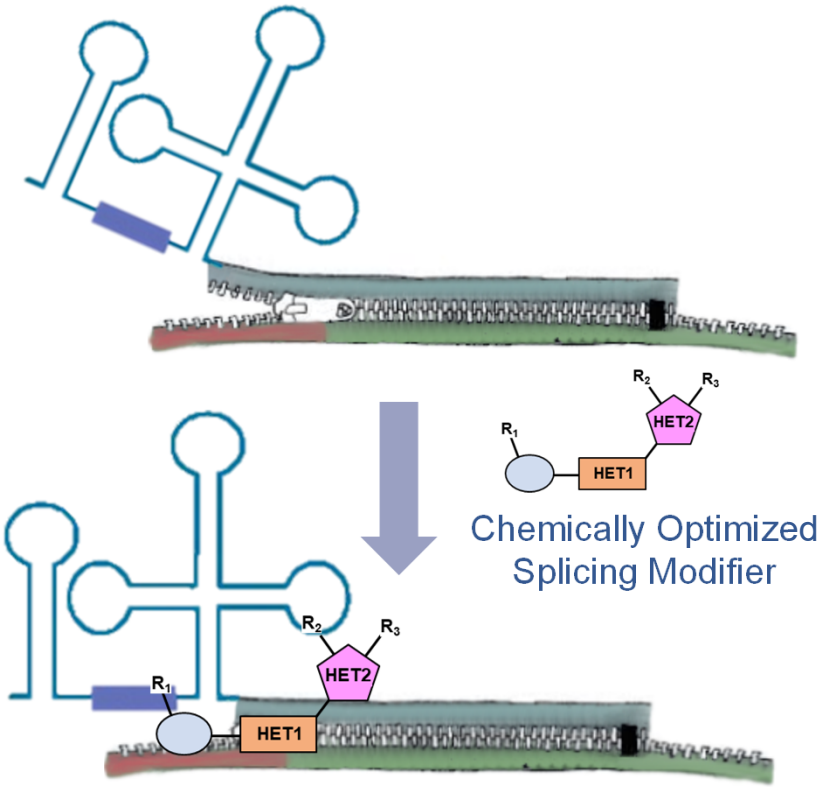
1. Endogenous non-canonical exons—10% of exons in the human genome
   – SMN2 exon 7 Inclusion
2. Mutation of canonical exons—DNA mutation that creates an exon with a non-canonical 5’ splice site
   – Familial dysautonomia -IKBKAP Exon 20 Inclusion
3. Pseudoexons—Non-canonical exons that are not recognized and spliced
   – Htt pseudoexon

**Each category has many potential druggable targets**

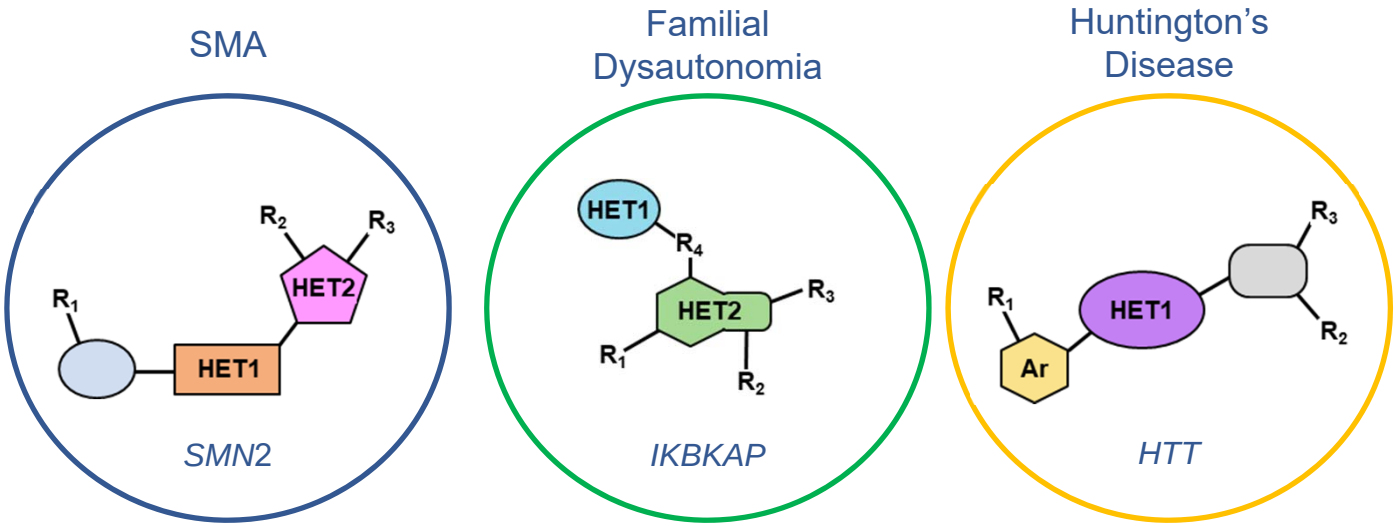
# How do splicing modifiers target the recognition step of splicing?



# Binding of splicing modifiers to the non-canonical U1-pre-mRNA structure induces splicing

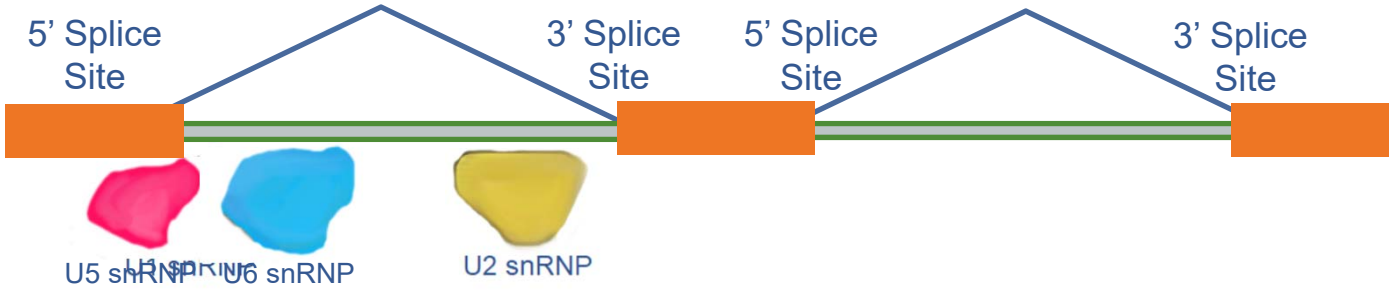


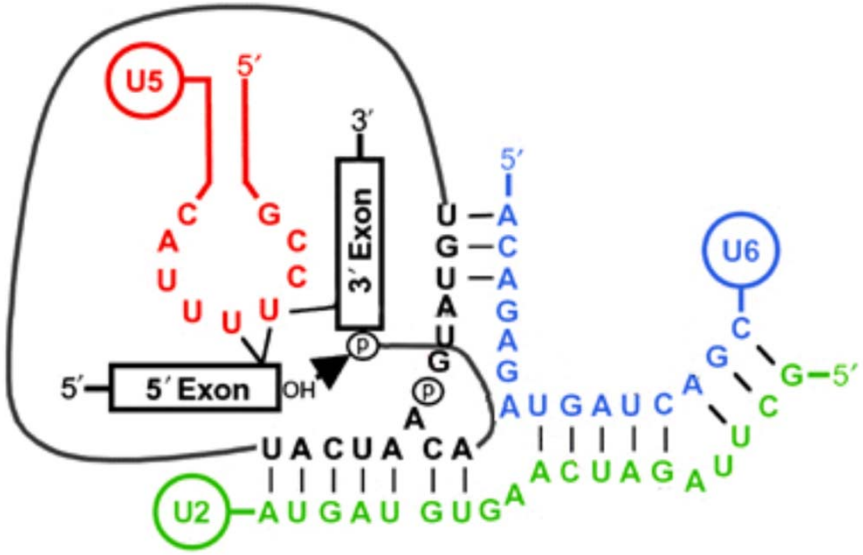
# Defining the universe of small molecule splicing modifiers




**Pre-mRNA splicing provides a rich set of targets to discover and develop new small molecule therapeutics**

# Just scratching the surface: Specific interactions within the catalytic step of splicing




Sequence diversity of U2, U5, and U6 binding sites creates additional RNA structures that can be drug targets

# The PTC splicing platform: Discovery of small molecule splicing modifiers to regulate gene expression

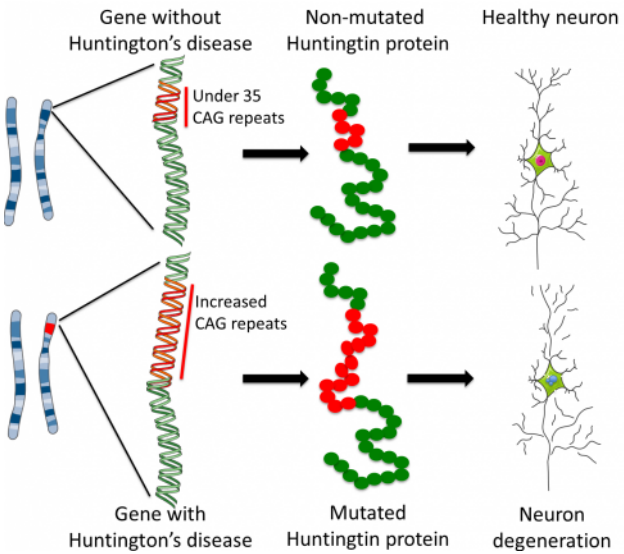
- PTC has developed a deep understanding of the druggable interactions in the splicing of pre-mRNA
  - Identified and advanced small molecules that directly interact with RNA-RNA complexes of the spliceosome
  - Targeted the diversity of RNA structures at the recognition step in splicing
  - Developing knowledge of the structural diversity within the catalytic step of splicing

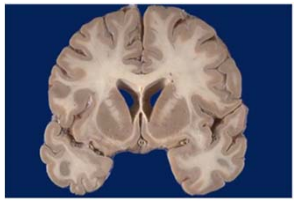

# Splicing Platform: Huntington's Disease

Christopher Trotta, VP R&D Biology

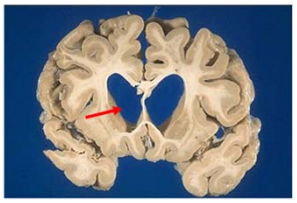
# Huntington's Disease is caused by a CAG repeat expansion in the HTT gene

- Mutated HTT protein leads to severe neuron degeneration predominantly in the striatum and cerebral cortex
- High unmet medical need:
  - No approved disease modifying treatment
  - 30,000 US; 100,000 WW patients



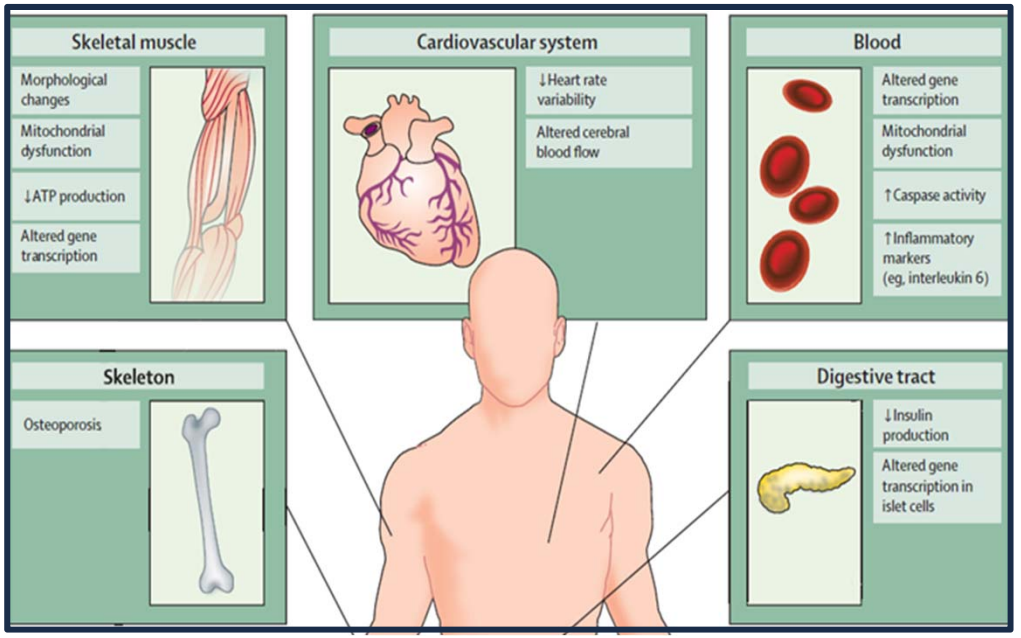
Healthy brain



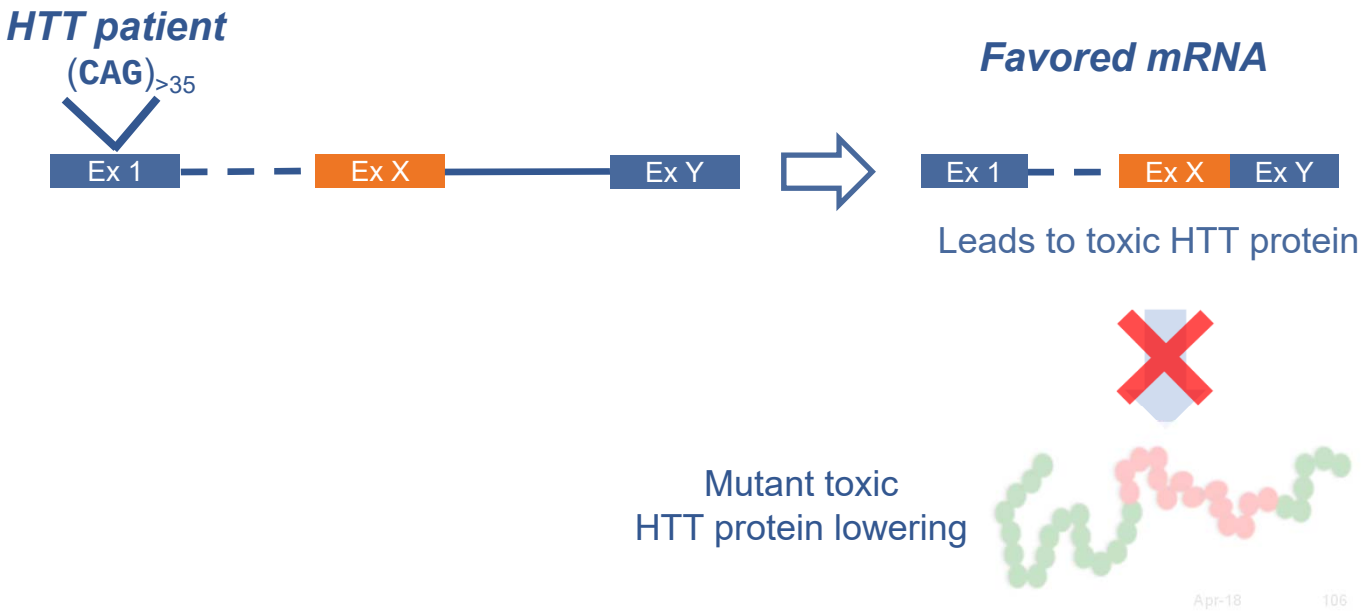
HD brain

# Mutant HTT affects key tissues throughout the periphery

- HD patients experience a wide array of peripheral organ dysfunction
  - Pronounced skeletal muscle wasting
  - High rate of heart failure
  - Weight loss
  - Increased insulin intolerance



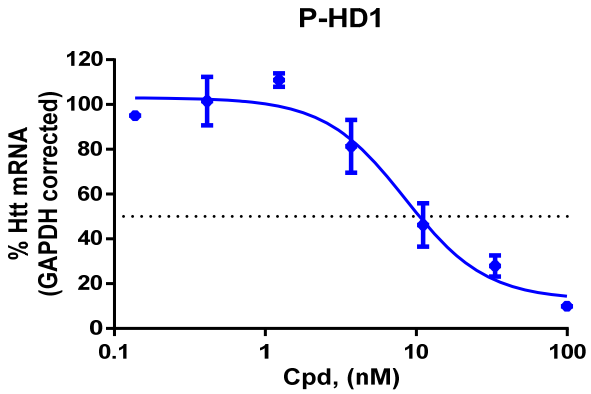
# PTC's strategy to treat HD



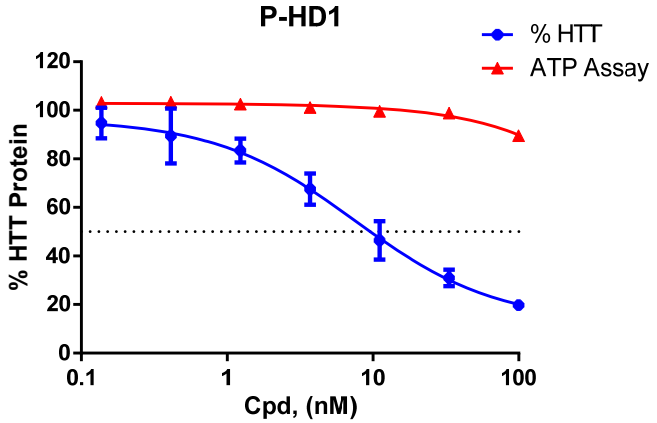

**Identification of small molecules that target the post-transcriptional regulation of HTT expression**

# Discovery of small molecules that target HTT expression

Screened the PTC compound library and identified molecules that lowered both mutant HTT protein and mRNA

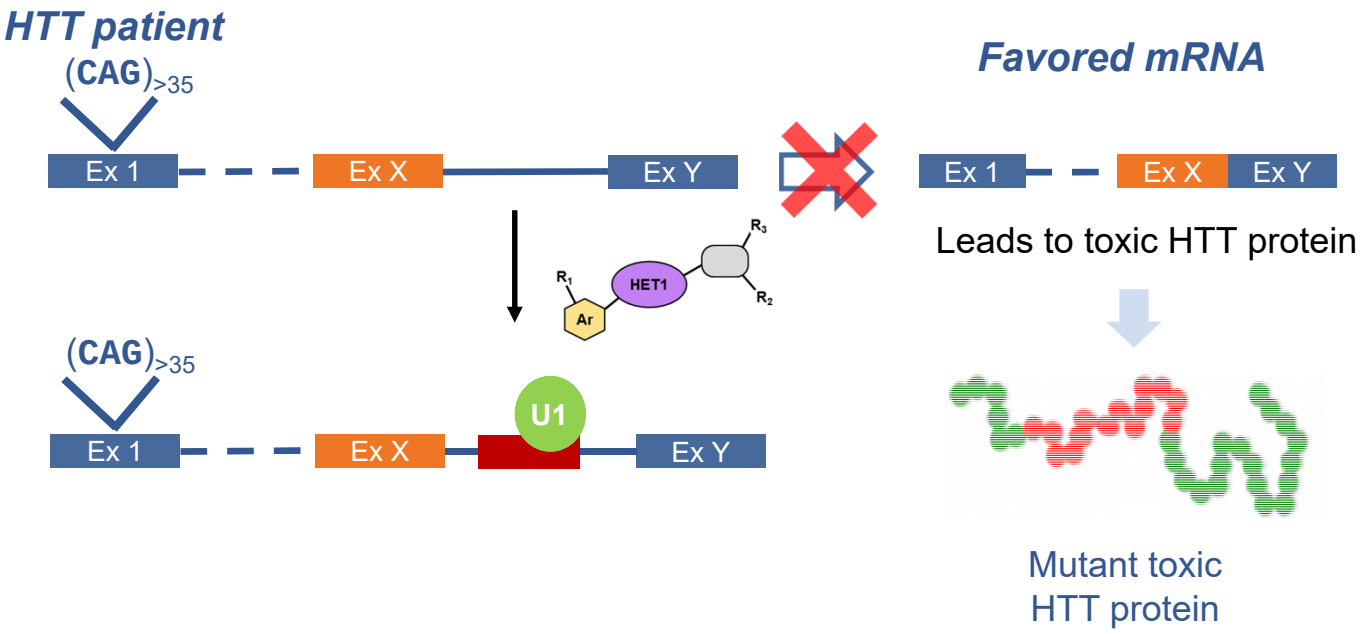



HTT mRNA lowering

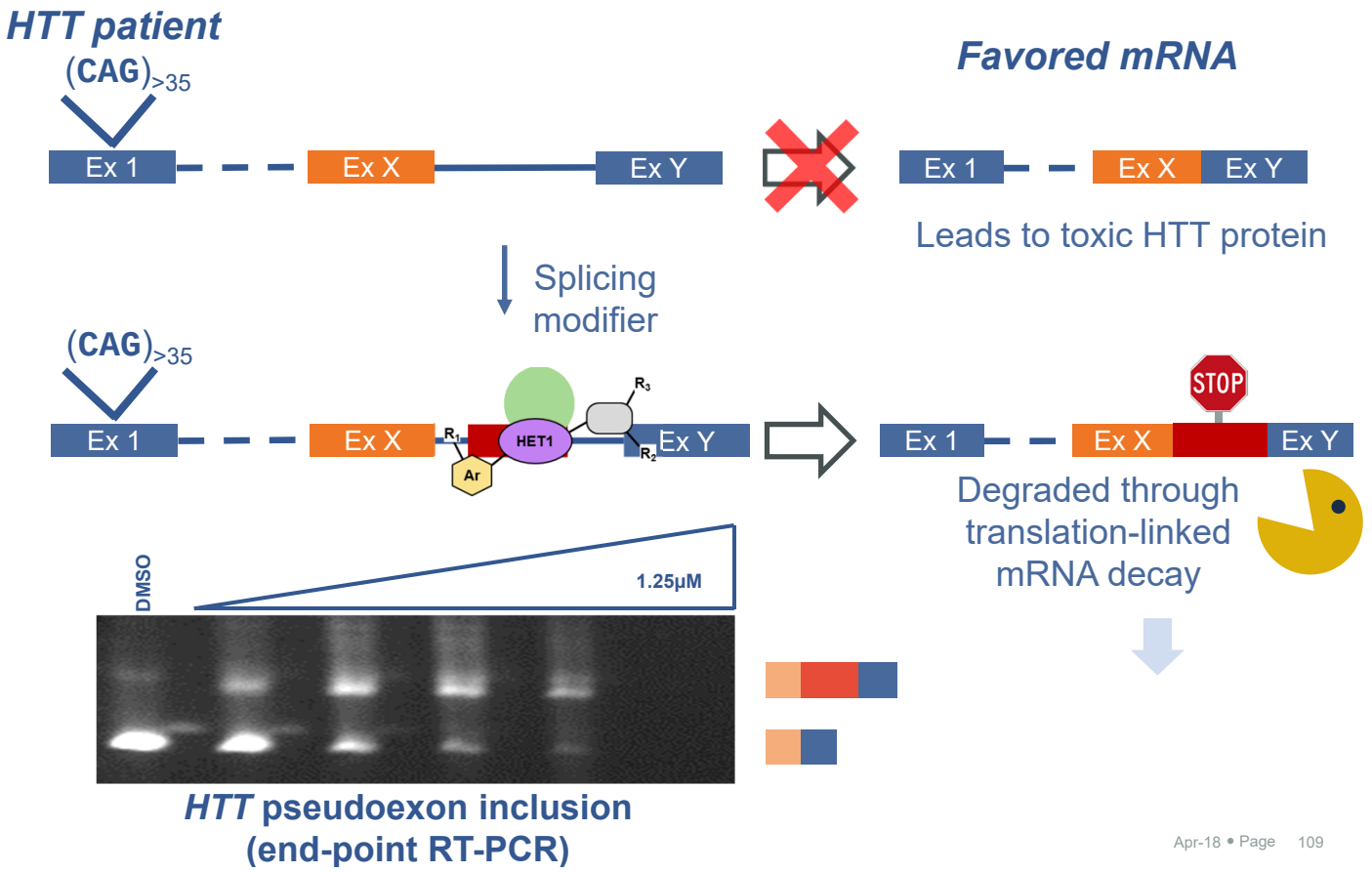



HTT protein lowering

# Identification of a novel mechanism to lower HTT protein



# Splicing modifiers activate a pseudoexon within the HTT mRNA leading to mRNA degradation



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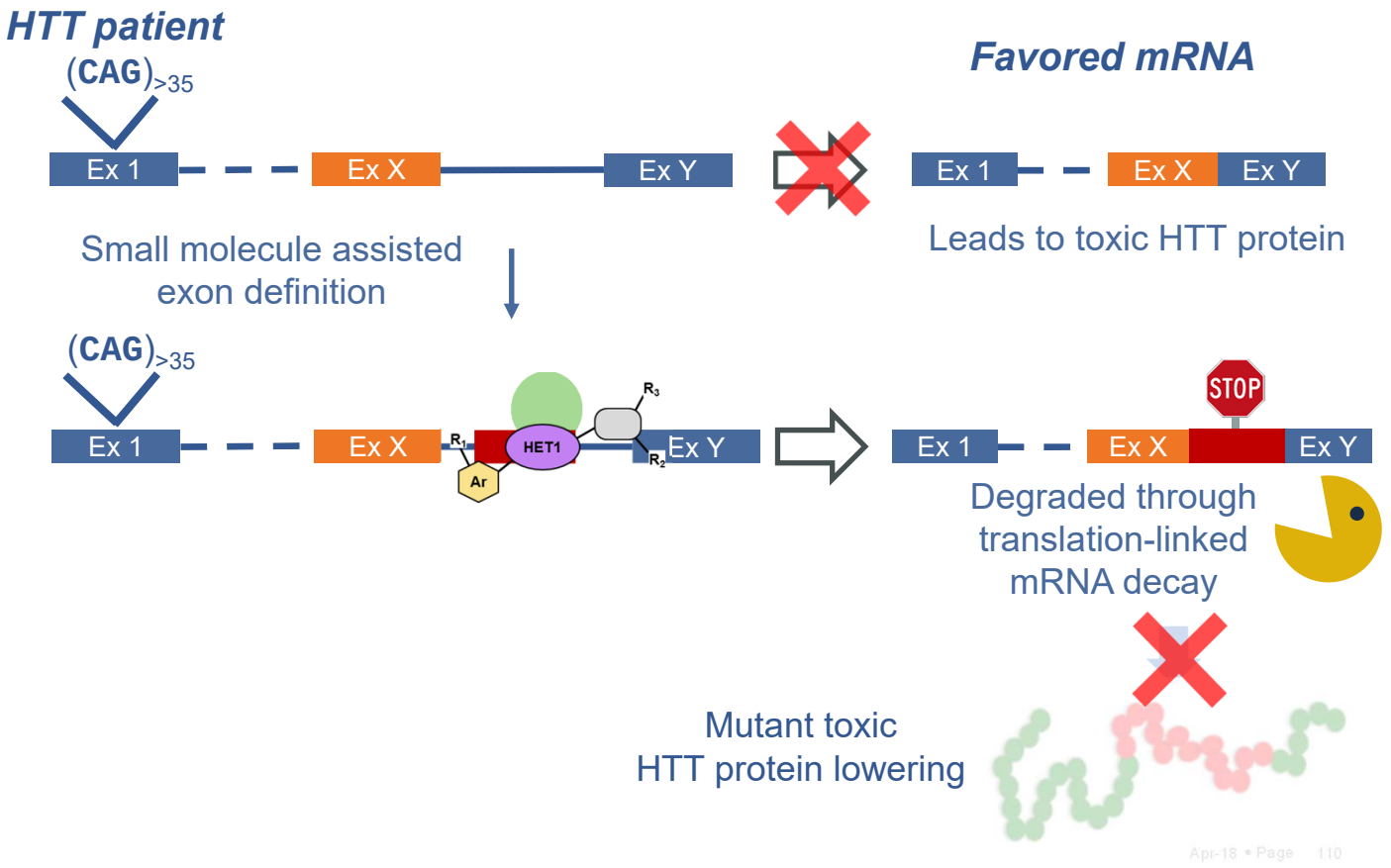


# From *in vitro* to *in vivo*: Humanized mouse model of HD

BACHD mice used to demonstrate HTT lowering

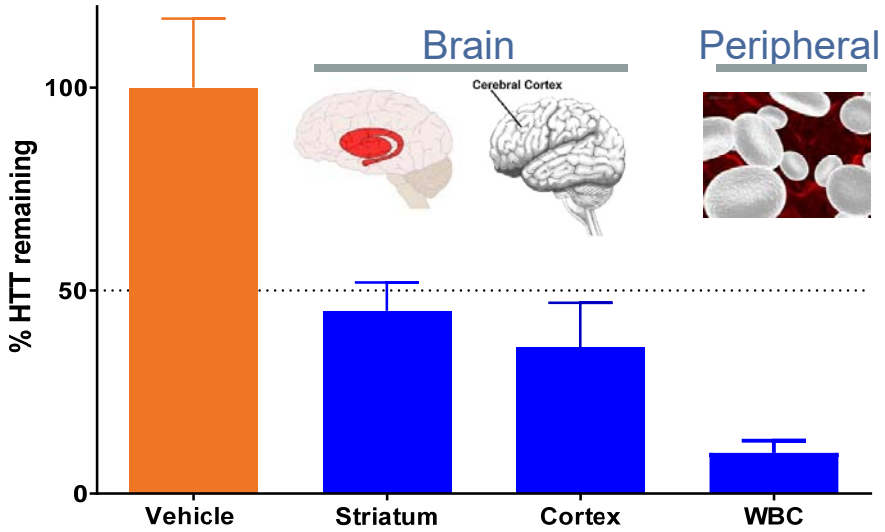
BACHD

Full-length human HTT transgene polyQ97 expansion

# PTC compounds lower human HTT in key regions of the brain and tissues in a mouse model of HD

## Optimization has led to the discovery of several classes of small molecules

- Widely distributed in animals
- Potent and selective to lowering of HTT mRNA and protein in the brain and periphery



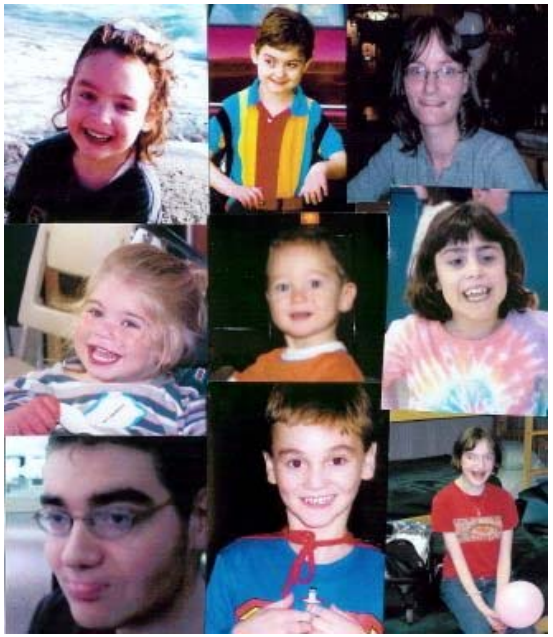

**Continued optimization of molecules with a projected 2020 target for entry into the clinic**


# FD and SMA: Applications of Splicing Platform

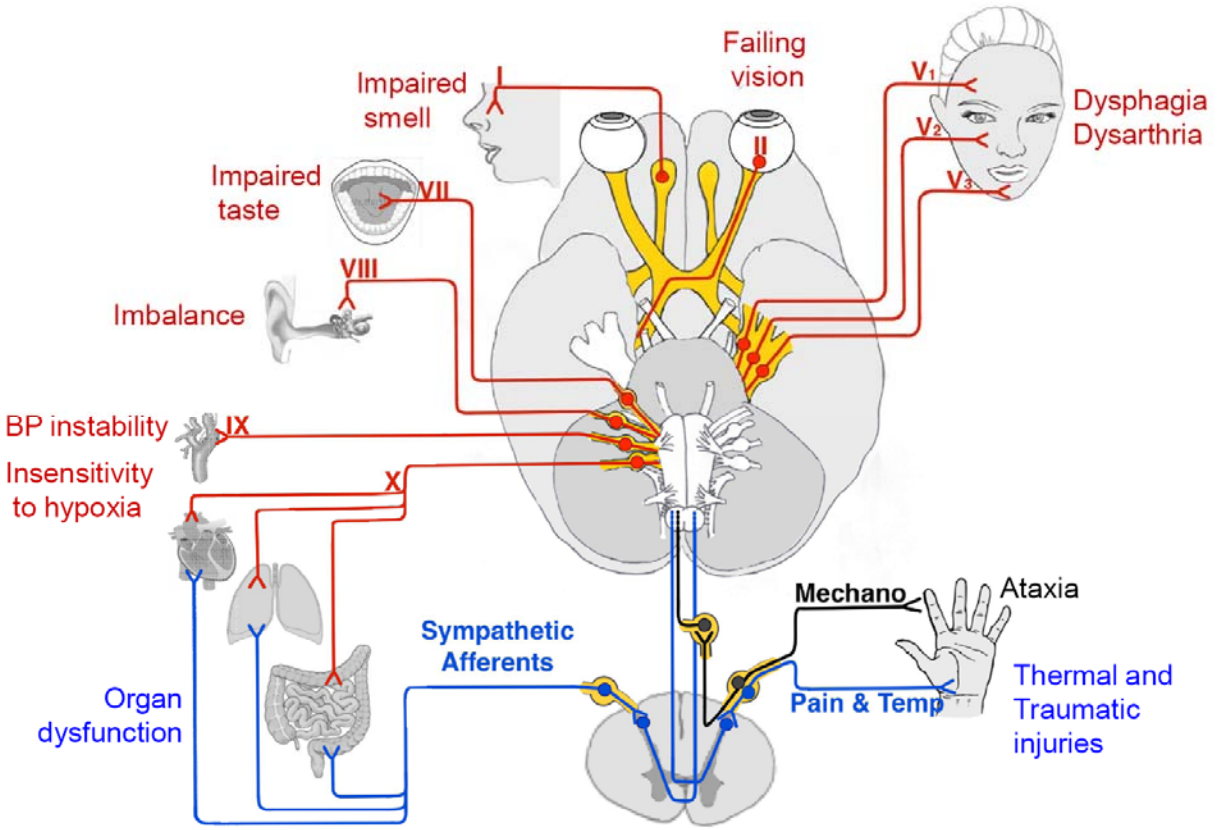
Nikolai Naryshkin, VP R&D Biology

# Familial dysautonomia: The disease of IKBKAP missplicing

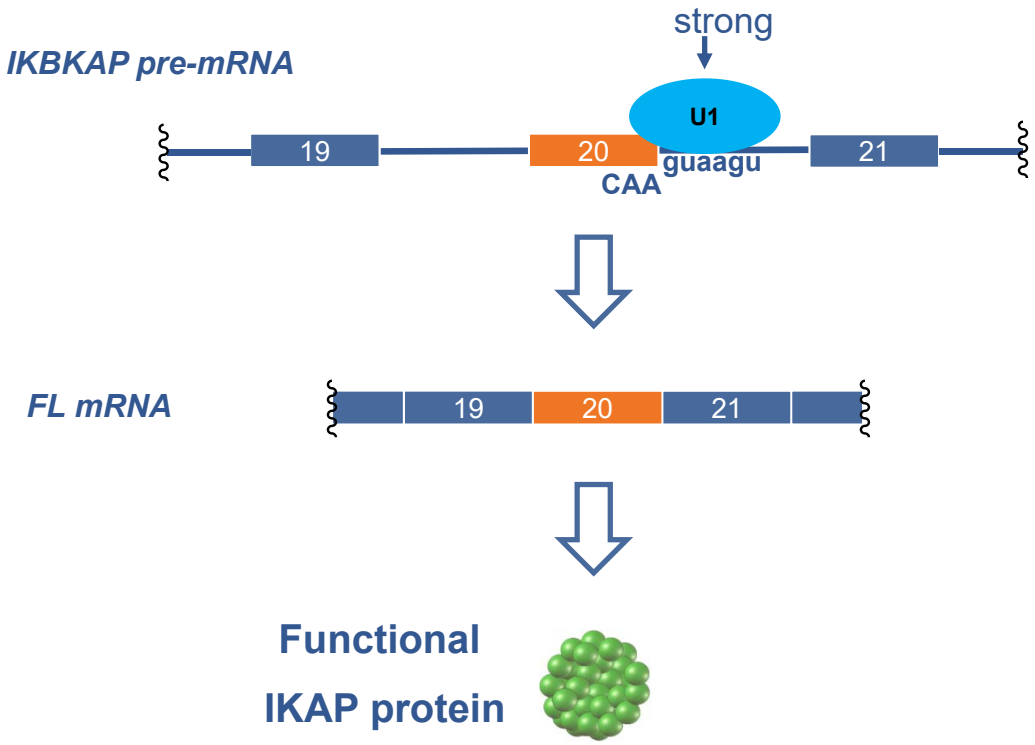
- Genetic disorder primarily affecting the sensory and autonomic neurons
- Caused by a splicing-altering mutation in the IKBKAP (ELP1) gene resulting in low levels of IKAP protein
- Ashkenazi Jewish ancestry, carrier frequency is ~1:30
- No marketed therapies are currently available for FD, only supportive treatments
- PTC is collaborating with MGH and NYU to advance treatments for FD



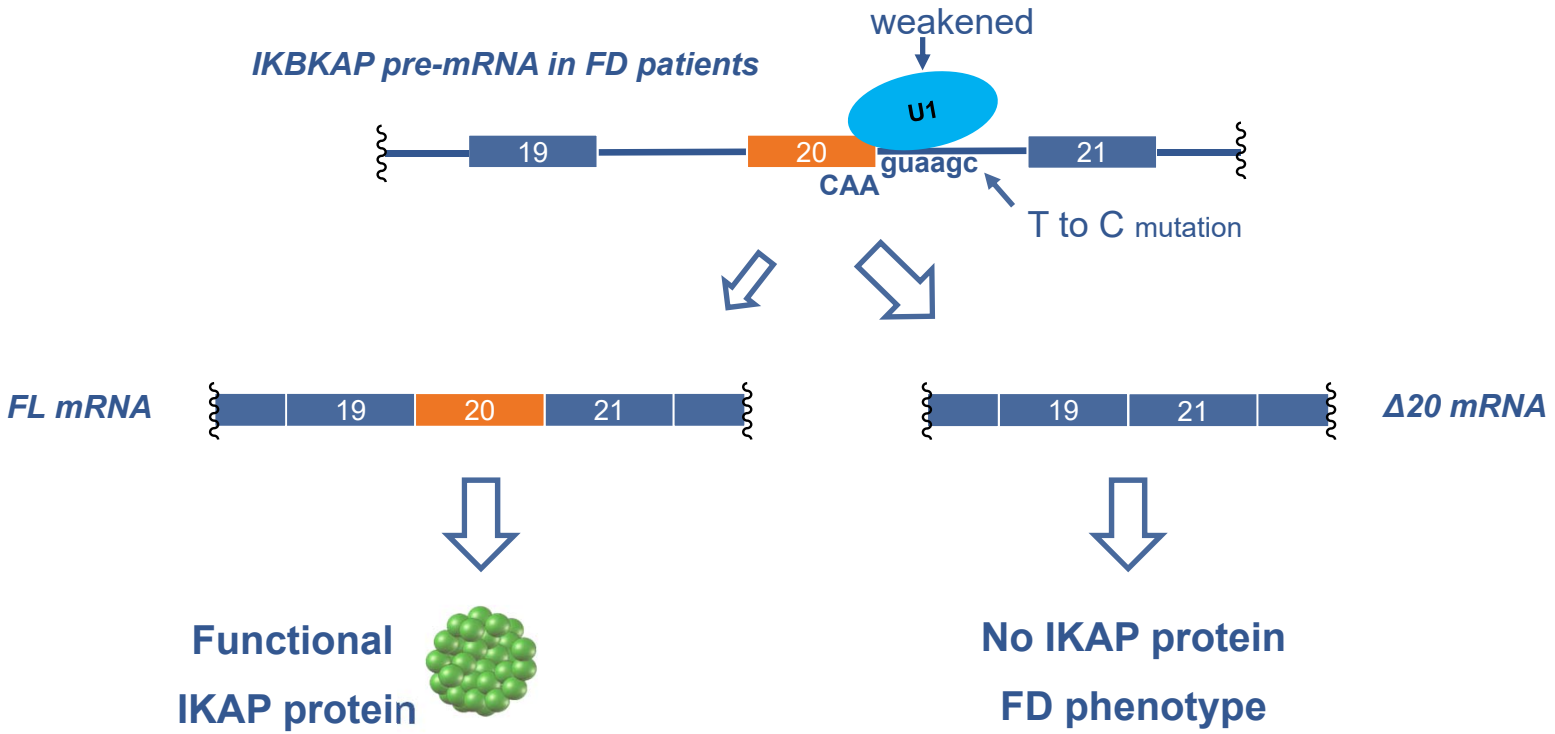
# IKAP deficiency: Aberrant development and function of autonomic and sensory neurons



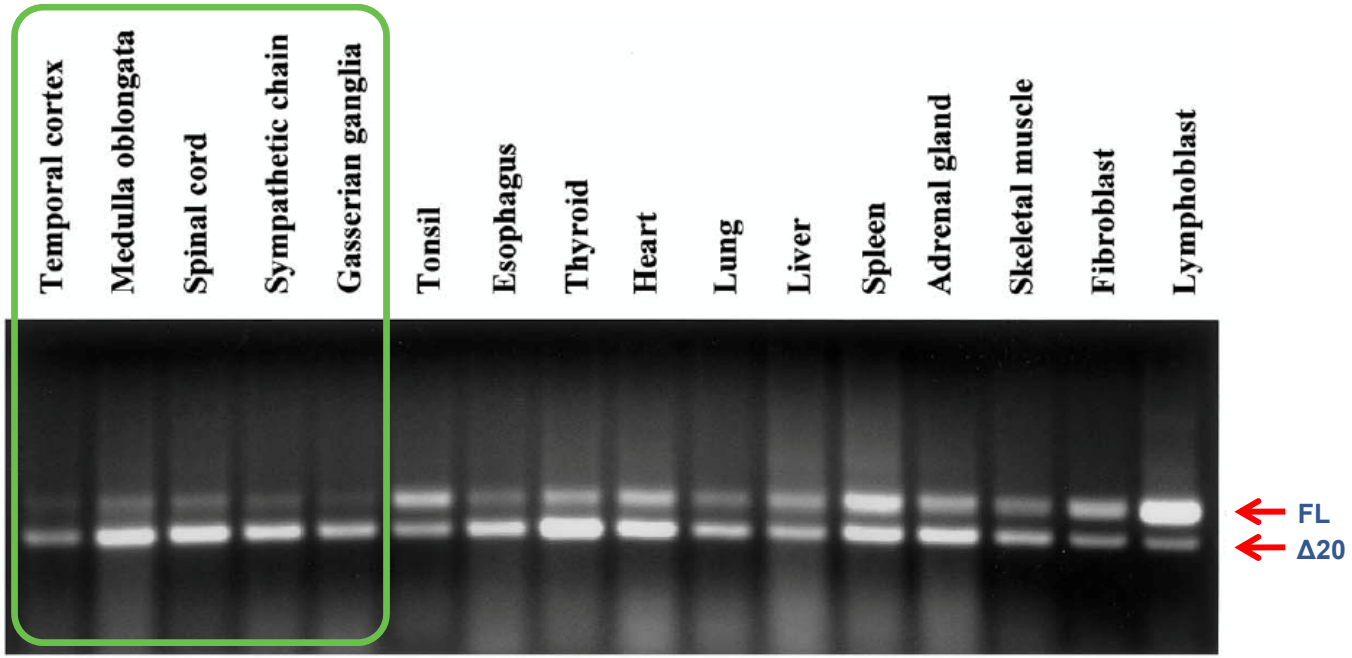
# Wild type IKBKAP generates full-length mRNA from a noncanonical CAA 5' splice site



# In FD patients, T to C transition further weakens the 5' splice site and results in exon 20 skipping



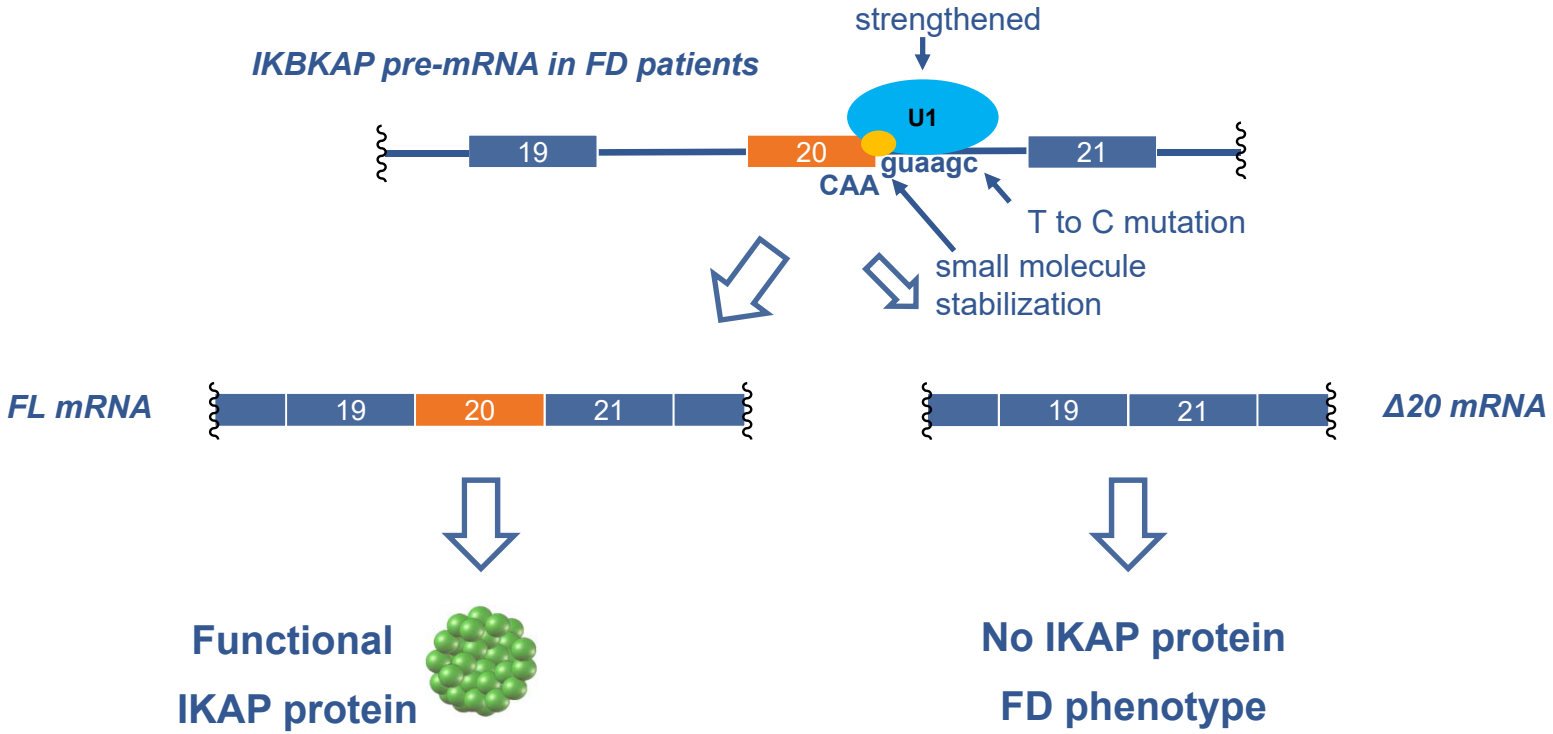
# IKBKAP exon 20 skipping is tissue-dependent; nervous system affected the most



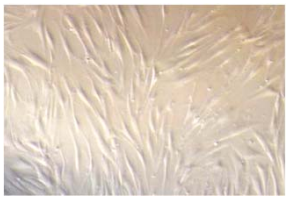


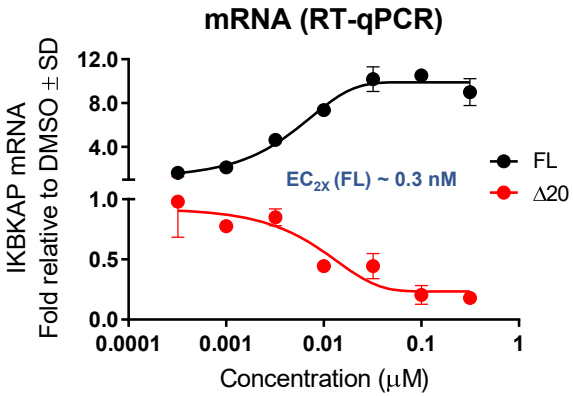
Slaugenhaupt SA, et al. *Am J Hum Genet*. 2001;68(3):598-605.
Cuajungco MP, et al. *Am J Hum Genet*. 2003;72(3):749-758.

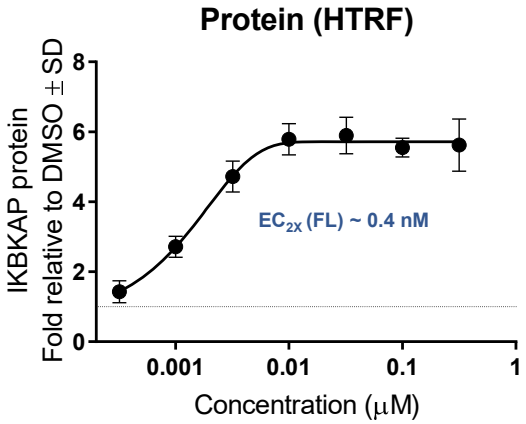
# Targeting alternative splicing to treat FD



# Compound IKBKAP splicing increases IKAP protein in FD patient-derived cells

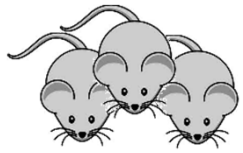


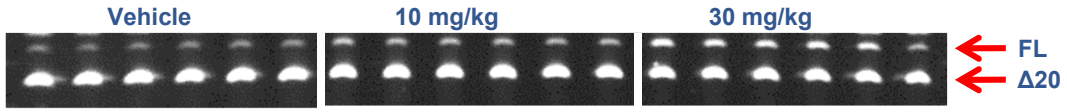


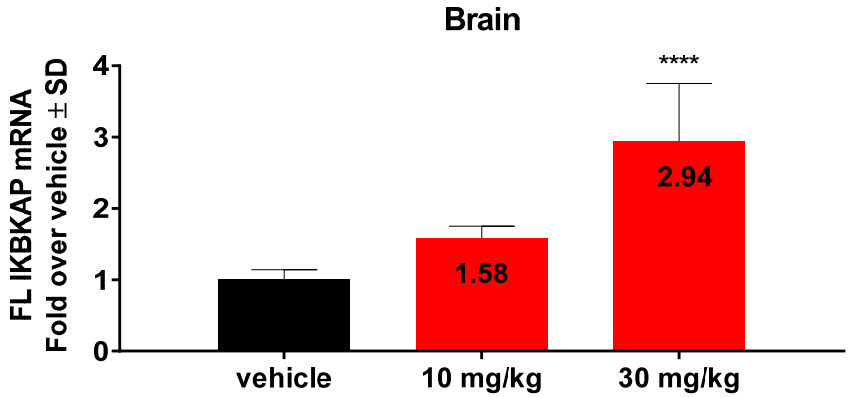



# Compound shifts splicing of mutant IKBKAP toward the production of full-length (wt) mRNA *in vivo*

*Ikbkap*$^{+/+}$, *IKBKAP TG*$^{FD9}$ mice[1]



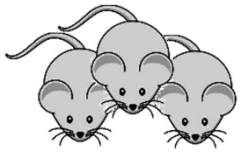


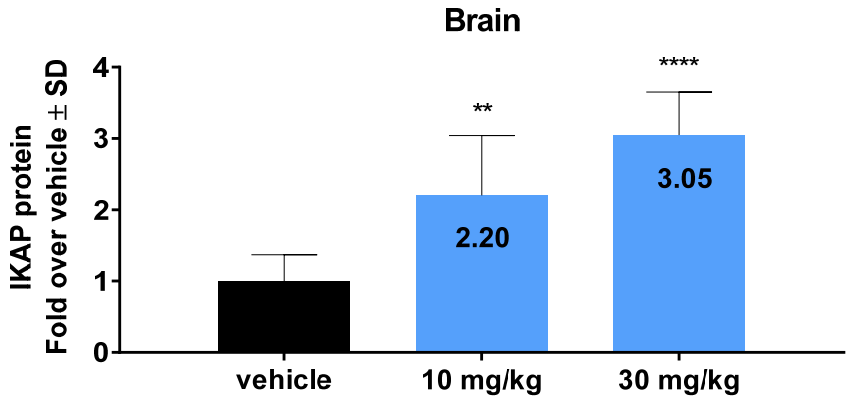




Hims MM, et al. *Genomics*. 2007;90(3):389-396.

# Compound increases IKAP protein level *in vivo*

*Ikbkap*$^{+/+}$, *IKBKAP TG*$^{FD9}$ mice[1]

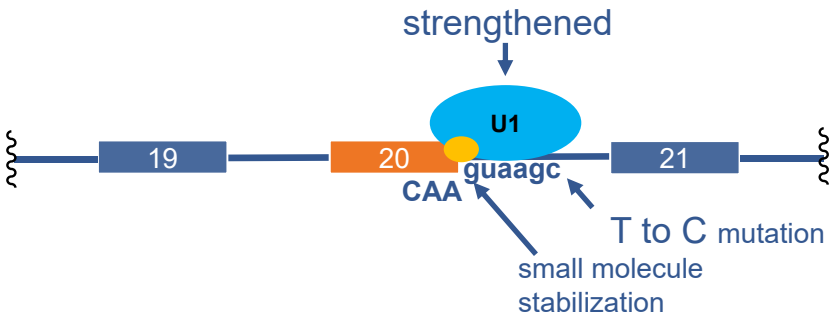


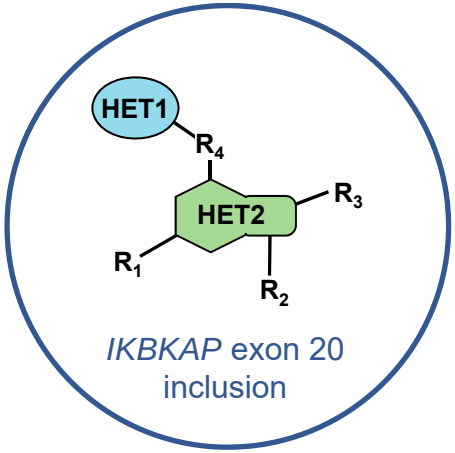



**Lead optimization is underway**
**Program scheduled to enter the clinic in 2019**

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

# IKBKAP splicing modifiers define a class of CAA-targeting small molecules



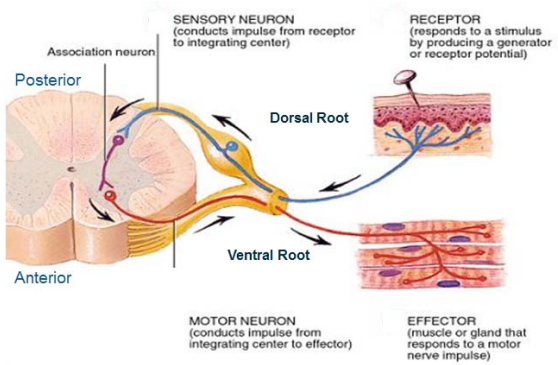



# SMN2 Splicing Modifiers to Treat Spinal Muscular Atrophy

Roche in collaboration with SMA FOUNDATION and PTC THERAPEUTICS 20 YEARS OF COMMITMENT

# Spinal muscular atrophy: 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 Roche and the SMA Foundation to advance treatments for SMA



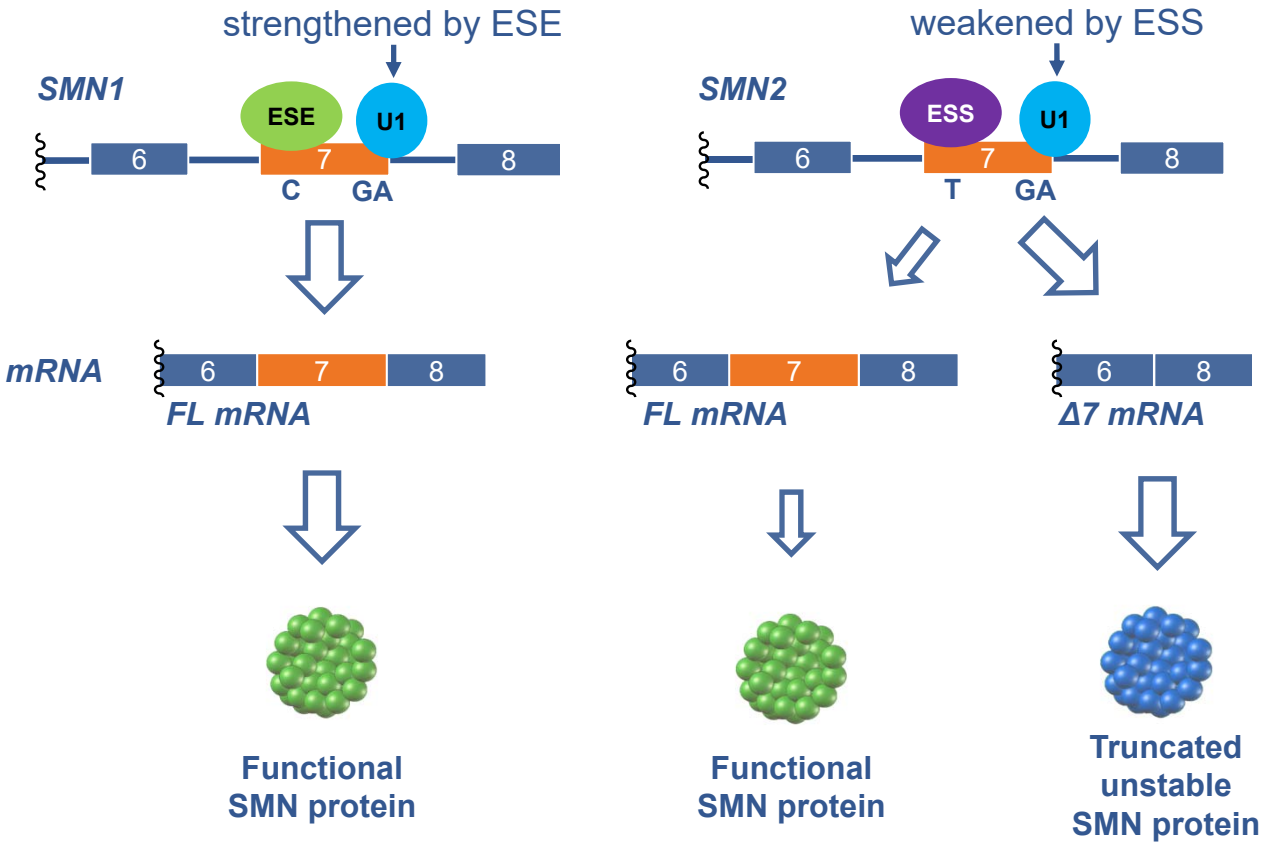

Sugarman EA, et al. *Eur J Hum Genet*. 2012;20(1):27-32.

# Spinal muscular atrophy: Types and symptoms

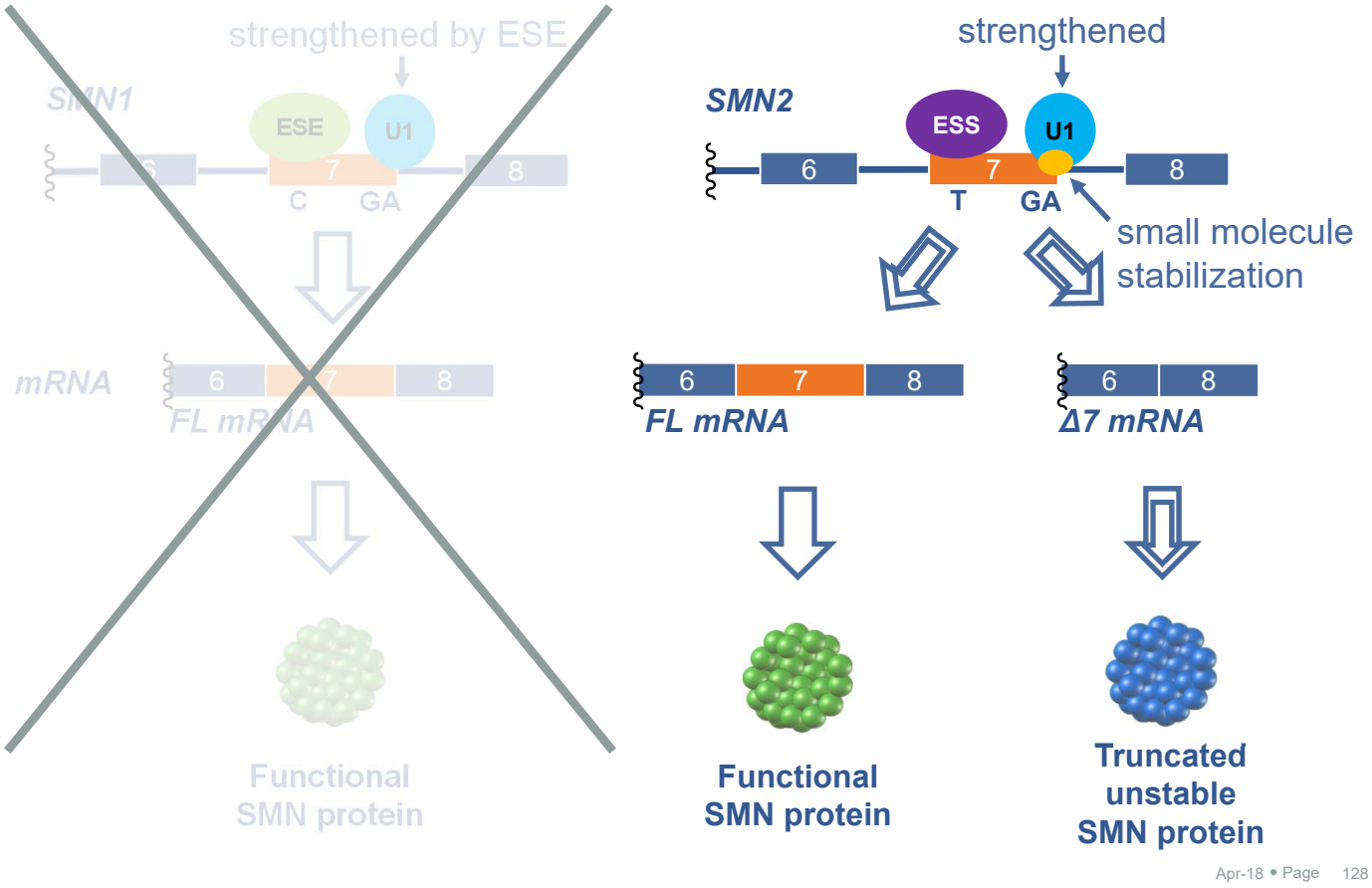
| Type | Age of symptom onset and disease severity | Common SMN2 copy # and SMN protein levels[1] |
|---|---|---|
| I | <6 months<br>Most severe, infants have trouble feeding and breathing, never sit, don't usually live past 2 years of age | ~2 copies<br>25-40% |
| II | <18 months<br>Intermediate, achieve unsupported sitting, contractures and scoliosis later in life, reduced life expectancy | ~3 copies<br>50-60% |
| III | >18 months<br>Can stand and walk unsupported; proximal muscle weakness and fatigue, loss of ambulation in some | 3 or 4 copies<br>70-80% |
| IV | >30 years<br>Rare; gradual weakening of muscles in adulthood | 4-5 copies |

1. Protein levels measured *in vitro* fibroblast cells as a percent of heterozygous levels.

# In the general population, SMN1 generates sufficient amount of SMN protein



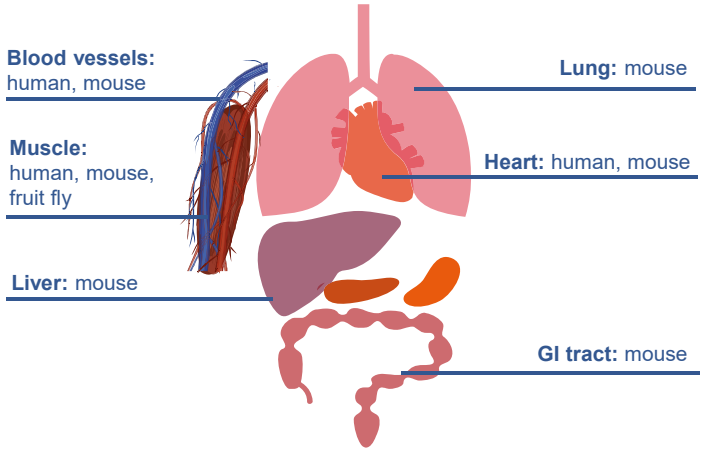
# Targeting alternative splicing of SMN2 in SMA



# Role of SMN protein beyond the motor neuron: SMA as a multi-system disorder

- Increasing evidence suggests reduced SMN levels may affect cells and tissues in both the CNS and periphery[1]
  - Increasing evidence of NMJ involvement[2]
  - SMN is important for skeletal muscle differentiation and function[1,3]
  - Vascular and cardiac abnormalities reported in patients with severe SMA[1,4]

Animal models: Peripheral and central SMN restoration was required for long-term rescue of a severe SMA mouse model[5]




1. Hamilton G, et al. *Trends Mol Med.* 2013;19(1):40-50. 2. Martínez-Hernández R, et al. *J Pathol*. 2013;229(1):49-61.). 3. Bricceno KV, et al. *Hum Mol Genet.* 2014;23(18):4745-4757). 4. Wijngaare CA, et al. *Orphanet J Rare Dis*. 2017;12(1):67. 5. Hua Y, et al. *Nature*. 2011;478(7367):123-126.

# RG7916: Over a decade in the making

- 2006: PTC Therapeutics and SMA Foundation enter into collaboration to find a small molecule-splicing modifier for SMN2 gene based on PTC technology
- 2011: Roche becomes 3rd partner in an innovative 3-party collaboration
- 2016: RG7916 enters clinical development
- 2017: RG7916 advances to a pivotal stage
- 2018: RG7916 preliminary clinical data presented

# Advancing toward planned registration of RG7916

- Sunfish[1]
  - Clinical study in SMA type 2 and 3 patients between 2 and 25 years old
    - Ongoing pivotal part will enroll 168 patients, placebo-controlled 2:1, endpoint of total motor function measure (MFM-32) at 12 months
- Firefish[2]
  - Clinical study in SMA type 1 patients between 1 and 7 months old
    - Ongoing pivotal part will enroll 40 babies, open-label, expected to complete enrollment during 2018
    - Endpoint of sitting unsupported as measured by Bayley infant scales

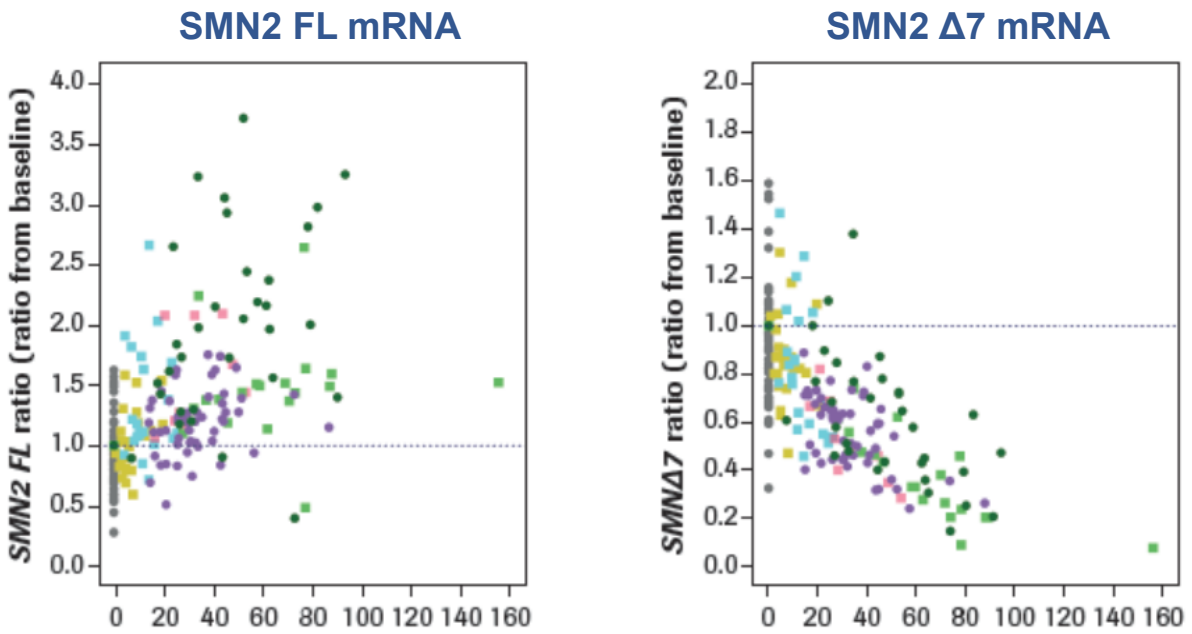
**Firefish dose escalation survival data presented in January**
**Ongoing data presentations expected in 2018**

Clinicaltrials.gov: 1. NCT02908685; 2. NCT02913482.



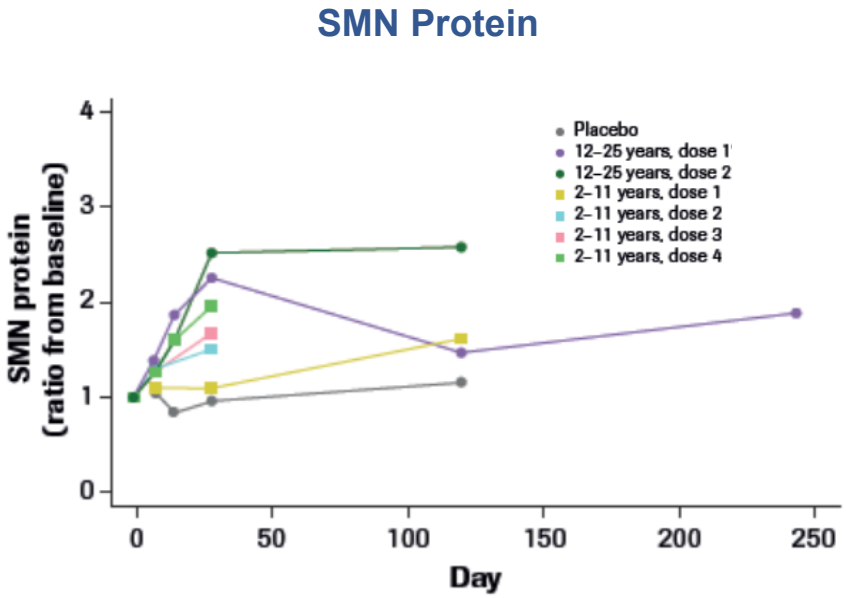
PTC THERAPEUTICS 20 YEARS OF COMMITMENT

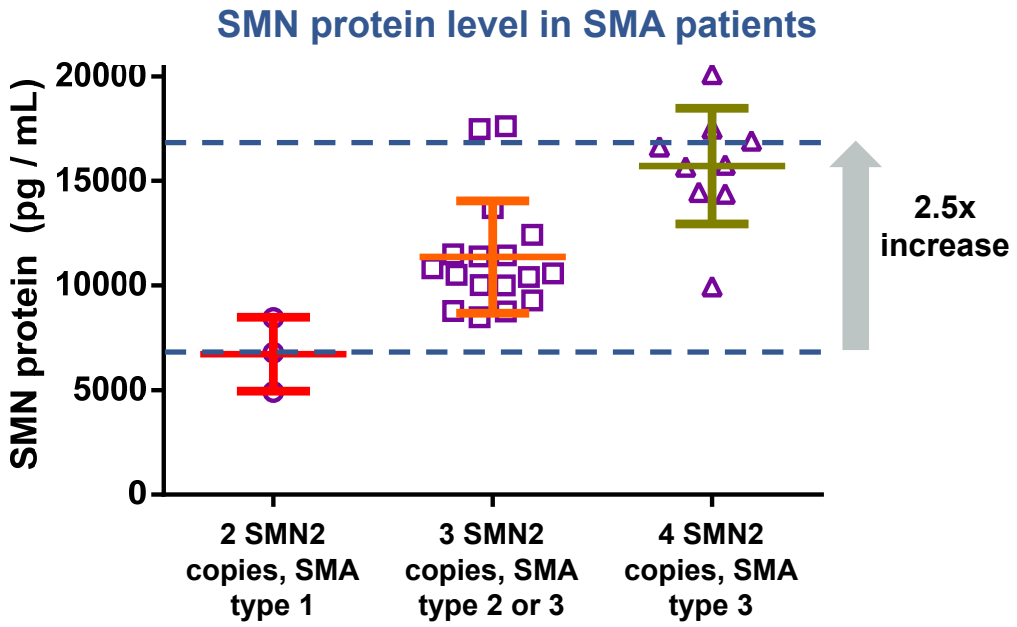
# RG7916 modifies SMN2 splicing in type 2 and 3 SMA patients (Sunfish part 1)




**A complete conversion to full-length mRNA at higher exposures**

# RG7916 increases SMN protein levels in type 2 and 3 SMA patients (Sunfish part 1)

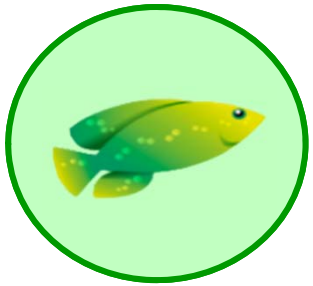


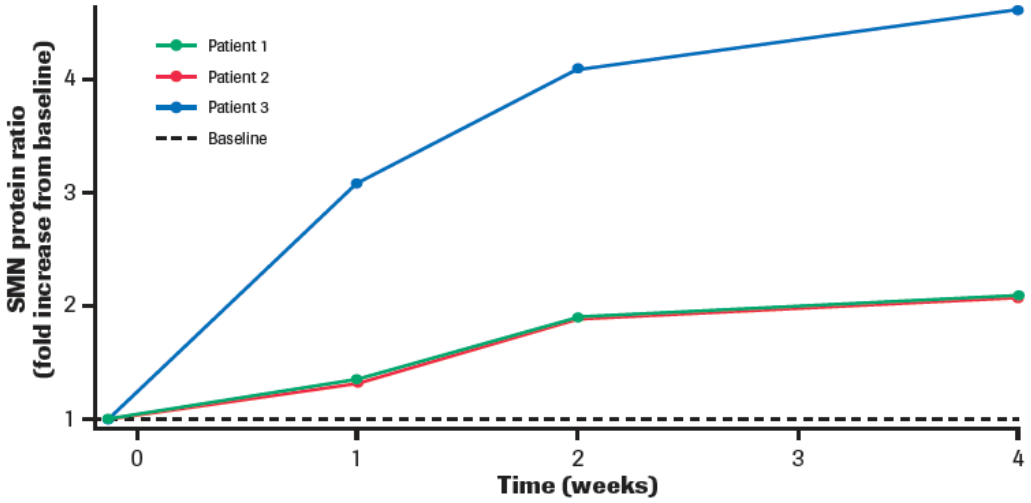

2.5-fold SMN protein level increase corresponds to a change from type 1 to higher end of type 3 SMA SMN levels

# RG7916 increases SMN protein levels in SMA patients previously received with splicing therapy

## JEWELFISH[1]



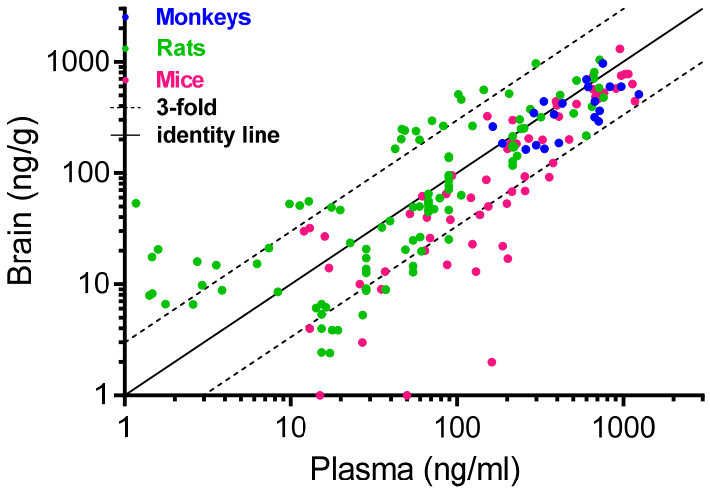
**Assess the safety, tolerability, and PK/PD of RG7916 in children and adults, aged 12–60 years with SMA, who previously participated in studies with other SMN2-targeting therapies (24 patients)**



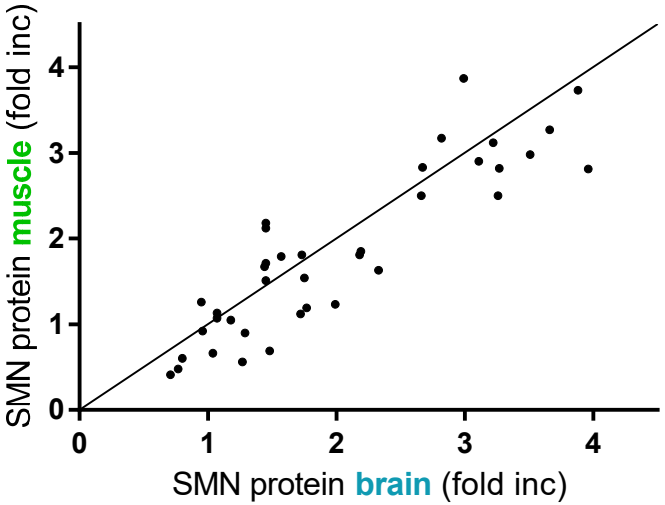

Clinicaltrials.gov: 1. NCT03032172.

# RG7916 is systemically distributed and elicits similar SMN level increases in all tissues

**RG7916**



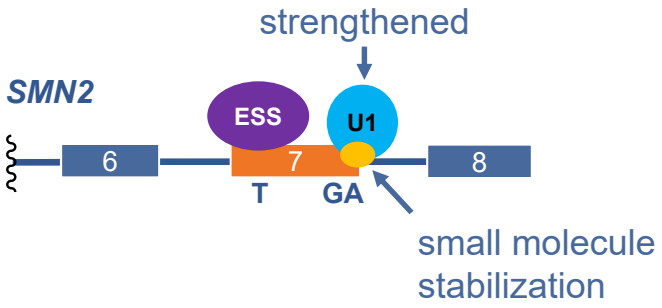

**RG7916**

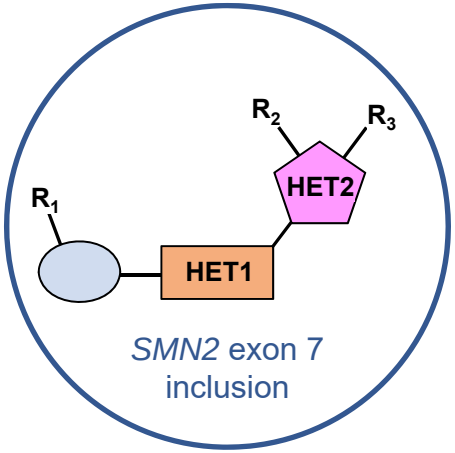


# RG7916 has the opportunity to be best-in-class SMA therapy

- Well-tolerated with no drug-related safety findings leading to withdrawal
- Demonstrated complete restoration of SMN RNA in SMA patients
- Median 2.5-fold persistent increase in SMN protein levels in patients
- Orally administered small molecule has potential for broad tissue distribution key to SMA treatment

# SMN2 splicing modifiers define a class of GA-targeting small molecules



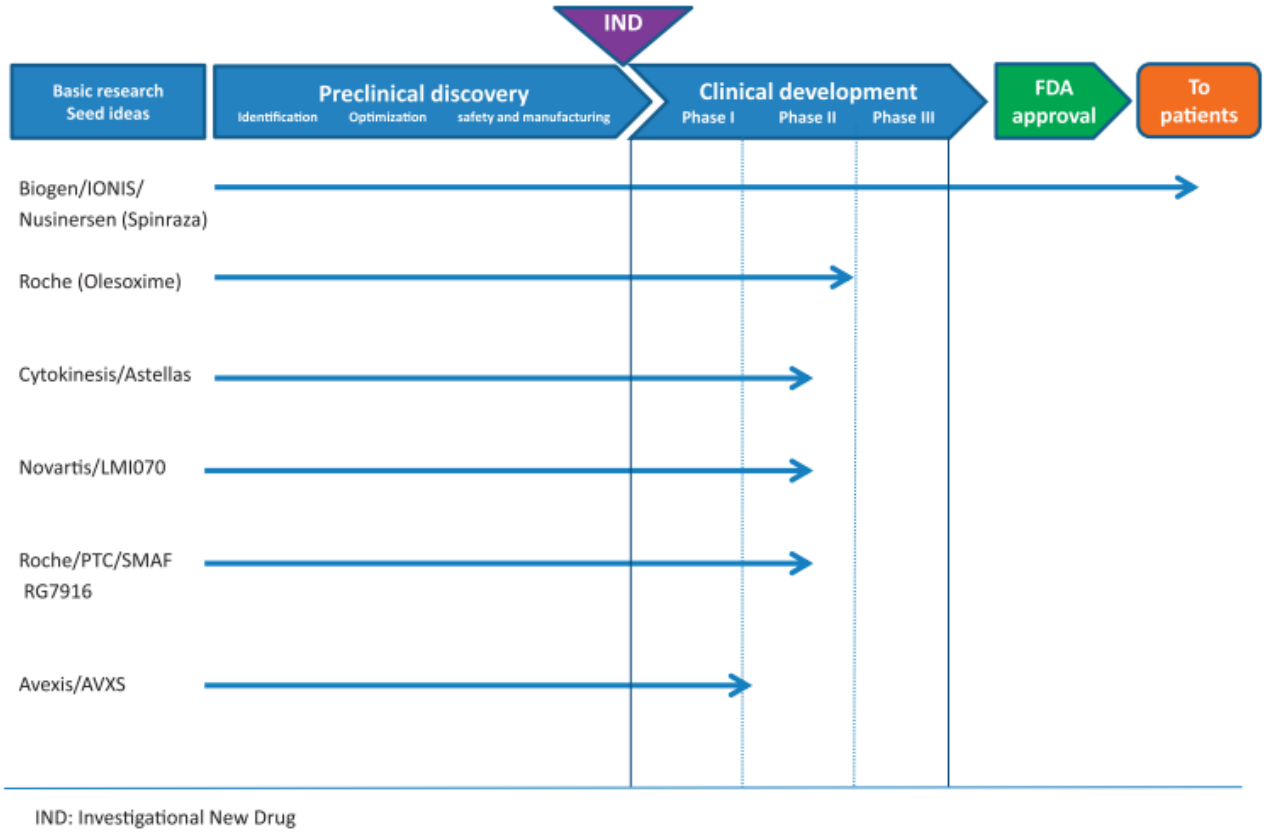
PTC Analyst Day, April 17, 2018

# Evolving Treatment Landscape in Spinal Muscular Atrophy

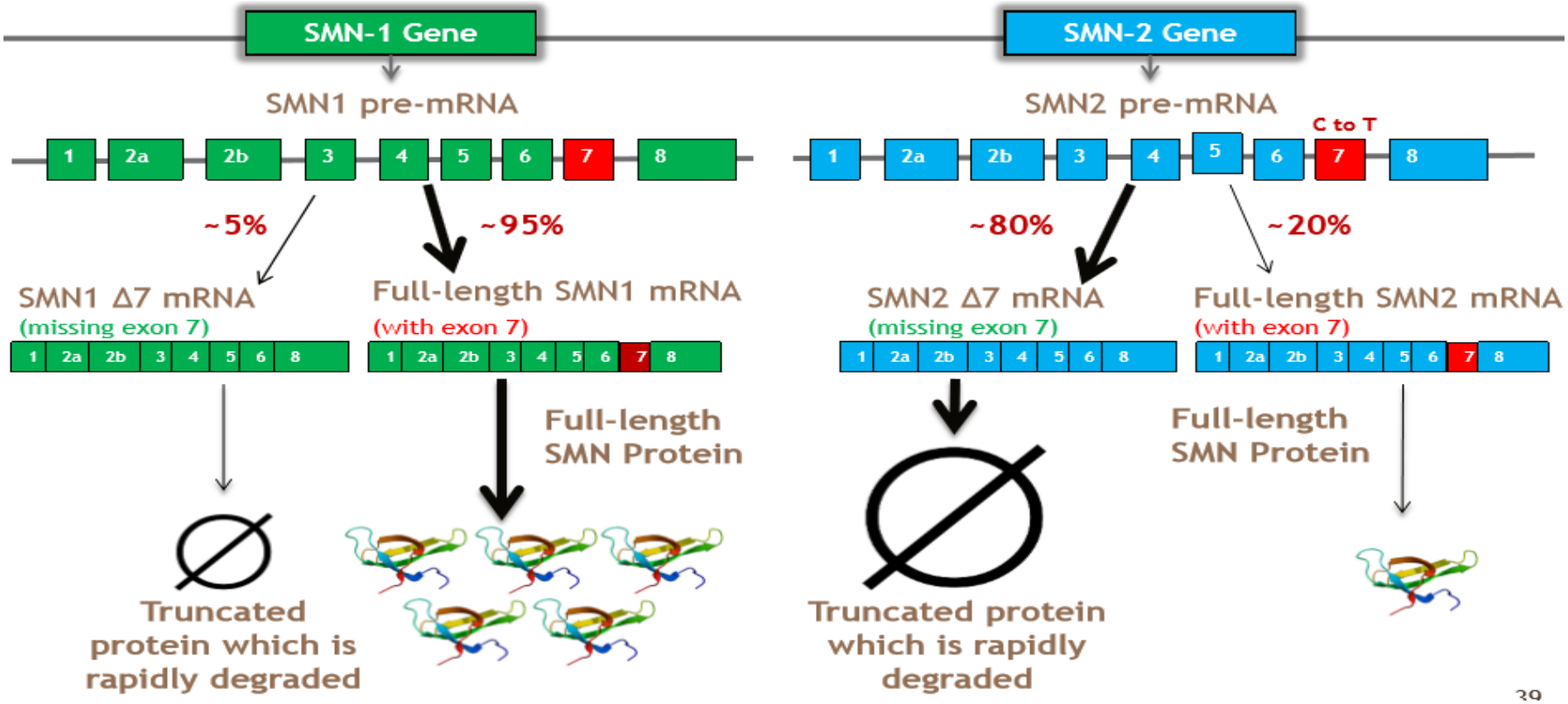
**Giovanni Baranello**
**Developmental Neurology Unit**
**Carlo Besta Neurological Research Institute**
**Milan, Italy**

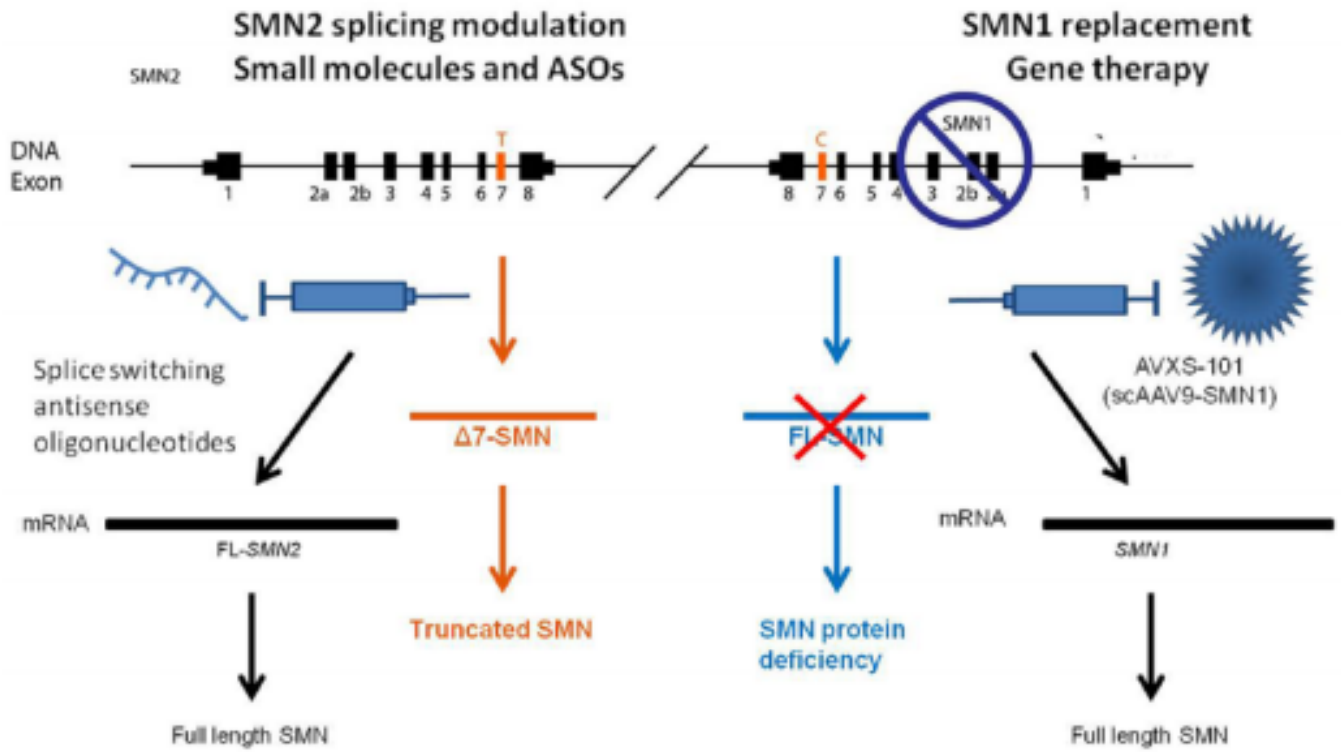
Fondazione I.R.C.C.S.
Istituto Neurologico Carlo Besta

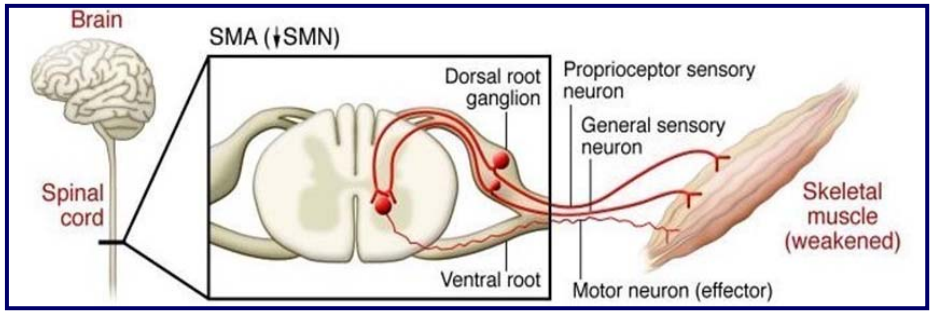
Sistema Socio Sanitario
Regione Lombardia

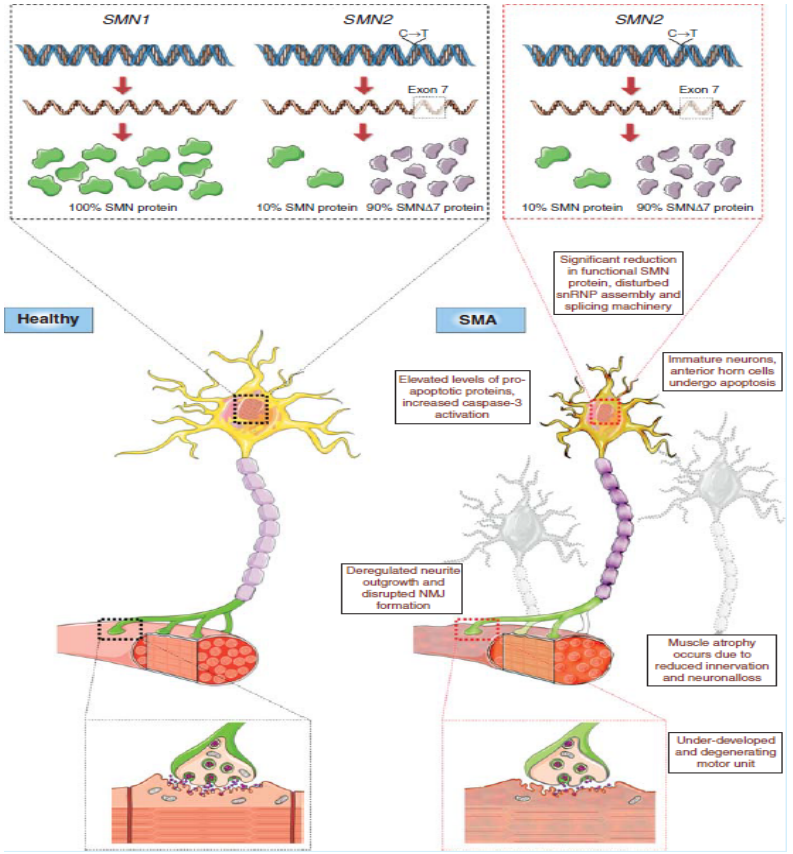



IND: Investigational New Drug

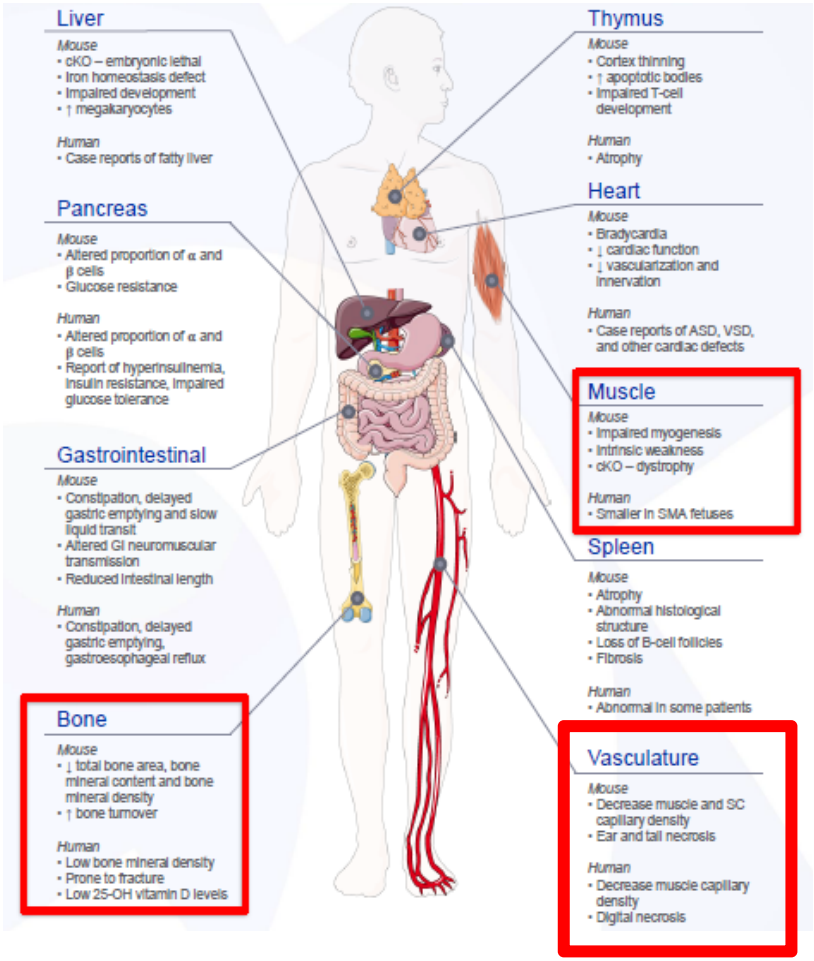

SMN-1 Gene
SMN-2 Gene
SMN1 pre-mRNA
SMN2 pre-mRNA
C to T
1 2a 2b 3 4 5 6 7 8
~5%
~95%
~80%
~20%
SMN1 Δ7 mRNA
(missing exon 7)
Full-length SMN1 mRNA
(with exon 7)
SMN2 Δ7 mRNA
(missing exon 7)
Full-length SMN2 mRNA
(with exon 7)
Full-length
SMN Protein
Full-length
SMN Protein
Truncated
protein which is
rapidly degraded
Truncated protein
which is rapidly
degraded


SMN2 splicing modulation
Small molecules and ASOs
SMN1 replacement
Gene therapy
SMN2
DNA
Exon
T
C
SMN1
1
2a
2b
3
4
5
6
7
8
Splice switching
antisense
oligonucleotides
Δ7-SMN
FL-SMN
AVXS-101
(scAAV9-SMN1)
mRNA
FL-SMN2
mRNA
SMN1
Truncated SMN
SMN protein
deficiency
Full length SMN
Full length SMN


Brain
SMA (↓SMN)
Spinal cord
Dorsal root ganglion
Proprioceptor sensory neuron
General sensory neuron
Skeletal muscle (weakened)
Ventral root
Motor neuron (effector)


SMN1
SMN2
C→T
Exon 7
100% SMN protein
10% SMN protein
90% SMNΔ7 protein
Healthy
SMA
Significant reduction in functional SMN protein, disturbed snRNP assembly and splicing machinery
Elevated levels of pro-apoptotic proteins, increased caspase-3 activation
Immature neurons, anterior horn cells undergo apoptosis
Deregulated neurite outgrowth and disrupted NMJ formation
Muscle atrophy occurs due to reduced innervation and neuronalloss
Under-developed and degenerating motor unit

# SMA as a multi-organ disorder



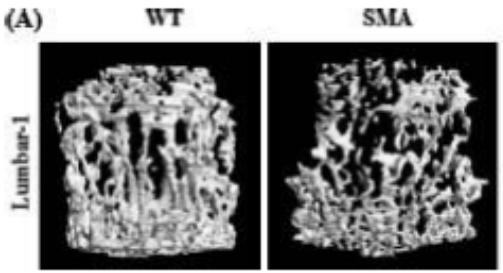
# Role of SMN in muscle: Overview

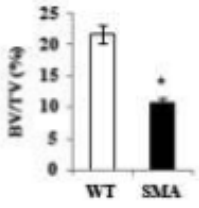
| Muscle defect | Source | Reference |
|---|---|---|
| Decreased satellite cell number | Biopsies from older SMA patients<br>C/C mice | *Lee Sweeney, unpublished* |
| Premature satellite cell differentiation | $Smn^{-/-}$; $SMN2^{+/+}$ mouse satellite cells | *Hayhurst et al, 2012* |
| Abnormal expression of myogenic markers | Biopsies from SMA patients<br>Delta7 mouse myoblasts<br>Delta7 mice<br>$Smn^{-/-}$; $SMN2^{+/+}$ and $2B/^{-}$ mouse myoblasts and mice | *Ripolone et al, 2015*<br>*Bricceno et al, 2014*<br>*Kong et al, 2009*<br>*Boyer et al, 2014* |
| Myotube fusion defects | Type I SMA patient myoblasts<br>$Smn^{-/-}$; $SMN2^{+/+}$ mouse myoblasts<br>Delta7 mouse myoblasts<br>$Smn^{-/-}$; $SMN2^{+/+}$ and $2B/^{-}$ mouse myoblasts<br>C2C12 SMN-deficient myoblasts | *Arnold et al, 2004*<br>*Hayhurst et al, 2012*<br>*Bricceno et al, 2014*<br>*Boyer et al, 2014*<br>*Shafey et al, 2005* |
| Defects in cell migration, cytoskeleton organization and focal adhesions | Delta7 mouse myoblasts | *Bricceno et al, 2014* |
| Muscle maintenance defects | HSA-Cre; $Smn^{F7/F7}$ mice<br>Pharmacological model | *Nicole et al, 2003*<br>*Chien-Ping Ko, unpublished* |
| Muscle regeneration defects | CreER; $Smn^{F7/-}$ mice<br>C/C mice | *Kariya et al, 2014*<br>*Lee Sweeney, unpublished* |

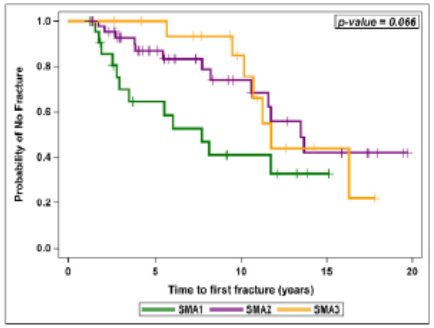
*Courtesy of SMA Foundation*

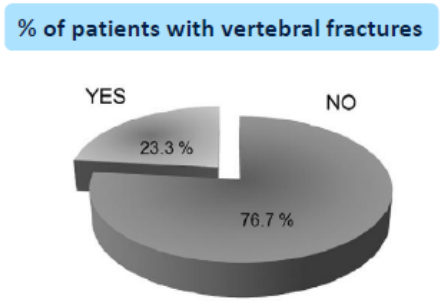
# Evidence suggests bone defects in SMA

- Decreased bone observed in SMA mouse models with various degrees of severity
- Enhanced osteoclast formation, bone resorption and fractures observed in SMA mice (Shanmugarajan et al., 2007, 2009)
- Children with SMA Types 2 and 3 exhibit reduced bone density, increased bone resorption markers, and asymptomatic vertebral fractures (Vai et al, 2015; *Wasserman et al, 2017*)

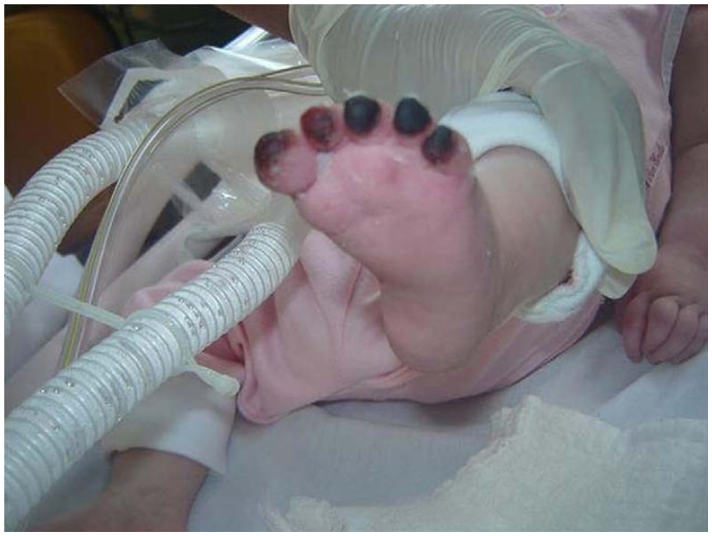


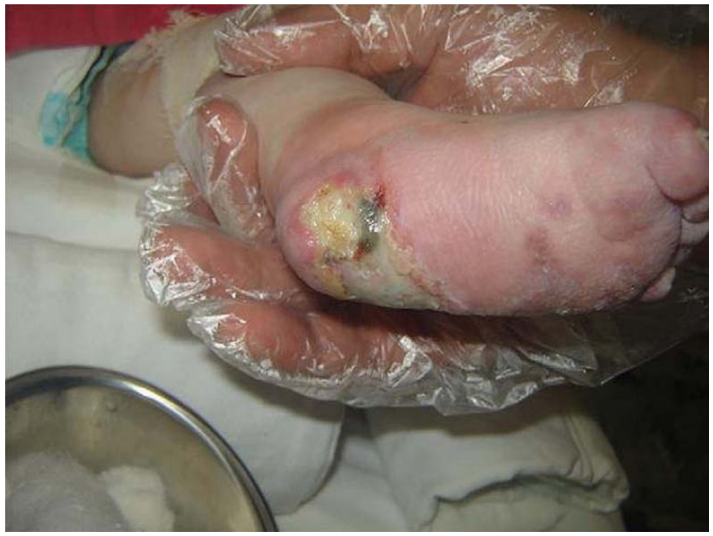



# Vascular defects in SMA

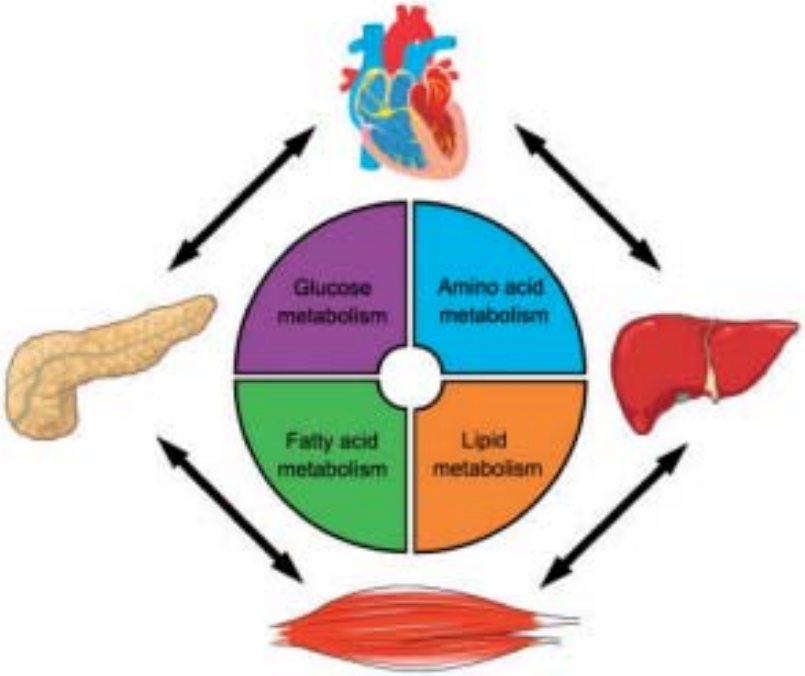






de Queiroz Campos Araujo, 2009;
Somers, 2015

# Metabolic abnormalities in SMA



SMA is a severe, progressive neuromuscular disease leading to loss of motor function and reduced life expectancy.

Most of SMA Type 1 patients die by their 2$^{nd}$ birthday if they do not receive ventilatory and nutritional support while losing their motor function (no further motor milestone achievements).

## Natural History of SMA Type 1

- Two recent reports on natural history of SMA
  - Finkle et al. Neurol. 2014; 83:810
  - Kolb et al. Ann. Neurol. 2017; 82:883
- End point of survival or >16 hours on permanent ventilation for 14 days
  - 50% by 10.5 months
  - 25% by 13.6 months
  - 8% by 20 months

# RG7916 ongoing clinical studies


**FIREFISH[1]**
Type 1 SMA,
1–7 months

**SUNFISH[2]**
Type 2 or 3 SMA,
2–25 years

**JEWELFISH[3]**
Type 2 or 3 SMA,
non-naïve, 12–60 years

RG7916 is an orally administered, centrally and peripherally distributed *SMN2* pre-mRNA splicing modifier that increases SMN protein levels

- Preclinical data show similar RG7916 concentrations in blood, brain, and muscle tissue
- Similar SMN protein increases in the brain and muscle in SMA mouse models following RG7916 administration
- Proof-of-mechanism of oral SMN2 splicing modifiers was previously established in preclinical models and in Type 2 and 3 SMA patients with RG7916

# RG7916 ongoing clinical studies

**FIREFISH[1]**
Type 1 SMA,
1–7 months

| 2016 | 2017 | 2018 | 2019 | 2020 |
|---|---|---|---|---|
| Part 1 Safety and PK/PD of RG7916* 2 dose levels; n=8–24 | Part 2 Safety and efficacy of RG7916* Dose selected from Part 1; open-label; n=40 | | | |

**SUNFISH[2]**
Type 2 or 3 SMA,
2–25 years

| 2016 | 2017 | 2018 | 2019 | 2020 |
|---|---|---|---|---|
| Part 1 Safety and PK/PD of RG7916* 2 dose levels; n=36–72 | Part 2 Safety and efficacy of RG7916* Dose selected from Part 1; n=168; non-ambulatory patients | | | |

**JEWELFISH[3]**
Type 2 or 3 SMA,
non-naïve, 12–60 years

| 2016 | 2017 | 2018 | 2019 | 2020 |
|---|---|---|---|---|
| Safety and tolerability of RG7916* in previous participants of studies with other *SMN2*-targeting therapies Single-dose, open-label, exploratory, N=24 | | | | |

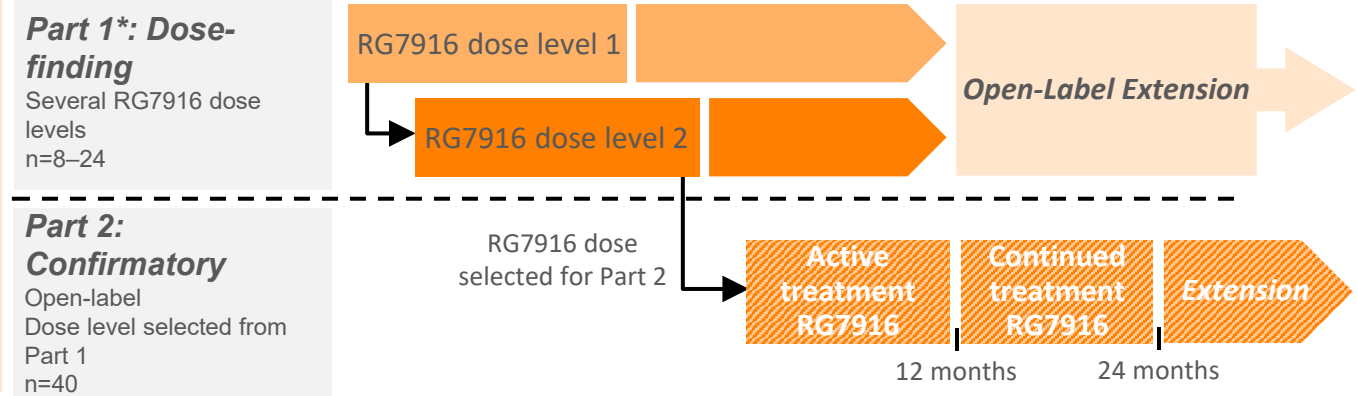
*RG7916 is an investigational medicine.
Clinicaltrials.gov 1. NCT02913482; 2. NCT02908685; 3. NCT03032172. Accessed June 2017.

# FIREFISH: Study overview

**FIREFISH**
Type 1 SMA
1–7 months old

***Part 1*: Dose-finding***
Several RG7916 dose levels
n=8–24

***Part 2: Confirmatory***
Open-label
Dose level selected from Part 1
n=40




| | |
|---|---|
| **Key inclusion criteria** | • Genetic confirmation of homozygous deletion or compound heterozygosity predictive of loss of function of SMN1<br>• Clinical history, signs or symptoms attributable to SMA type 1 after 28 days but prior to 3 months<br>• Adequate nutrition at time of enrollment and willing to consider tube if required<br>• Two SMN2 gene copies (confirmed by central testing during screening) |
| **Key exclusion criteria** | • Concomitant or previous participation in a SMN2-targeting or gene therapy study<br>• Invasive ventilation or tracheostomy<br>• Awake, non-invasive ventilation or with awake hypoxemia ($SaO_2$ <95%) with or without ventilator support<br>• Hospitalization for pulmonary event within the last 2 months, or planned at the time of screening<br>• Recent history (<1 year) of ophthalmological disease |

**Detailed study information**: clinicaltrials.gov/ct2/show/NCT02913482 www.roche-sma-clinicaltrials.com

*Comprises minimum two dose-ranging cohorts; Patients to be enrolled in a stepwise fashion based on PK findings to minimize exposure.
https://clinicaltrials.gov/ct2/show/NCT02913482, accessed Jan 2018.

# FIREFISH: Outcome measures

| | Part 1 | Part 2 |
|---|---|---|
| **Primary endpoint** | • **Safety, tolerability, PK and PD of RG7916**<br>• **Dose selection for Part 2** | **% infants sitting without support for 5 seconds at 12-months assessed by Gross Motor Scale of the BSID-III** |
| **Secondary endpoints** | | • Motor function (HINE-2, CHOP-INTEND)<br>• Pharmacodynamics/PK<br>• Safety<br>• Time to death or permanent ventilation<br>• Respiratory Plethysmography (RP)<br>• Compound Muscle Action Potential Negative Peak Amplitude (CMAP) |

https://clinicaltrials.gov/ct2/show/NCT02913482. Accessed January 2018.
BSID-III, Bayley Scales of Infant and Toddler development Third Edition; CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HINE-2, Hammersmith Infant Neurological Examination Module 2.

# Patient demographics and baseline characteristics from the first 13 patients and study status

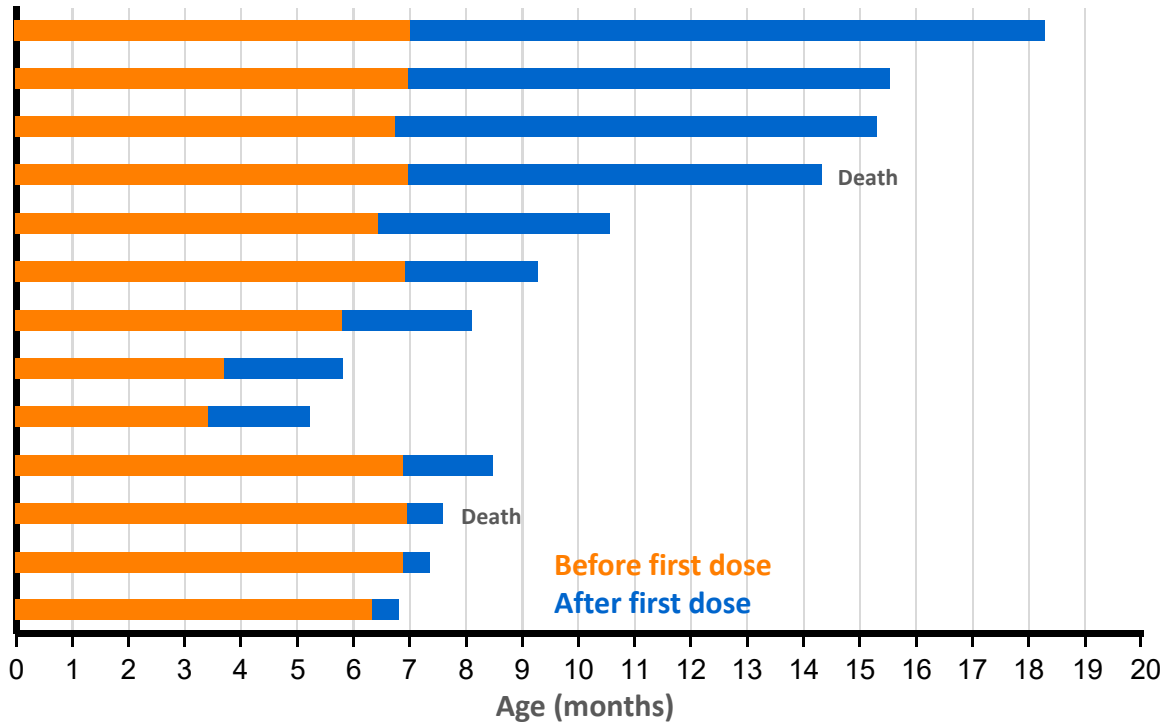
- Part 1 (dose-finding)
- 10 active sites: Italy, France, USA, Belgium, Switzerland, Turkey
- Data presented here are from the first 13 patients recruited
- Part 2 ongoing

*

| | All Treatments (N=13) |
|---|---|
| **Age at first dose (months)** | |
| Median (IQR) | 6.9 (6.3–6.9) |
| **Gender** | |
| Female, n (%) | 10 (76.9) |
| **Weight at baseline (g)** | |
| Median (IQR) | 6720 (5650–7600) |
| **Age at diagnosis (months)** | |
| Median (IQR) | 3.5 (2.1–4.6) |

IQR=interquartile range.
Data current as of December 7, 2017.
RG7916 is an investigational medicine and benefit/risk profile has not yet been fully established. The information presented is from early interim analysis.

# Age of patients and duration of exposure to treatment




Study duration is measured from start date of first dose to date of data extraction. Data current as of December 7, 2017.
RG7916 is an investigational medicine and benefit/risk profile has not yet been fully established. The information presented is from early interim analysis.

# Summary of clinical outcomes

## No patients have required tracheostomy or permanent ventilation*

*Permanent ventilation defined as ≥16 hours of assisted ventilation per day for more than 2 weeks or continuous intubation ≥30 days

## No patient has lost the ability to swallow

| Visit | All Treatments |
|---|---|
| **Baseline** | **N=13** |
| Able to swallow, n | 12 |
| Unable to swallow, n | 1 |
| **Week 8** | **N=9** |
| Able to swallow, n | 8 |
| Unable to swallow, n | 1 |
| **Week 17** | **N=4** |
| Able to swallow, n | 4 |
| Unable to swallow, n | 0 |
| **Week 26** | **N=4** |
| Able to swallow, n | 4 |
| Unable to swallow, n | 0 |
| **Week 35** | **N=3** |
| Able to swallow, n | 3 |
| Unable to swallow, n | 0 |

Data current as of December 7, 2017.

RG7916 is an investigational medicine and benefit/risk profile has not yet been fully established. The information presented is from early interim analysis.

# Summary of safety outcomes

- Overall 10 (77%) out of 13 patients experienced at least one adverse event. Most events were mild in intensity and resolved despite ongoing treatment
- Adverse events reported in more than one patient were pyrexia (n=5), upper respiratory tract infection (n=3), diarrhea (n=2), vomiting (n=2), erythema (n=2)
- Serious adverse events were reported in 4 patients: Viral respiratory tract infection, pneumonia and neutropenia, acute respiratory failure, and hypoxia
- Ophthalmological monitoring conducted every 2 months did not show any evidence of the retinal toxicity seen in preclinical monkey studies in any patient exposed to RG7916
- Fatal events were reported in two patients:
  - Viral respiratory tract infection with fatal outcome on study Day 21
  - Cardiac arrest and respiratory arrest with fatal outcome on study Day 236*

*Event reported after cut-off date November 15, therefore not included in serious adverse events count.
Reference: interim safety summary BP39056 part 1 dated January 8, 2018.

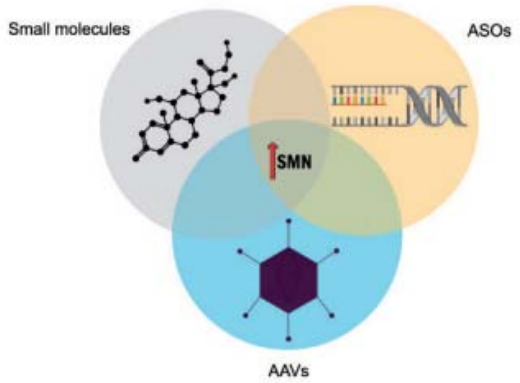
# Conclusions

- **To date, RG7916 has been safe and well-tolerated at all doses and there have been no drug-related safety findings leading to withdrawal in any SMA patients exposed to RG7916**
- Ophthalmologic monitoring did not show any evidence of the retinal toxicity seen in preclinical monkey studies in any patient exposed to RG7916
- Early interim clinical data reported:
  - No patient lost the ability to swallow
  - No patient has required tracheostomy or reached permanent ventilation
- Study updates will continue to be communicated at congresses in 2018
- Part 2 is currently recruiting

# In summary: The evolving treatment landscape in SMA

- One treatment based on repeated intrathecal injections in now available
- A few systemic approaches (eg single endovenous AAV-SMN1 gene transfer; oral splicing modifier) are currently under clinical investigation
- A relationship between timing of the therapeutic intervention and response has been identified in animal studies, but is still unknown in humans
- It is still unclear whether clinical responses to either repeated intrathecal treatment or single endovenous SMN1 gene transfer will be sustained over time, especially in the growing child.

- Animal models and data in humans have provided evidence that SMA pathology is not restricted to motor neurons, but rather is a composite of pathology involving different organs and tissues
- It remains uncertain whether treatments targeting motor neurons and not systemic tissues (continuously) will lead to the development of multi-organ system dysfunction over time
- A possible integrated treatment of SMA will be part of a life-long strategy for management of disease symptoms and tailored to each individual patient in the future



# AAN RG7916 Preview

**RG7916 Significantly Increases SMN Protein in SMA Type 1 Babies**

004 (Emerging Science platform), Tuesday, 24 April, 5:54 PM oral 3 min presentation followed by a poster presentation

**Updated pharmacodynamic and Safety Data from SUNFISH Part 1**, a Study Evaluating the Oral SMN2 Splicing Modifier RG7916 in Patients with Type 2 or 3 Spinal Muscular Atrophy, P4.453 (poster), Wednesday, 25 April

**Preliminary Evidence for Pharmacodynamics Effects of RG7916 in JEWELFISH**, a Study in Patients with Spinal Muscular Atrophy who Previously Participated in a Study with Another SMN2-Splicing,S46.003 (platform), Thursday, 26 April

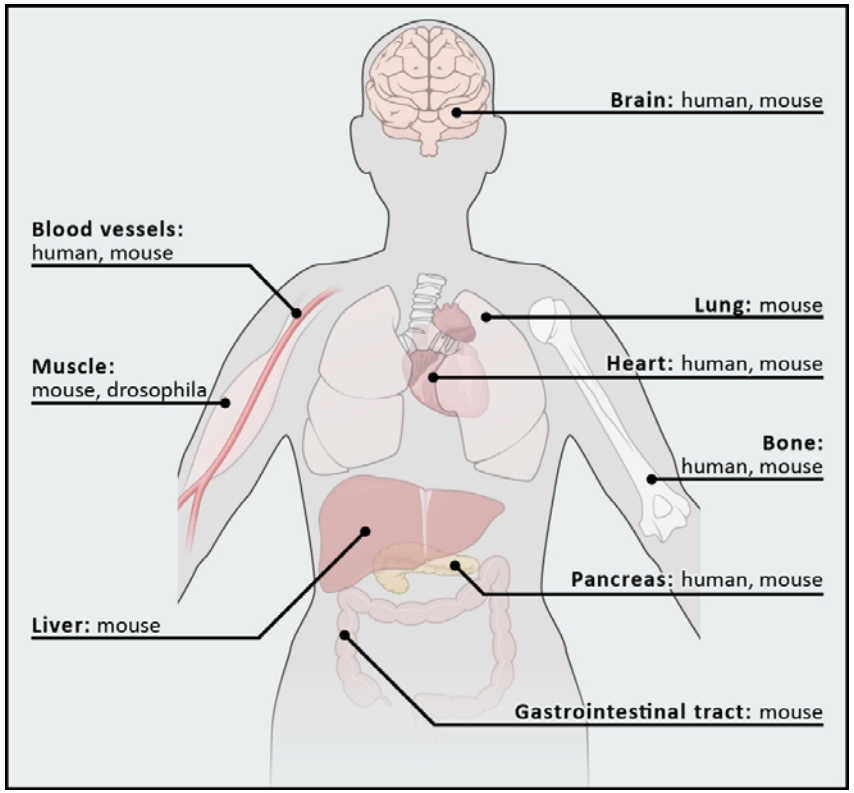
**Relationship Between Central and Peripheral SMN Protein Increase Upon Treatment with (RG7916)**
S46.007 Platform Neuromuscular and Clinical Neurophysiology (EMG), Thursday, April 26

# The Unmet Need in Spinal Muscular Atrophy

PTC Therapeutics Science Day

April 17, 2018

# SMA IS A WHOLE BODY DISEASE




*Hamilton and Gillingwater, 2013*

# SMA IS A MULTI-SYSTEM DISORDER

| Tissue | SMA mouse | SMA patients (mostly Type I) |
|---|---|---|
| **Bone** | • Decreased bone volume and density (Smn−/−SMN2)<br>• Increase in number of osteoclasts | • Lower bone mineral density<br>• High prevalence of fractures |
| **Connective tissues** | • ? | • Joint hypermobility/hyperextensibility, prominent heels, progressive foot collapse, joint pain, abdominal wall hernias<br>• Poor wound healing |
| **Vasculature** | • Decreased capillary density in symptomatic SMA mice in both muscle and spinal cord (Taiwanese and delta 7)<br>• Depleted vasculature results in vivo hypoxia in spinal cord and defective blood brain barrier<br>• Necrosis in tail, ears, eyes (various models) | • Reduced capillary density in muscles of Type 1 and 2 patients<br>• Microvascular abnormalities reported in Type 2 and 3 patients: decrease in the number of endothelial progenitor cells; microvascular injury and impaired vascular repair (Muntoni)<br>• A few reported cases of finger necrosis– not common |
| **Gastro-Intestinal** | • Reduced numbers of villi; villi of different shape, intramural edema (Taiwanese)<br>• Blood-filled GIs observed (2B/-)<br>• Diarrhea, necrotic bowel, small spleen, liver (Taiwanese) | • Progressive intolerance to bolus feeding, failure to absorb nutrients<br>• Poor motility reflux, acute ileus, pseudo-obstruction<br>• No gross necrosis in GI |
| **Pancreas** | • Abnormalities in islet cells (↑alpha, ↓ beta) (2B/-)<br>• Fasting hyperglycemia, hyperglucagonemia, glucose resistance (2B/-)<br>• Hypoglycemia with increased ketone production (delta7) | • Abnormalities in islet cells (↑alpha, ↓ beta)<br>• Reports of abnormal glucose levels (hyperinsulinemia with resistance to insulin, hypoglycemia and ketonuria)<br>• High glucose levels observed in 39% of Type I (nusinersen trial data) |
| **Liver** | • Liver restricted SMN depletion results in embryonic lethality<br>• Reduced expression of IGFals<br>• Liver abnormalities: Dark colored, iron deposits, immature sinusoids congested with blood, increased immature red blood cells, increased and persistent megakaryocytes(Taiwanese) | • Abnormal levels of esterified carnitine, dicarboxylic aciduria<br>• Increased dodecanoic to tetradecanoic acid (C12:C14)<br>• Development of ketonuria upon fasting<br>• Fatty acid-filled vacuoles in autopsy material were reported |
| **Heart** | • Bradycardia (various severe models)<br>• Dilated cardiomyopathy with a concomitant decrease in contractility (delta7, Burgheron)<br>• Thin heart walls and dilated ventricles (delta7) | • No evident cardiac abnormalities for most patients<br>• However, reported cases of cardiac defects in very severe Type I patients |
| **Kidney** | • Enlarged kidneys and adrenal glands (2B/-) | • Elevated protein in urine observed in 20% of Type I (nusinersen trial data) |
| **Spleen** | • Reduced spleen size (delta7, Taiwanese, 2B/-)<br>• Reduced red pulp size, changes in lymphocyte macrophages | • Various abnormal splenic pathologies |

# REFERENCES FOR A PERIPHERAL PHENOTYPE IN SMA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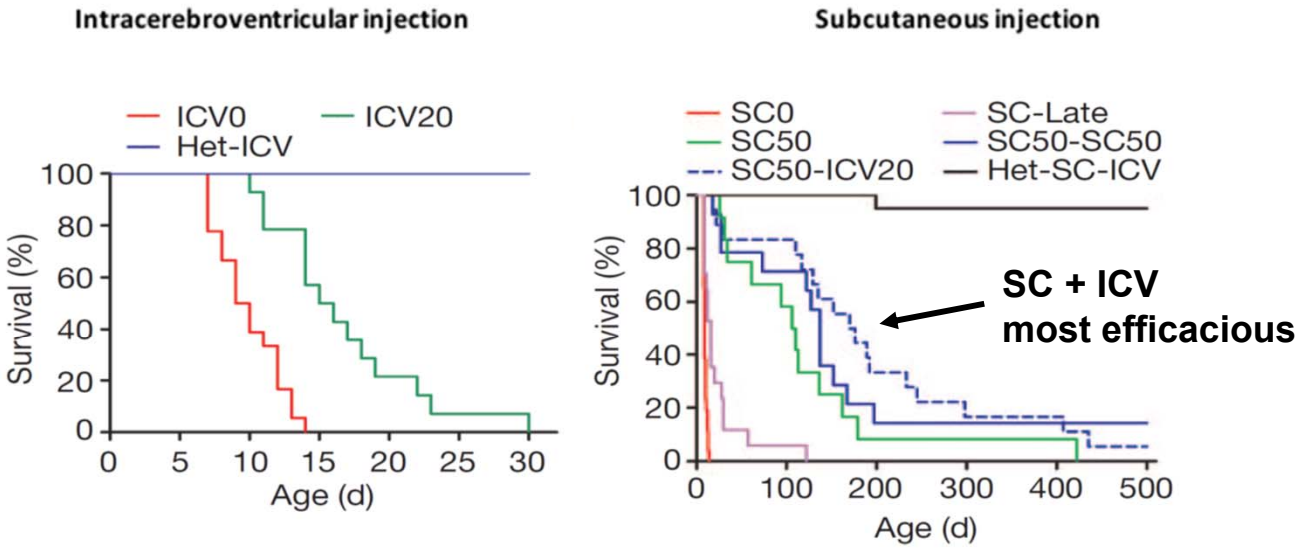
# SYSTEMIC SMN-UPREGULATION IS MORE EFFICACIOUS THAN CNS-ONLY SMN-UPREGULATION IN SMA MICE




*Subcutaneous injection increased median survival from 17 to 100+ days compared to ICV injection*

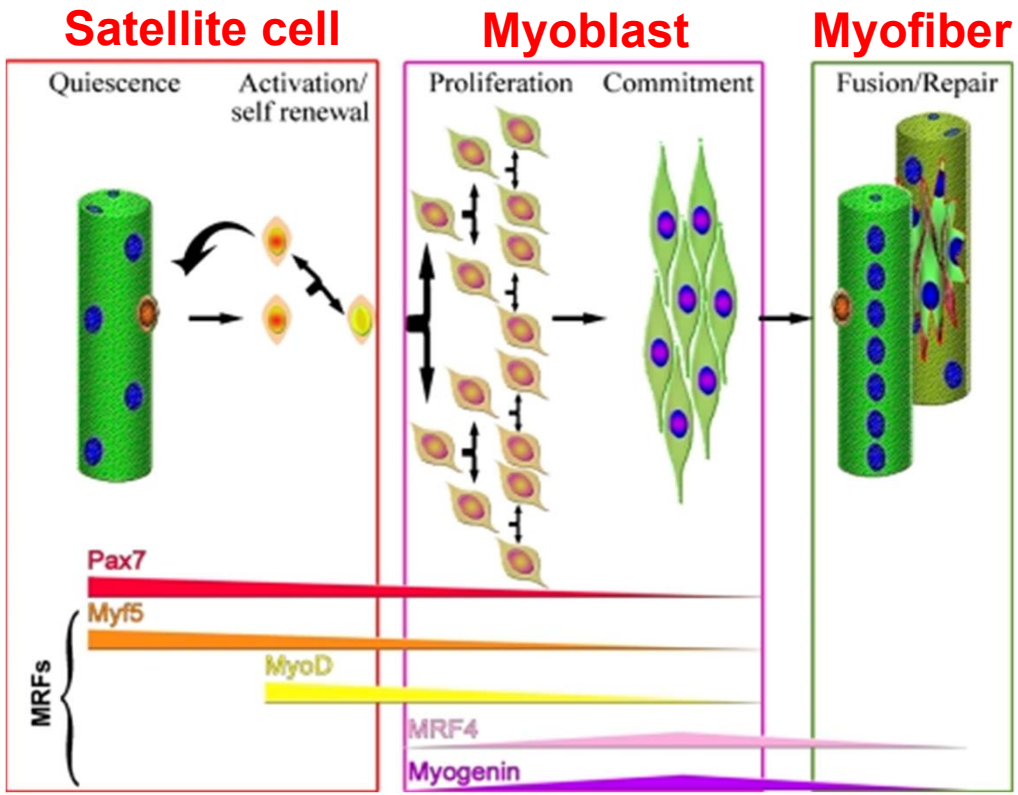


Hua Y, et al. *Nature*. 2011;478(7367):123-126.

# SMN ROLE IN THE MUSCLE

| Muscle defect | Source | Reference |
|---|---|---|
| Decreased satellite cell number | Biopsies from older SMA patients<br>C/C mice | *Lee Sweeney, unpublished* |
| Premature satellite cell differentiation | $Smn^{-/-}$; $SMN2^{+/+}$ mouse satellite cells | *Hayhurst et al, 2012* |
| Abnormal expression of myogenic markers | Biopsies from SMA patients<br>Delta7 mouse myoblasts<br>Delta7 mice<br>$Smn^{-/-}$; $SMN2^{+/+}$ and $2B/^{-}$ mouse myoblasts and mice | *Ripolone et al, 2015*<br>*Bricceno et al, 2014*<br>*Kong et al, 2009*<br>*Boyer et al, 2014* |
| Myotube fusion defects | Type I SMA patient myoblasts<br>$Smn^{-/-}$; $SMN2^{+/+}$ mouse myoblasts<br>Delta7 mouse myoblasts<br>$Smn^{-/-}$; $SMN2^{+/+}$ and $2B/^{-}$ mouse myoblasts<br>C2C12 SMN-deficient myoblasts | *Arnold et al, 2004*<br>*Hayhurst et al, 2012*<br>*Bricceno et al, 2014*<br>*Boyer et al, 2014*<br>*Shafey et al, 2005* |
| Defects in cell migration, cytoskeleton organization and focal adhesions | Delta7 mouse myoblasts | *Bricceno et al, 2014* |
| Muscle maintenance defects | HSA-Cre; $Smn^{F7/F7}$ mice<br>Pharmacological model | *Nicole et al, 2003*<br>*Chien-Ping Ko, unpublished* |
| Muscle regeneration defects | CreER; $Smn^{F7/-}$ mice<br>C/C mice | *Kariya et al, 2014*<br>*Lee Sweeney, unpublished* |

# SMN PLAYS AN IMPORTANT ROLE IN MUSCLE DEVELOPMENT



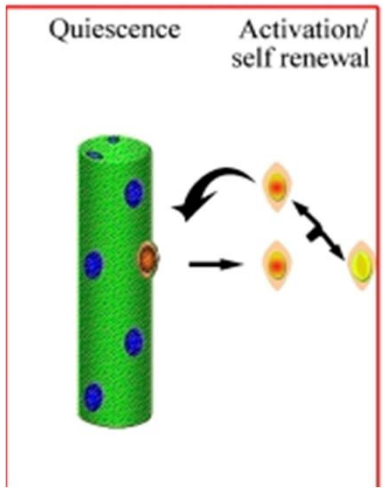

*Boldrin et al., 2010*



SMA FOUNDATION

# SMN PLAYS AN IMPORTANT ROLE IN MUSCLE DEVELOPMENT

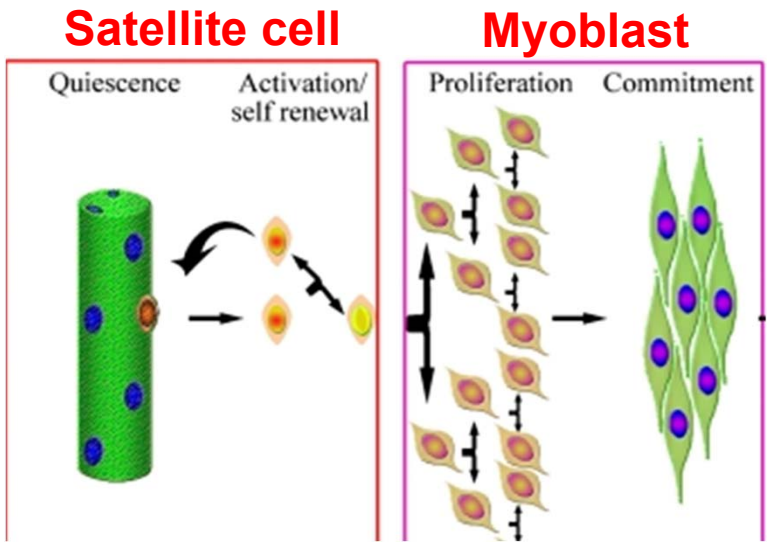
**Satellite cell**




***Satellite cell (SC) number is reduced***
***(Rashmi Kothary)***

*Boldrin et al., 2010*

# SMN PLAYS AN IMPORTANT ROLE IN MUSCLE DEVELOPMENT

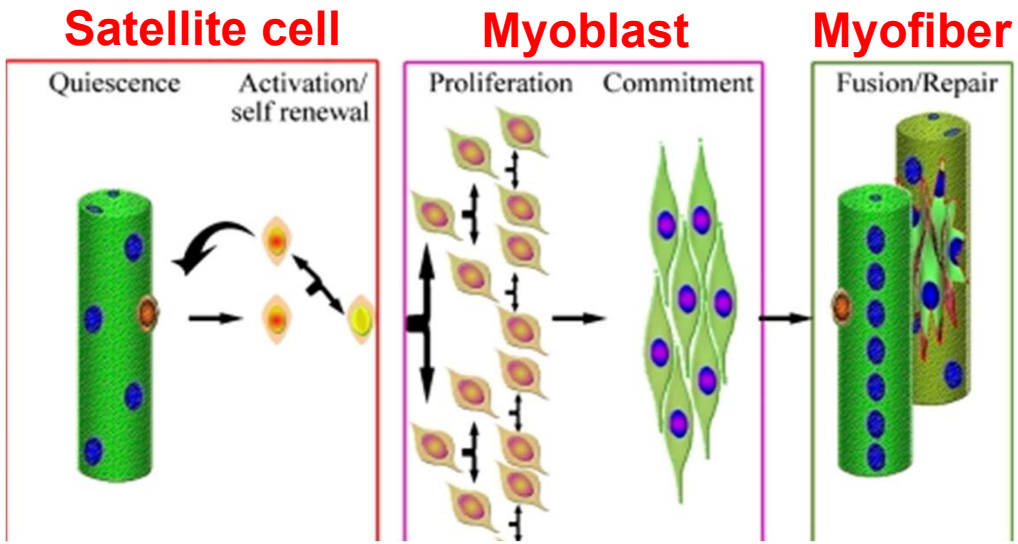



***Satellite cell (SC) number is reduced***
***(Rashmi Kothary)***

***Myoblasts differentiate prematurely***
***(Lee Rubin)***

*Boldrin et al., 2010*

# SMN PLAYS AN IMPORTANT ROLE IN MUSCLE DEVELOPMENT




***Satellite cell (SC) number is reduced***
***(Rashmi Kothary)***

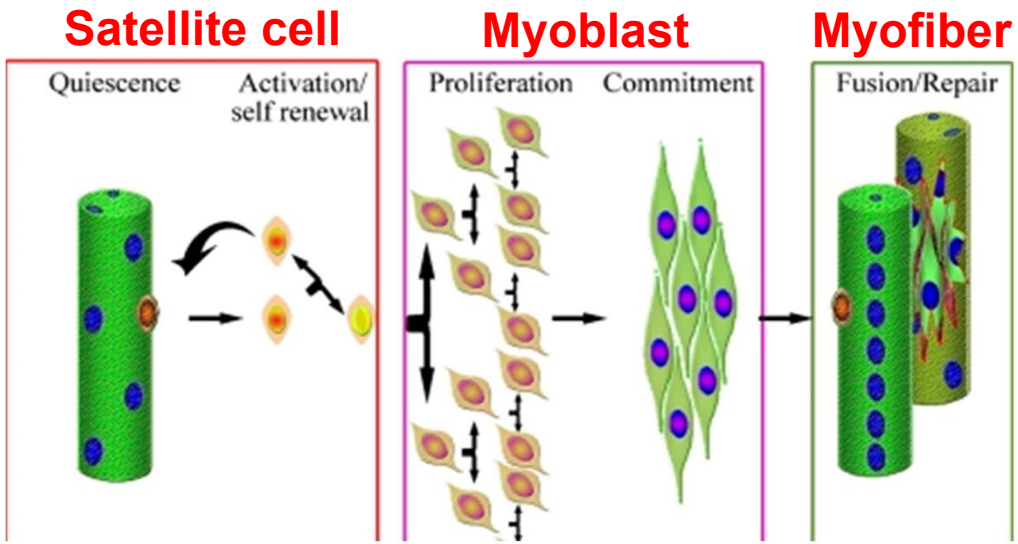
***Myoblasts differentiate prematurely***
***(Lee Rubin)***

***Myoblasts form fewer myotubes***
***(Lee Rubin)***

***Myonuclei number is reduced in myofibers***
***(Rashmi Kothary)***

*Boldrin et al., 2010*

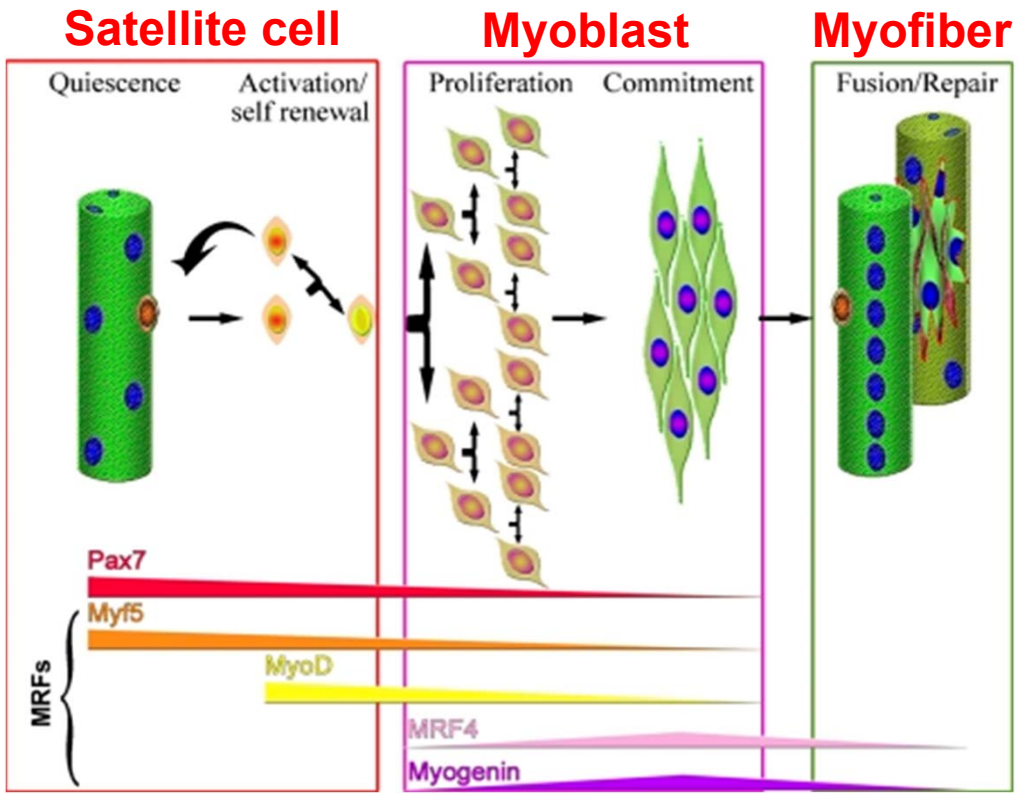
# SMN PLAYS AN IMPORTANT ROLE IN MUSCLE DEVELOPMENT




- ***Satellite cell (SC) number is reduced*** ***(Rashmi Kothary)***
- ***Myoblasts differentiate prematurely*** ***(Lee Rubin)***
- ***Myoblasts form fewer myotubes*** ***(Lee Rubin)***
- ***Myonuclei number is reduced in myofibers*** ***(Rashmi Kothary)***
- ***Muscle regeneration defects*** ***(Lee Rubin)***

*Boldrin et al., 2010*

# SMN PLAYS AN IMPORTANT ROLE IN MUSCLE DEVELOPMENT




*Satellite cell (SC) number is reduced*
*(Rashmi Kothary)*

*Myoblasts differentiate prematurely*
*(Lee Rubin)*

*Myoblasts form fewer myotubes*
*(Lee Rubin)*

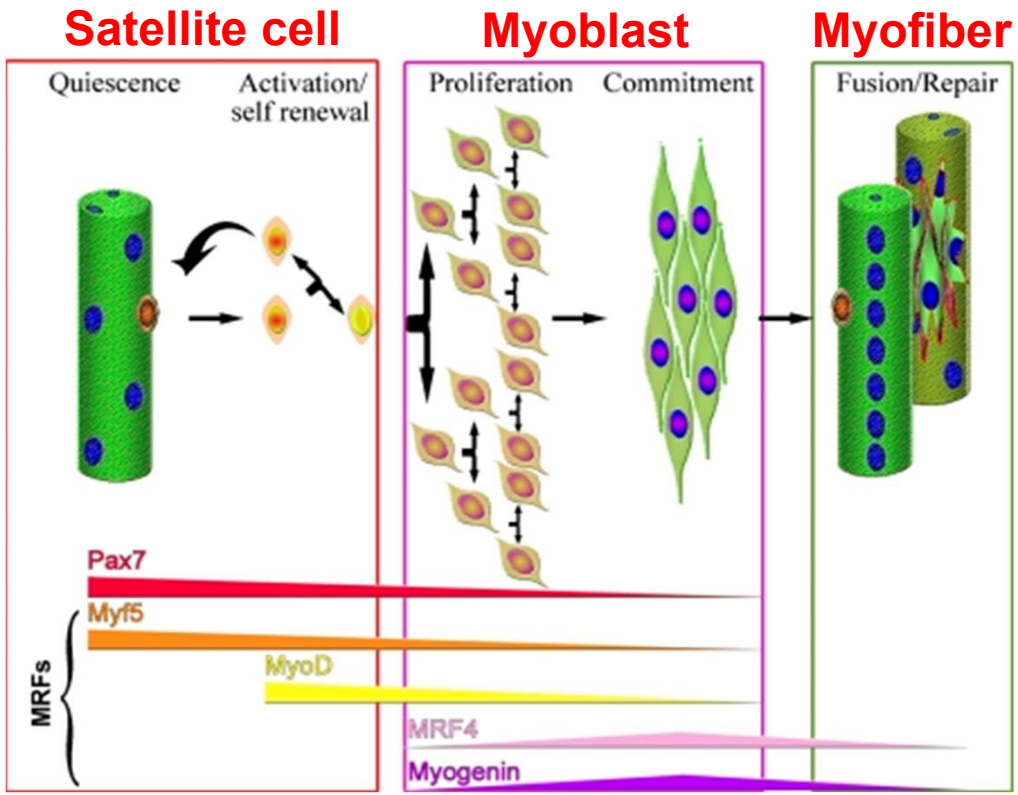
*Myonuclei number is reduced in myofibers*
*(Rashmi Kothary)*

*Muscle regeneration defects*
*(Lee Rubin)*

*Altered expression profiles*
*(Rashmi Kothary)*

*Boldrin et al., 2010*

# SMN PLAYS AN IMPORTANT ROLE IN MUSCLE DEVELOPMENT

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- *Myonuclei number is reduced in myofibers*
- *Muscle regeneration defects*
- *Altered expression profiles*

*Boldrin et al., 2010*

# POTENTIAL DRAWBACKS OF CNS-ONLY INTRATHECAL DRUGS

- Limited to spinal cord exposure
  - SMN is expressed ubiquitously and plays a role in other tissues outside CNS
- Intrathecal delivery presents issues
  - Burden to patients (6 doses 1st year, 3 doses every year after)
  - Requires sedation (risk of respiratory complications)
  - Can be complicated in patients with scoliosis, especially for patients with spinal fusions and growing rods
  - Could cause side effects related to the procedure such as meningitis, headaches, backaches, scarring after multiple punctures (in 32% of patients in the nusinersen open-label study “adverse events were attributed to lumbar puncture” [Haché et al., *J Child Neurol*, 2016])
- Expensive
  - Drug/dose cost (eg, $125K x 6 = $750K in first year; $125K x 3 = $375K every year after)
  - High procedural cost: OR, fluoroscopy, general anesthesia, etc. (relative to small molecules)
  - Insurance reimbursement

## GENE THERAPY MAY NOT BE A SOLUTION FOR ALL PATIENTS

- Viral transduction varies in different tissues (virus will not get into every cell)
- Virus will eventually be lost from dividing cells (eg, muscle)
- Patients can only be given gene therapy once in their lifetime
- Possible immune response (neutralizing antibodies to the viral vectors) limits population that can be treated

## STILL AN UNMET NEED IN SMA

Need for a drug that

- Has systemic exposure
- Is orally administered
- Continues to be efficacious over time
- Is available to all patients

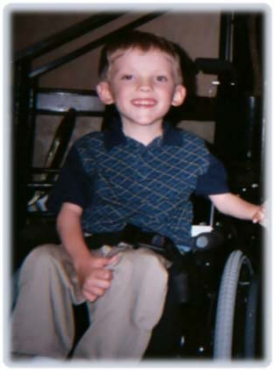
# THANK YOU!











SMA FOUNDATION

# Splicing platform Q&A panel

- Dr. Giovani Baranello, Pediatric Neurologist at Carlo Besta Neurological Research Institute
- Dr. Alexandra Prufer, Associate Professor of Pediatric Neurology, Department of Pediatrics, Medical School, The Federal University of Rio de Janeiro
- Dr. Basil Darras, Associate Neurologist-in-chief; Chief-Division of Clinical Neurology; Director, Neuromuscular Center and Spinal Muscular Atrophy Program
- Karen Chen, SMA foundation, CSO & COO
- Chris Trotta, R&D Biology
- Nikolai Naryshkin, R&D Biology
- Anu Bhattacharyya, R&D Biology

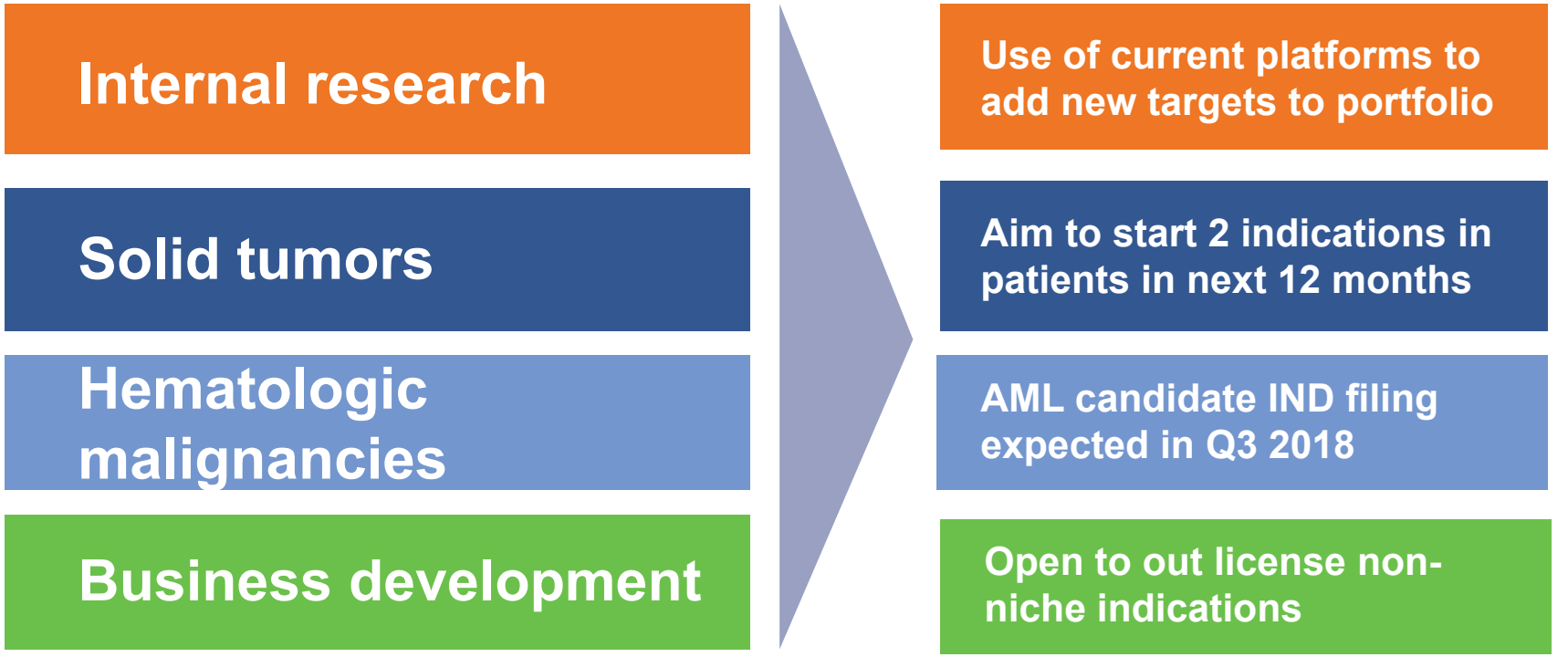
# Niche Oncology Portfolio Strategy

Marcio Souza, COO

# Niche oncology leveraging PTC's RNA biology expertise

- High unmet need with few (if any) therapies in development
- Ability to form networks and partner with key stakeholders
- Current assets have unique features to deliver value to adult and pediatric patients and shareholders

# Development strategy in niche oncology prioritizes value creation



# Today's focus will be on the most advanced candidates

| Pathway | BMI-1/ Tubulin | DHODH |
|---|---|---|
| Focus and Stage of Development | • Phase 1 combination therapy ready in brain tumors and sarcomas<br>• Clinical trials to start in 2018 in combination to standard of care treatment<br>• Dose and preliminary safety defined in completed Phase 1 program<br>• Addresses high unmet need | • IND enabling studies being finalized<br>• IND filing expected in Q3 2018 with AML study starting shortly thereafter<br>• Highly potent DHODH inhibitor<br>• Back-up candidate well underway<br>• Patient selection criteria in refinement to maximize effect |

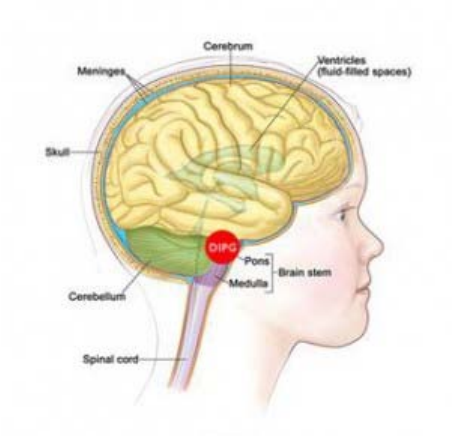
# PTC596 for the Treatment of Rare Solid Tumors

Ed O'Mara, VP Clinical Development - Oncology

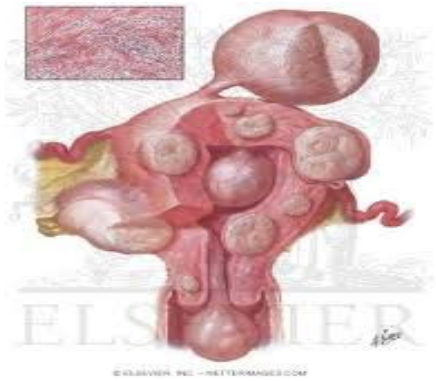
# Focus on rare tumors with high unmet medical need

- Current development strategy includes:
  - Initial focus on rare malignancies with high unmet need and few therapeutic options:

Diffuse interstitial pontine glioma (DIPG)

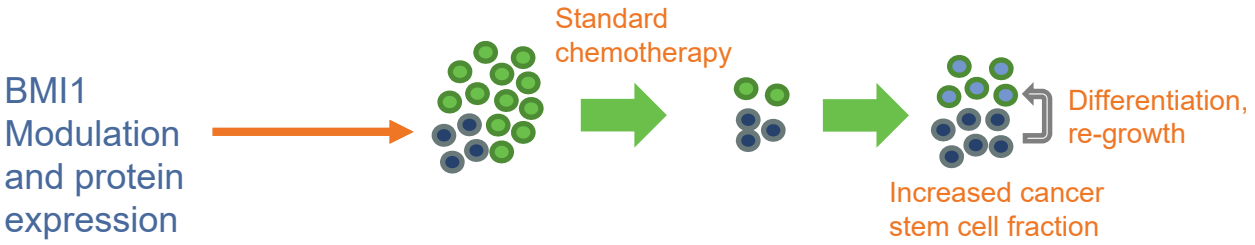


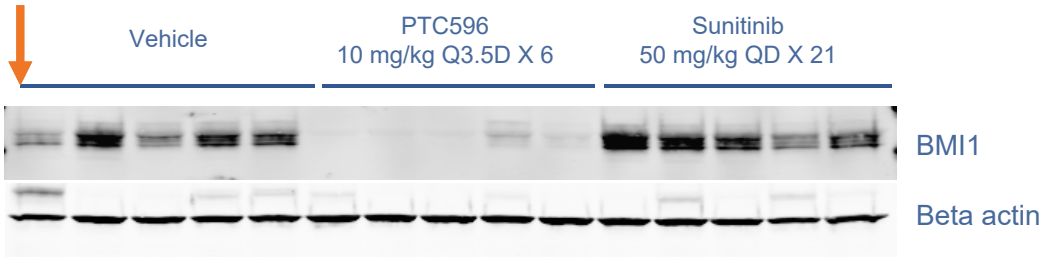

Leiomyosarcoma



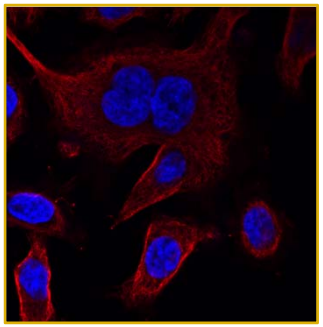
https://www.google.com/search?q=frank+netter+leiomyosarcoma+images&tbm=isch&tbo=u&source=univ&sa=X&ved=0ahUKEwic1a_u7LLaAhVP11MKHTerD

# Increased understanding of PTC596 MOA



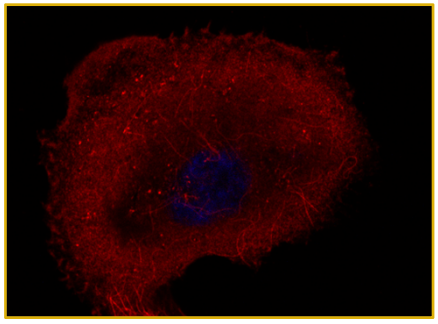




G2/M
Arrest



Vehicle

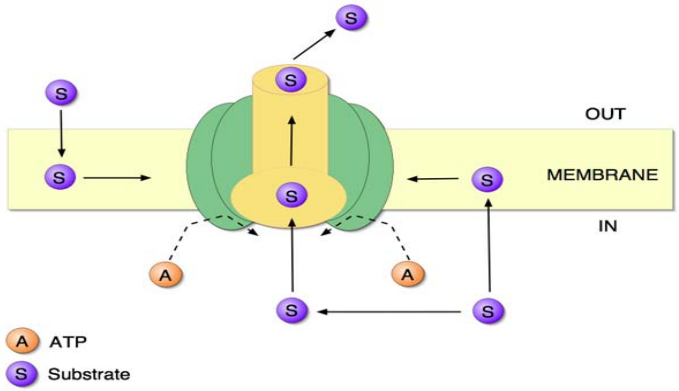
**PTC596**



Spindle fiber collapse

# PTC596 has potential to address unmet medical need in rare solid tumors

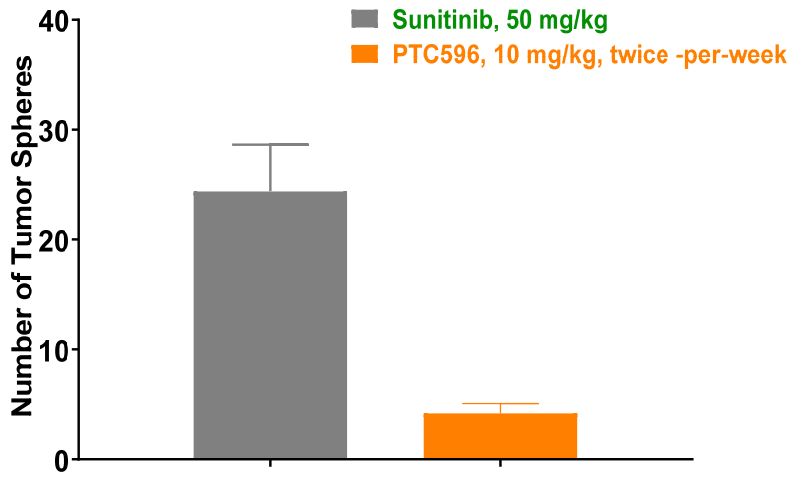
- Common drug failure issues with aggressive tumors
  - Cancer stem cells (CSC) resistant to chemotherapy
    - Glioma CSCs display marked resistance to temozolomide, carboplatin, VP16, and Taxol relative to the non-CSC population
  - Resistance mediated by transport pumps
    - Temozolomide, cyclophosphamide, and vincristine all P-gp substrates and that transporter associated with resistance



# PTC596 treatment in vivo depletes U87MG tumorspheres ex vivo

- Cancer cells hijack BMI1 to maintain stem-cell properties
  - Stem cells are a subset that sustain tumor and promote resistance
  - High tumor BMI1 expression correlated with poor clinical prognosis across many tumor types

Tumor stem cell [U87MG (primary glioblastoma)] frequency



# Key differentiation features of PTC596

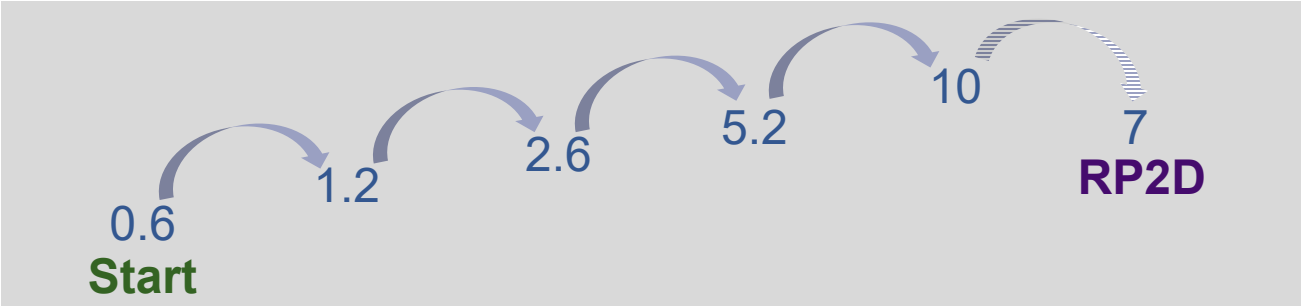
- Tumor resistance often occurs because therapies cannot access a compartment or maintain efficacious levels
- PTC596 penetrates the blood-brain barrier (BBB)
- Demonstrates enduring exposure in the CNS as it is not a substrate for transporters
  - Evades P-gp-mediated efflux

# PTC596: Overview of the Clinical Development Plan

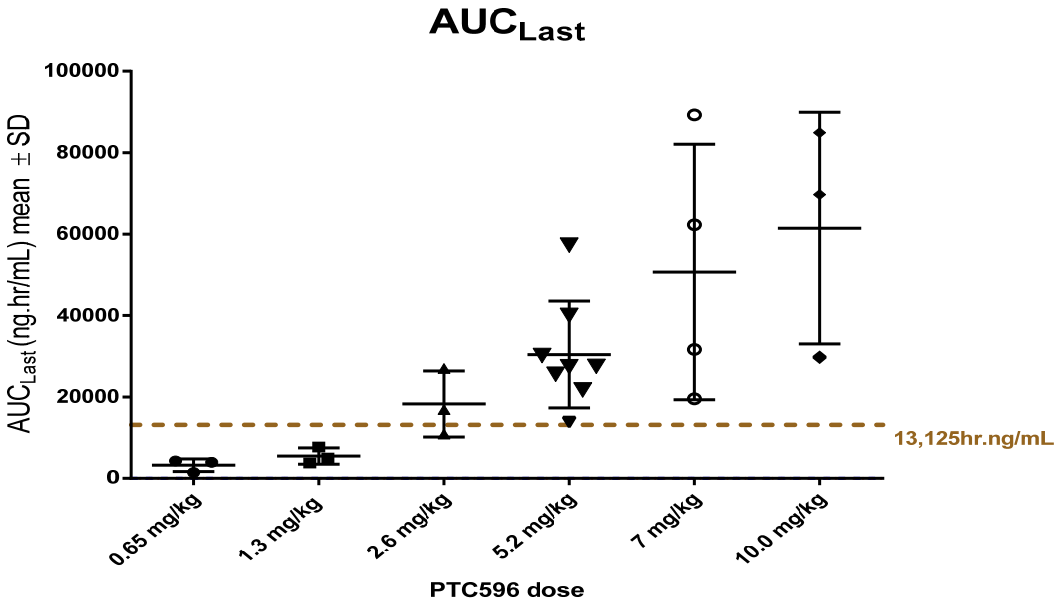
# PTC596: Initial dose finding study

- Design: Standard 3+3, evaluating dose range of 0.65-10 mg/kg
- Population: All solid tumors, refractory/relapsed patients
- Key objectives:
  - Safety assessments
  - Drug concentrations to ascertain PK parameters

Dose escalation scheme (mg/kg) PTC596 given twice weekly



# PTC596 was well-tolerated in Phase 1b human with target exposures reaching those expected to be efficacious




- Dashed line represents data from mice
- Doses ≥ 2.6 mg/kg → exposures in therapeutic range

# PTC596: Safety results helped inform clinical path

Pretreated population (1-8 regimens) (n=31)

- Most frequent TEAEs: diarrhea (61%), fatigue (54%), nausea (51%), vomiting (45%), decreased appetite (45%)
- SAEs
  - 14 SAEs in 10 patients with no consistent signal
  - 2 patients had 4 events possibly/probably related to study drug
- Adverse events leading to discontinuation: 5/31 (16%)
- Dose-dependent lowering of neutrophil count observed

**Safety and PK results combined with preclinical studies informed clinical strategy and indications**

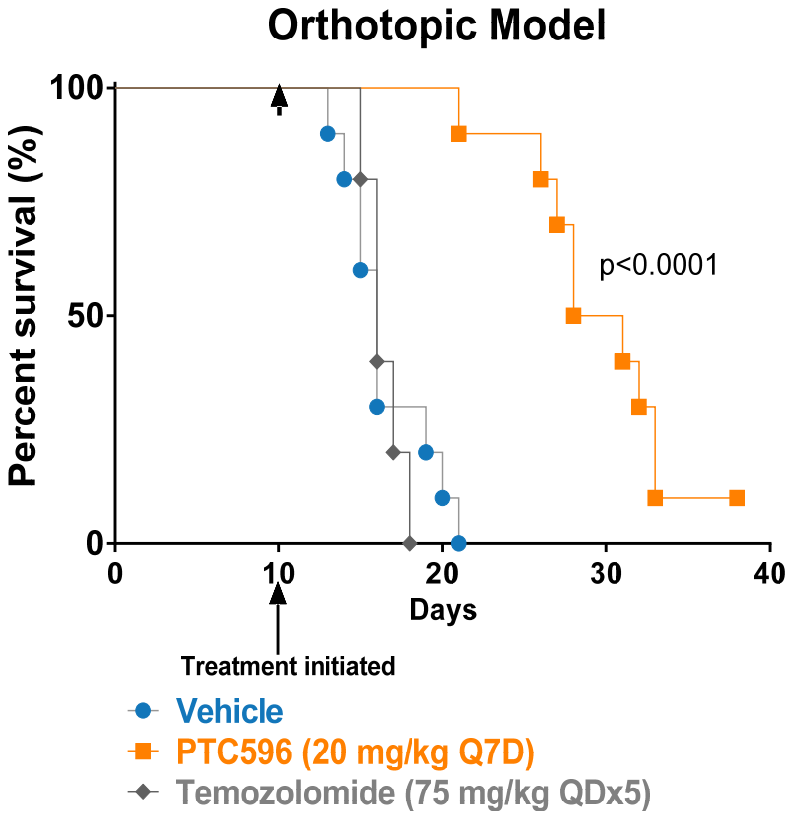
*TEAE: Treatment emergent adverse event; SAE severe adverse event.

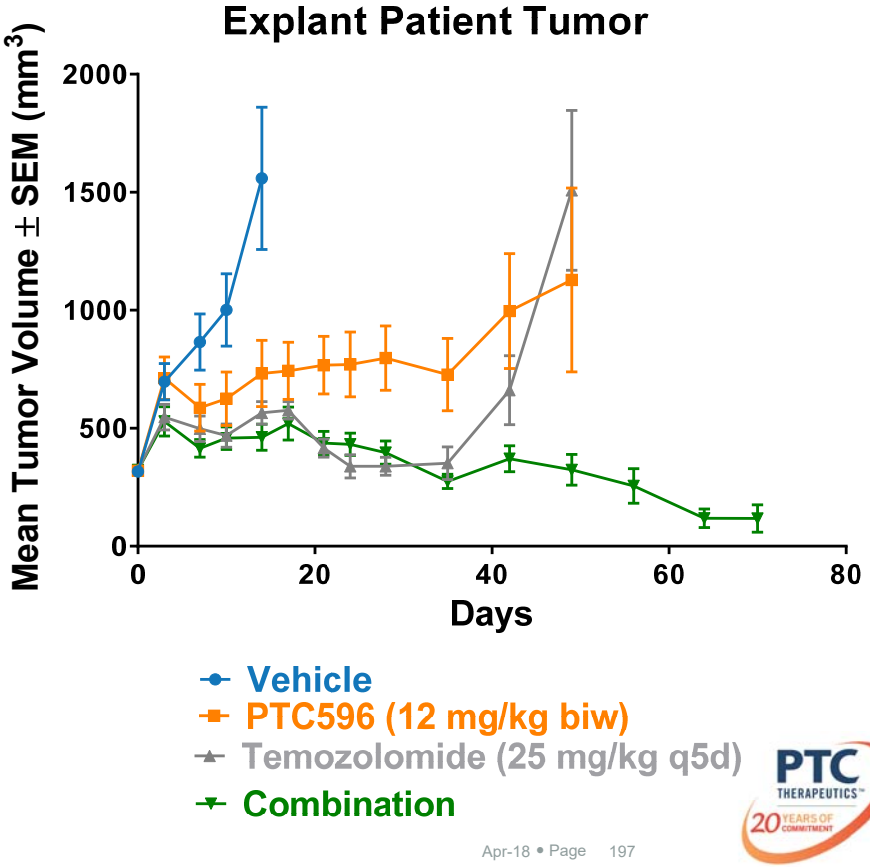
# PTC596 in the Treatment of Diffuse Interstitial Pontine Glioma (DIPG)

# DIPG is a rare pediatric tumor with high unmet medical need well-positioned for PTC596 development

- <1,000 cases per year reported in the US and Canada
  - Median age of diagnosis is 5-6 years
  - Advancing clinical trials using the DIPG clinical network
- DIPG is a non-resectable glioma (CNS tumor)
- These are rapidly fatal tumors with median overall survival: ~ 9 months and <2% at 2 years
- BMI1 levels are high in this tumor

# PTC596 demonstrates efficacy in mouse models of brain tumor as monotherapy and in combination



# PTC596: An initial clinical study in pediatric patients with DIPG

- Clinical study design: Dose-finding 3+3 in a treatment-experienced population with subsequent expansion
  - Dose regimen includes radiation (XRT)
- Key targets and anticipated timelines
  - First patient expected to dose in mid-2018
  - Potential preliminary readout in 2020
- Assessing expansion into other rare neural tumor types

# PTC596 in the Treatment of Rare Soft Tissue Sarcomas

# Leiomyosarcoma: A rare soft tissue tumor with high unmet medical need

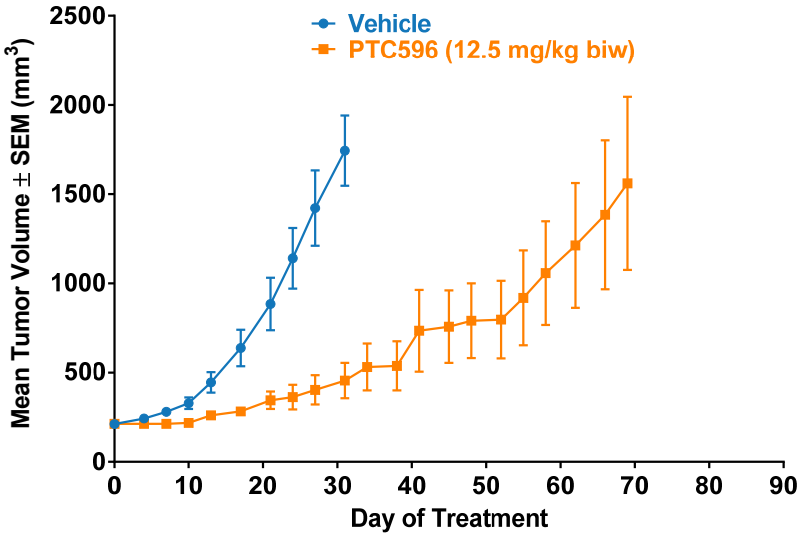
- Leiomyosarcomas are malignant soft tissue tumors of muscle tissue ~20-25% of sarcomas
- These are rare tumors with ~ 3,000 new cases per year in the US
  - Uterine leiomyosarcoma: 2,200-2,300
  - Retroperitoneal: 700-800
- There is a high unmet medical need with progression free survival (PFS) <6 months for relapsed/refractory patients (using SOC)
  - Response rate = 7%
  - Median PFS = 4.2 months
  - Median overall survival =13.7 months



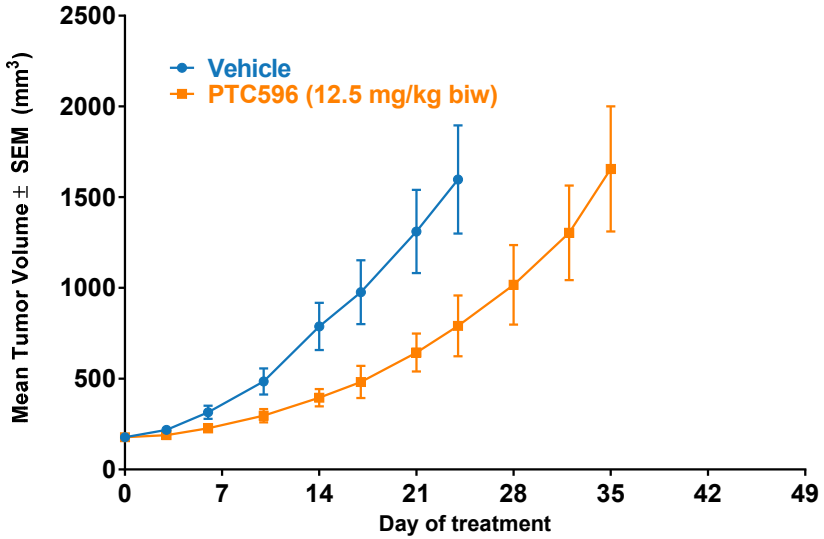
PTC THERAPEUTICS™ 20 YEARS OF COMMITMENT

# Efficacy as monotherapy in sarcoma models

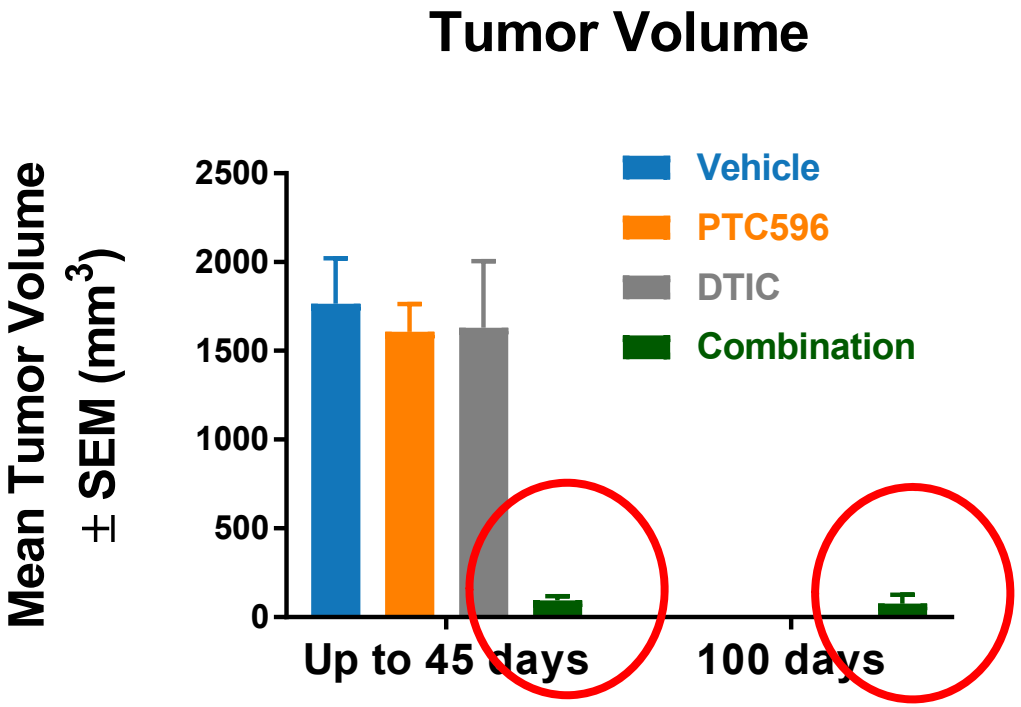
Leiomyosarcoma mouse model 1




Leiomyosarcoma mouse model 2



# PTC596 demonstrates synergistic activity with standard of care in mouse models of leiomyosarcoma




DTIC = Dacarbazine, MOA: alkylating agent, methylates guanine

# PTC596: The initial clinical study patients with leiomyosarcoma

- Clinical study design: Dose-finding 3+3 in a relapsed/refractory patient population with dacarbazine (DTIC)
  - Limited dose escalation
- Key targets and anticipated timelines
  - First patient dosing in next 12 months
  - Dosing regimen selection mid-2020
  - Expansion readout (20-30 patients)

# PTC596: How we focus to pursue new opportunities

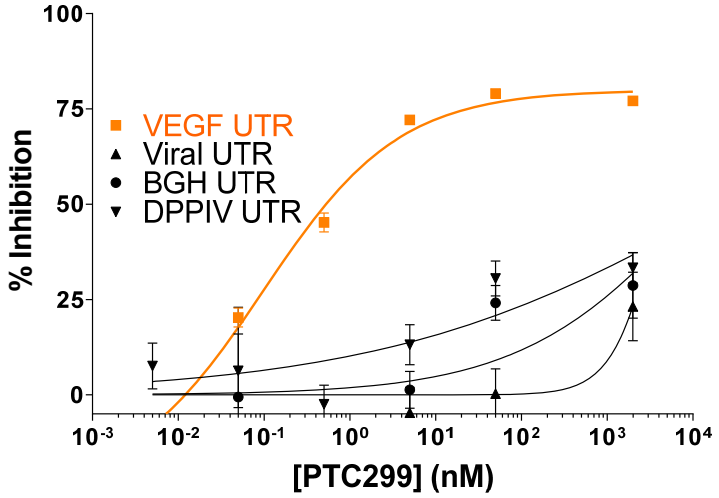
- Focus on niche oncology indications
- Address high unmet medical need
- Currently expanding understanding of rare oncology opportunities
  - *In vitro* cell lines
  - PDX mouse models
  - *Ex vivo* evaluations of patient tissues
  - Biomarkers
- Potential clinical path with measurable endpoints

# PTC299 for the Treatment of Leukemia

Marla Weetall, VP Pharmacology

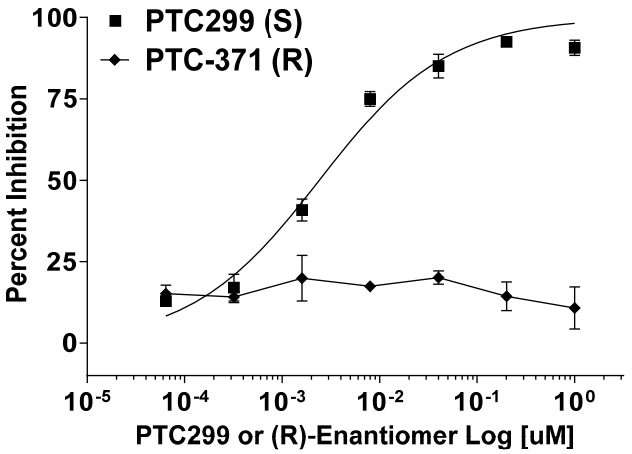
# PTC299 was identified as an inhibitor of VEGF protein synthesis

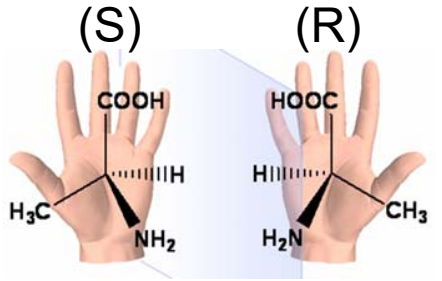
293-Cells with Reporter Gene



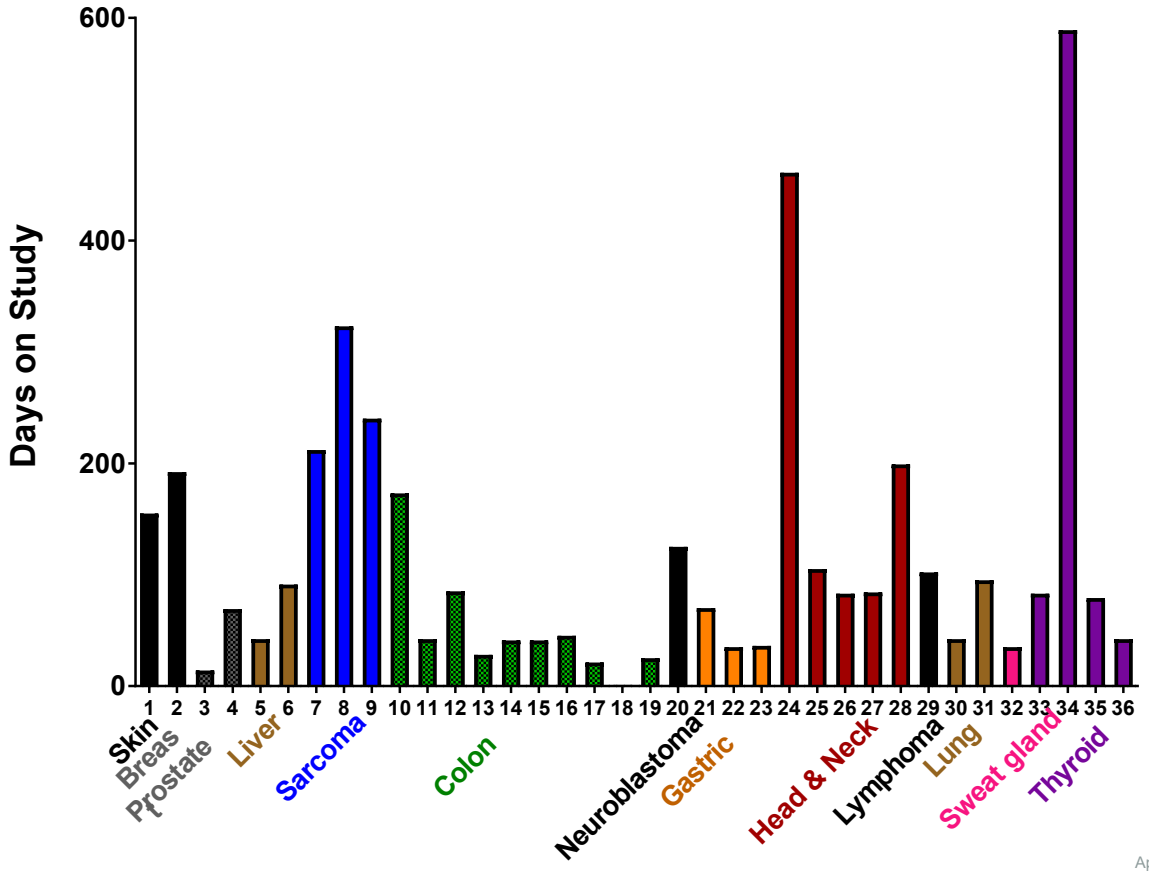


HT1080 Fibrosarcoma Cells



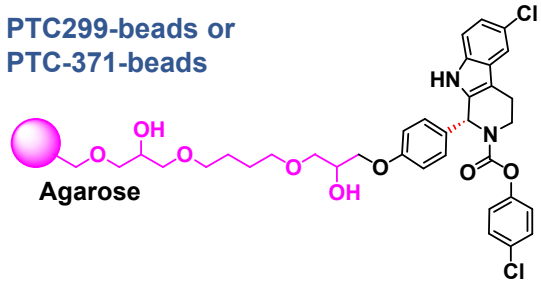
# In a phase 1b trail, 14/36 patients had stable disease and a few patients were stable for an extended time



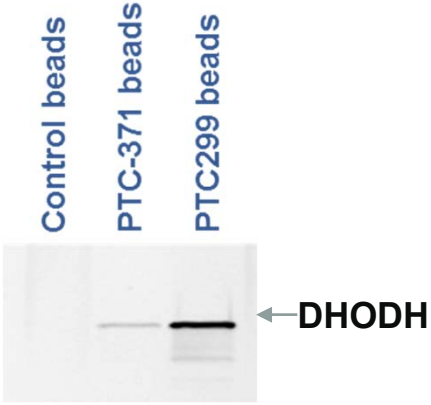
# Prior clinical experience with PTC299

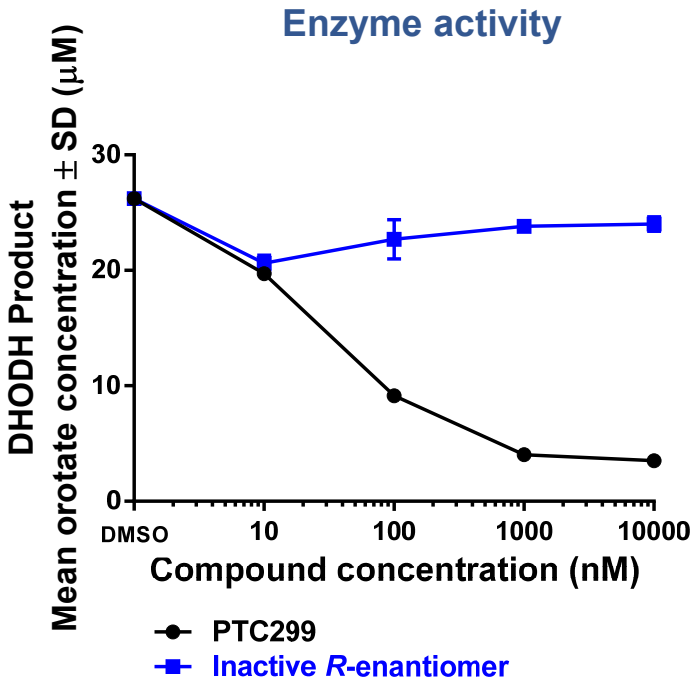
- Clinical testing across numerous doses and exposures
  - 279 subjects exposed: 145 healthy volunteers (in 4 studies) and 134 patients with solid tumor neoplasia (in 5 studies)
  - Range of doses explored 0.3 to 3 mg/kg and BID or TID, 40 mg BID to 160 mg TID
  - Good dose-linearity and pharmacodynamic responses measured
- While generally well-tolerated, 2 serious events of drug-induced liver injury (DILI) at high doses occurred resulting in a clinical hold and discontinuation of the program in solid tumors

# PTC299 binds and inhibits DHODH



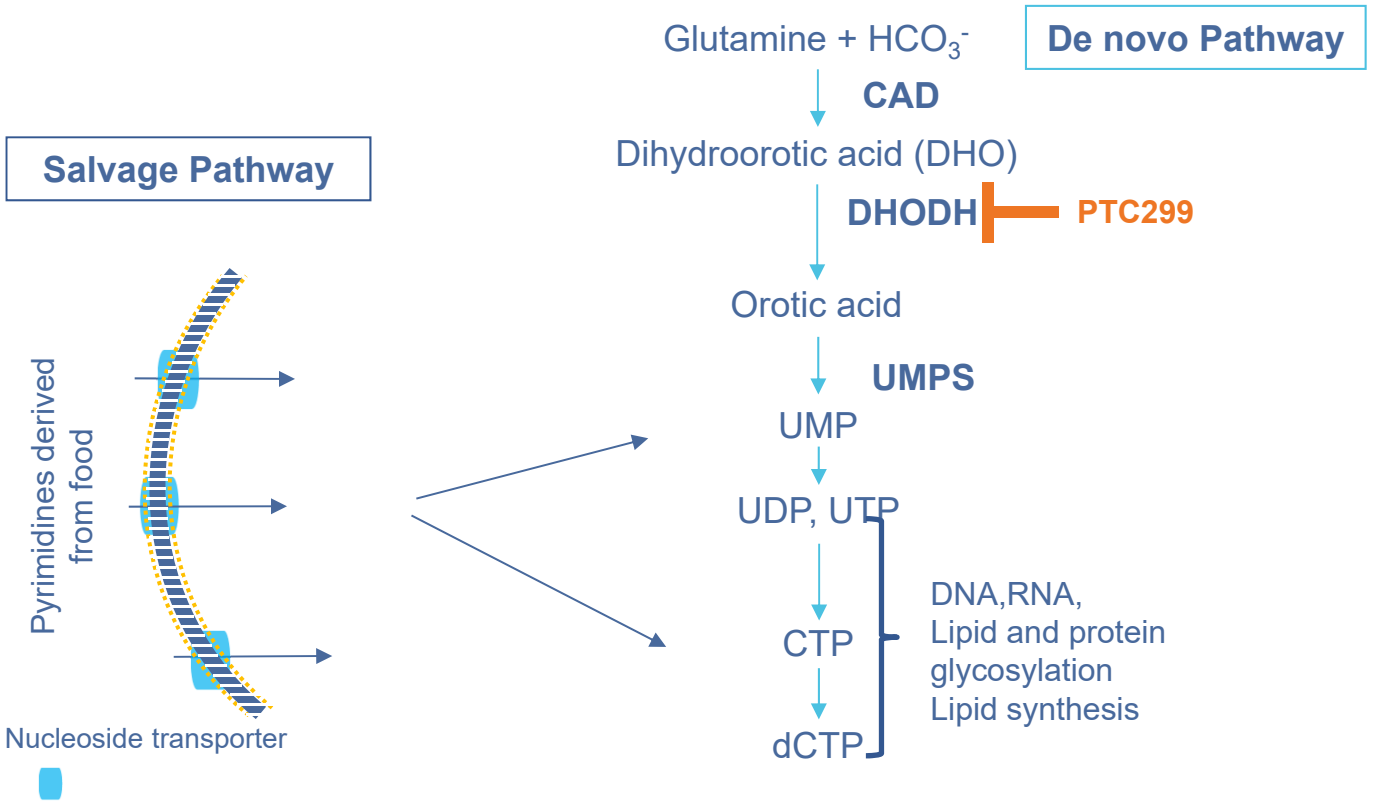

Binding to PTC299-beads or PTC371-beads



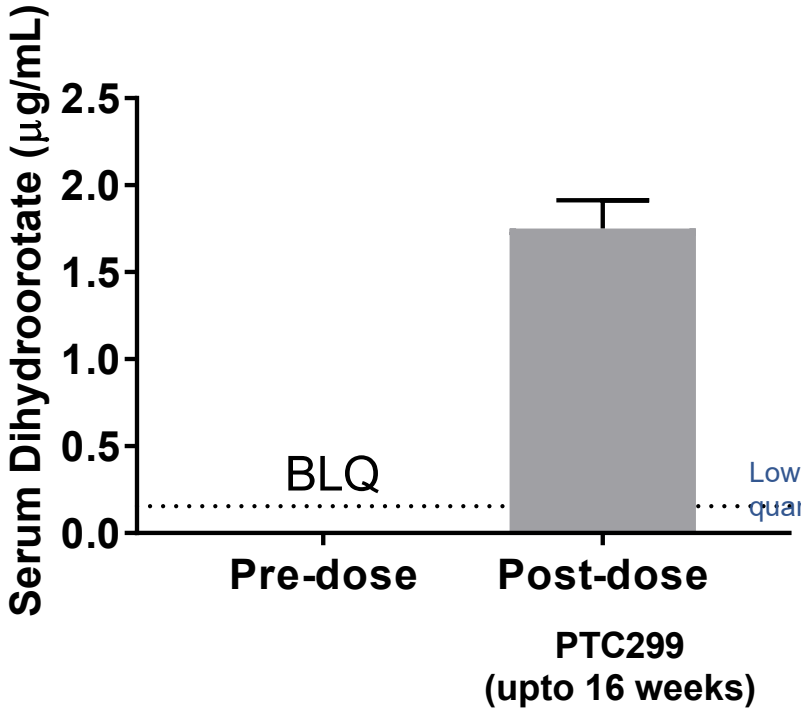



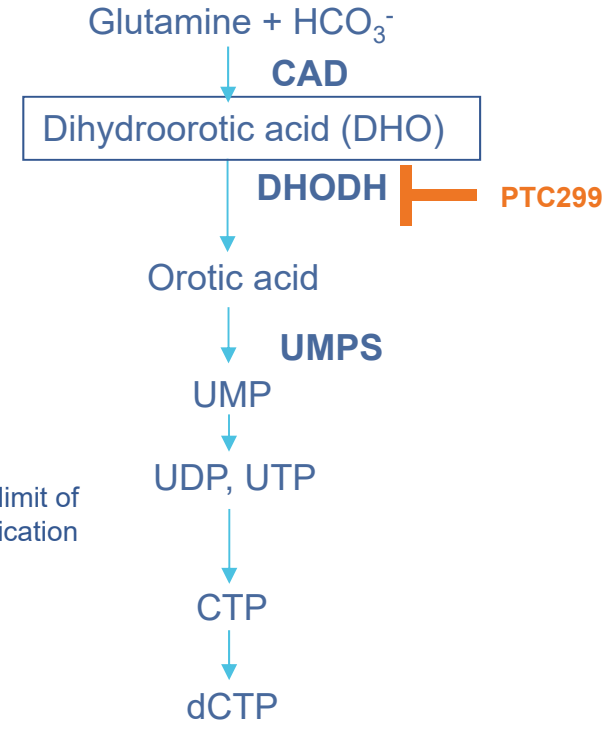

DHODH is a rate-limiting enzyme in pyrimidine nucleotide de novo synthesis

# Aggressive tumors are dependent on the dehydrogenase (DHODH) pathway



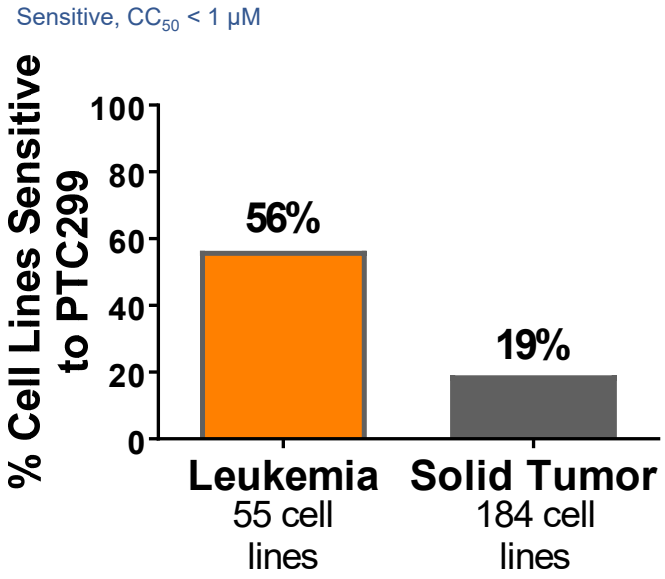
# Serum DHO levels increased in solid-tumor patients dosed with PTC299 (N=4)

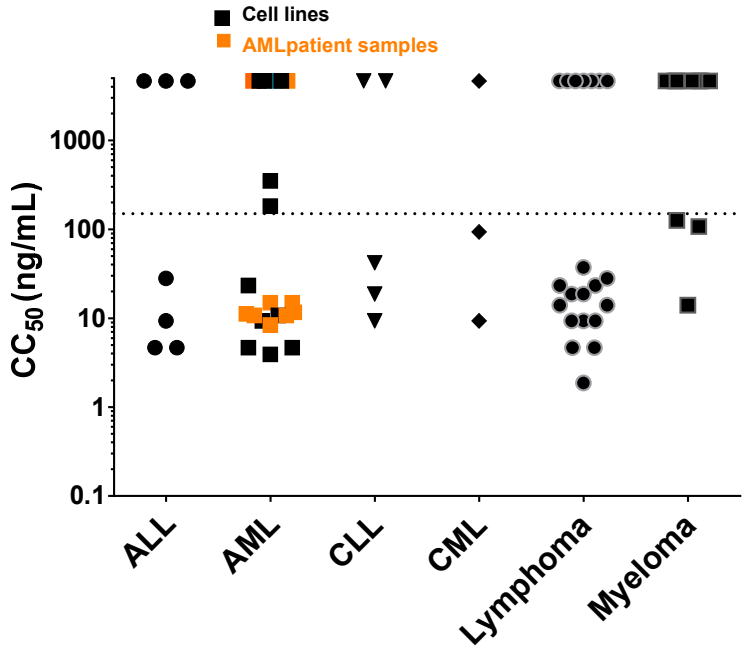



**Demonstrates DHODH was inhibited (as measured by increased DHO) in PTC299 clinical trials**

# PTC299 reduces growth of multiple leukemia cell lines *in vitro* assays




**Broader activity in leukemia cells than in solid tumor cells**

**$CC_{50}$s for sensitive cells less than 150 ng/mL**

# Literature provides external validation for the use of DHODH inhibitors in treatment of AML

***Cell 167***, Sept 22, 2016

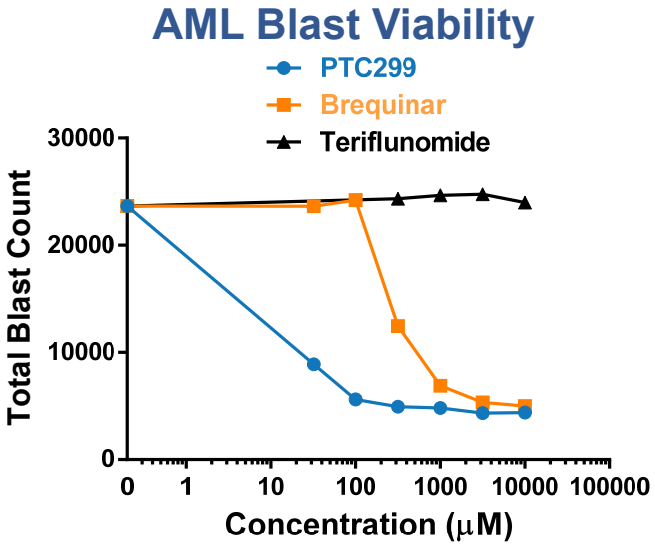
Article

Cell

## Inhibition of Dihydroorotate Dehydrogenase Overcomes Differentiation Blockade in Acute Myeloid Leukemia

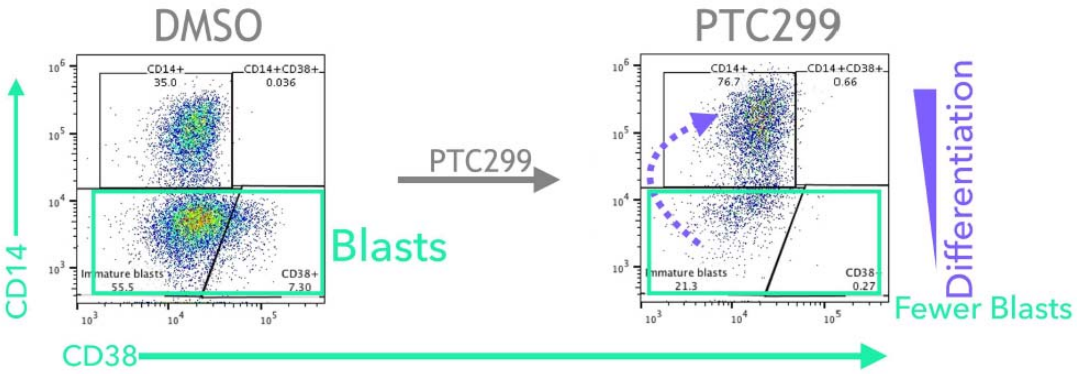
David B. Sykes,[1,2,11,12,15,*] Youmna S. Kfoury,[1,11,12] François E. Mercier,[1,11,12] Mathias J. Wawer,[3] Jason M. Law,[4,13] Mark K. Haynes,[5] Timothy A. Lewis,[4] Amir Schajnovitz,[1,11,12] Esha Jain,[1] Dongjun Lee,[1,11,12] Hanna Meyer,[6] Kerry A. Pierce,[7] Nicola J. Tolliday,[3] Anna Waller,[5] Steven J. Ferrara,[3] Ashley L. Eheim,[6] Detlef Stoeckigt,[6] Katrina L. Maxcy,[1] Julien M. Cobert,[1] Jacqueline Bachand,[1] Brian A. Szekely,[1] Siddhartha Mukherjee,[8] Larry A. Sklar,[5] Joanne D. Kotz,[4] Clary B. Clish,[7] Ruslan I. Sadreyev,[9,10] Paul A. Clemons,[4] Andreas Janzer,[6] Stuart L. Schreiber,[4,13,14] and David T. Scadden[1,2,11,12,*]

[1]Center for Regenerative Medicine, Massachusetts General Hospital, Boston, MA 02114, USA
[2]Cancer Center, Massachusetts General Hospital, Boston, MA 02114, USA
[3]Center for the Development of Therapeutics, Broad Institute of MIT and Harvard, Cambridge, MA 02142, USA
[4]Center for the Science of Therapeutics, Broad Institute, Cambridge, MA 02142, USA
[5]Center for Molecular Discovery, University of New Mexico, Albuquerque, NM 87131, USA
[6]Bayer Pharma AG, Berlin 13353, Germany
[7]Metabolite Profiling Platform, Broad Institute, Cambridge, MA 02142, USA
[8]Irving Cancer Research Center, Columbia University School of Medicine, New York, NY 10032, USA
[9]Department of Molecular Biology, Massachusetts General Hospital, Boston, MA 02114, USA
[10]Department of Pathology, Massachusetts General Hospital and Harvard Medical School, Boston, MA 02114, USA
[11]Department of Stem Cell and Regenerative Biology, Harvard University, Cambridge, MA 02138, USA
[12]Harvard Stem Cell Institute, Cambridge, MA 02138, USA
[13]Department of Chemistry and Chemical Biology, Harvard University, Cambridge, MA 02138, USA
[14]Howard Hughes Medical Institute, Cambridge, MA 02138, USA




| Drug | $CC_{50}$ (nM) |
|---|---|
| PTC299 | 26 |
| Brequinar | 394 |
| Teriflunomide | >100,000 |

# PTC299 effect on AML cell is in part through the induction of differentiation



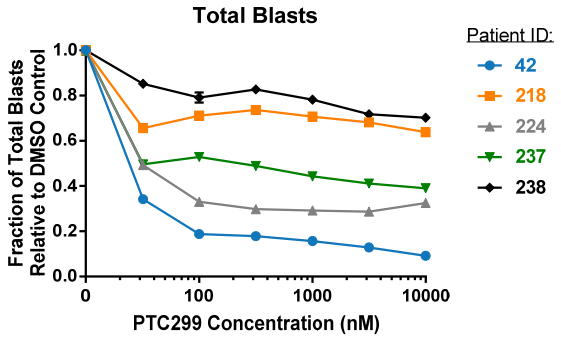

**Patient AML sample Analyzed by FACS**

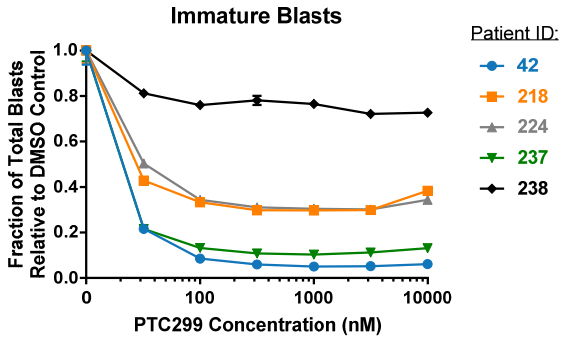
**PTC299 is additive/synergistic with retinoic acid**

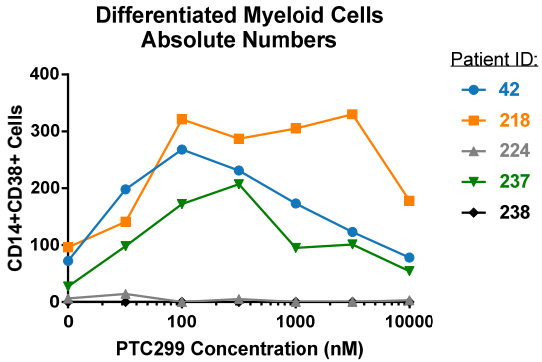
| Treatment | Percentage of MOLM-13 cells that are CD14+ CD11b+ (%) |
|---|---|
| DMSO | 2 |
| PTC299, 20 nM | 13 |
| Retinoic acid, 100 nM | 3 |
| PTC299 + Retinoic acid, 100 nM | 25 |

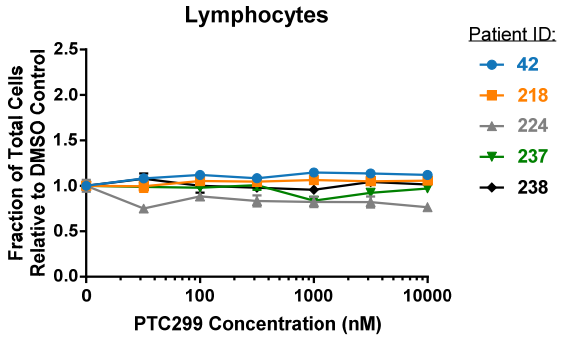
**MOLM-13 AML line analyzed by FACS**

# AML cells are sensitive to PTC299, but normal white blood cells are not reduced



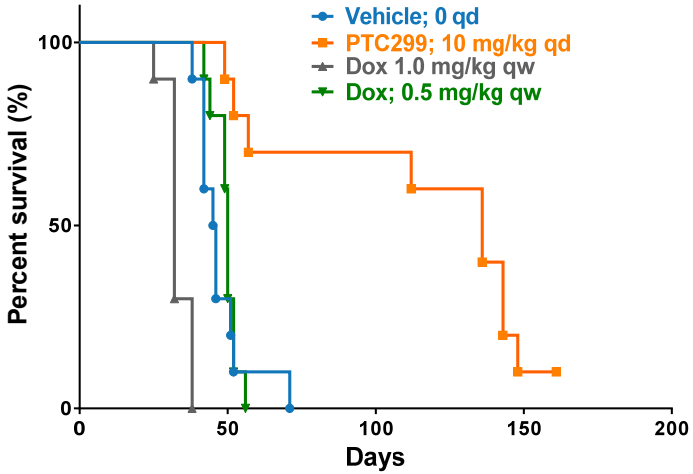



# PTC299 is efficacious in mouse models of human leukemia

MOLT-4 ALL (CD3-positive)



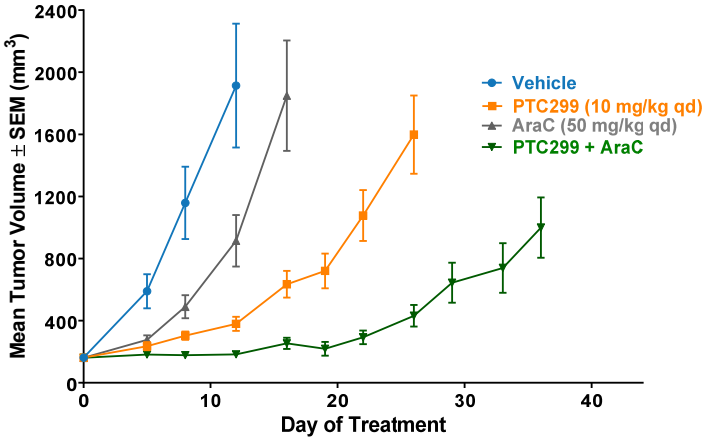

**Median survival time**

Vehicle–44.5 days

**PTC299–136 days**

Maximum tolerated dose of Doxorubicin in NOD/SCID mice did not demonstrate prolongation of survival.

MOLM13 AML (Flt3 ITD mut positive)




AraC – pyrimidine nucleotide analog, incorporates into DNA. Anticipate that depletion of pyrimidine nucleotides would increase AraC incorporation.

# PTC299 is well-aligned for clinical development in AML

- Identification of the appropriate indication
  - An orally bioavailable and highly potent inhibitor of DHODH
  - DHODH is required for de novo synthesis of pyrimidine nucleotide
  - Leukemia cells are highly reliant on de novo synthesis of pyrimidine nucleotides
- Potential for mechanism-driven selection of indication and patient population
- Understanding of the safety window

# PTC299 development program

- Clinical trials to utilize lower doses than previously used in solid tumors
- Current development strategy includes:
  - Focused development on AML based on available data
  - Developing of fast-follower with improved chemical characteristics
  - Expected to file IND in Q3-2018

# Oncology Q&A panel

- Dr. Roger Strair, Chief, Blood Disorders, Rutgers Cancer Institute of NJ
- Dr. Gary Schwartz Division Chief, Hematology/Oncology NY Presbyterian/ Columbia
- John Baird, Clinical Development – Oncology
- Marla Weetall, R&D Pharmacology
- Ed O'Mara, Clinical Development – Oncology
- Marcio Souza, COO


# Stuart Peltz, CEO

# Completing our 20th anniversary and thinking about what's next: Our strategic roadmap for the next 3 to 5 years

**Vision**

**PTC is a fully integrated, innovative rare disease company leveraging research capabilities and core technology platforms, building out world-class commercial capabilities, and being an ideal partner for late-stage, ultra-orphan diseases for which there is high unmet medical need.**

## STRATEGY

### *Fully Integrated Orphan Franchise*

- Prioritize development based on targeted rare disease parameters
- Leverage and strengthen commercial capability to bring treatments to patients with high unmet need
- Become an attractive in-licensing partner for ultra-orphan assets

### *Niche Oncology Development*

- Prioritize indications and focus the development of PTC299 and PTC596
- Flexible for late-stage development/ commercialization

## PHILOSOPHY

### *Flexible and Opportunistic*

- Remain adaptive to exploring emerging opportunities
- Foster discovery and development leadership with current and future technology platforms





PTC THERAPEUTICS™ 20 YEARS OF COMMITMENT

# PTC's value creation opportunities

- CHMP response for pediatric label expansion of Translarna™
- Establish Emflaza® as standard of care & grow Translarna globally
- Continue pursuit of further strategic transactions to expand pipeline
- SMA Firefish & Sunfish pivotal data for potential registration
- Niche oncology programs enter clinical stage development
- Translarna™ label expansion: U.S., aniridia, dravet/CDKL5, non-ambulatory
- Splicing platform development, Huntington's and FD to enter clinic


# Thank You