Targeting pre-mRNA splicing with small molecules for the treatment of neuromuscular disorders

Nikolai Naryshkin, World CNS summit 2017
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Our mission

To leverage our knowledge of RNA biology to bring novel therapeutics to patients affected by rare and neglected disorders.
PTC’s platform technologies target RNA biology to modulate gene expression with small molecules

<table>
<thead>
<tr>
<th>Platform</th>
<th>Mechanism targeted</th>
<th>Programs</th>
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<tbody>
<tr>
<td>Splicing</td>
<td>Target splicing event to restore or reduce protein</td>
<td>SMA - SMN2, FD – IKBKAP, HD – HTT</td>
</tr>
</tbody>
</table>
SMN2 splicing modifiers to spinal muscular atrophy
Spinal muscular atrophy: The leading genetic cause of mortality in infants

- Spinal muscular atrophy (SMA) is a rare genetic neuromuscular disorder caused by the inactivation of the SMN1 gene
- Low levels of SMN lead to the death of motor neurons in the spinal cord and muscle atrophy
- One in every 11,000 newborn children is affected with the disorder
- PTC is collaborating with Roche and the SMA Foundation to advance treatments for SMA
# Spinal muscular atrophy – types and symptoms

<table>
<thead>
<tr>
<th>Type</th>
<th>Age of onset</th>
<th>Symptoms</th>
<th>Lifespan</th>
</tr>
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<tbody>
<tr>
<td>I/0</td>
<td>&lt; 6 mos</td>
<td>Unable to sit</td>
<td>&lt; 2 yrs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Respiratory insufficiency</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>&lt; 18 mos</td>
<td>Unable to stand</td>
<td>&gt; 2 yrs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Wheelchair-bound</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>&gt; 18 mos</td>
<td>Can stand unsupported</td>
<td>Normal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Muscle weakness</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>&gt; 30 yrs</td>
<td>Gradual weakening of muscles in adulthood</td>
<td>Normal</td>
</tr>
</tbody>
</table>
Targeting alternative splicing in SMA

- SMA patients rely on a related SMN2 gene which produces only low levels of SMN protein due to a splicing defect.
Targeting alternative splicing in SMA

- SMA patients rely on a related SMN2 gene which produces only low levels of SMN protein due to a splicing defect
- Small molecule selectively targets SMN splicing to include exon 7 and produce functional SMN

**SMN1**

- DNA
- mRNA
- Functional SMN protein

**SMN2**

- DNA
- mRNA, missing exon 7
- Unstable SMN protein, rapidly degraded
- Functional SMN protein
Compound modifies SMN2 alternative splicing and increases SMN protein in vitro in SMA patient cells

**SMN2 alternative splicing correction**  
(RT-qPCR)  

**SMN protein increase**  
(HTRF)  

**SMN2 alternative splicing correction**  
(end-point RT-PCR)  

**SMN protein increase**  
(western blot)  

Naryshkin et al., 2014 Science, 345:688
Compound at an efficacious concentration affects very few splice junctions

- Type 1 SMA fibroblasts treated with 500 nM SMN-C3
- Analysis of annotated splice junctions in transcripts for 11,714 human genes

Naryshkin et al., 2014 Science, 345:688
Compound increases SMN protein in multiple tissues to near or above heterozygous levels

Brain

Peripheral Blood Mononuclear Cells

Oral dosing for 10 days in mild SMA mouse model

- SMN protein levels in peripheral blood cells correlate to those in brain
- Similar increases in SMN observed in spinal cord, muscle, heart, liver, skin

Naryshkin et al., 2014 Science, 345:688
Compound confers long-term survival and prevents body weight loss in severe SMA mouse model

Compound improves phenotype and survival in preclinical model

Naryshkin et al., 2014 Science, 345:688
Compound prevents muscle atrophy in severe SMA mouse model

Mice were treated with compound starting on day 3 after birth through 14 days old

Naryshkin et al., 2014 Science, 345:688
RG7916 first-in-human study – design and objectives

- Single-center study in healthy males, age 18-45
- SAD part including food effect
  - Randomized, double-blind, parallel design
  - Bayesian adaptive framework based on safety, exposure and PD
    - Exposure cap (AUC$_{0-24h}$) of 1,500 h·ng/mL due to preclinical findings
- 6 cohorts; 4-8 subjects per cohort
  - Assessment of safety, tolerability, PK including food effect, PD
- Drug-drug-interaction part: two periods, one sequence
  - Estimate of fm by CYP3A, interaction potential with CYP3A modulators

**Period 1:**
SD of RG7916 alone

- **Day 1:** RG7916

**Period 2:**
SD of RG7916 together with itraconazole

- **Day 1:** RG7916
- **Day 4:** RG7916
- **Day 8:** Itraconazole

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Proof of mechanism for RG7916

- Exposure dependent increase in SMN2 FL and decrease in SMNΔ7 mRNA
  - Increased SMN2/SMNΔ7 mRNA ratio after single oral dose of 0.6 - 18 mg RG7916
  - Maximum effect between 4 and 8 hours post-dose
- No change in SMN1 full length mRNA

SMN2/SMNΔ7 mRNA ratio vs. time post dose

Exposure (AUC) vs. Effect (AUE)

RG7800 (another oral SMN2 splicing modifier) showed significant increase in systemic SMN protein in SMA patients in Moonfish study.
Pivotal portion of both Sunfish & Firefish trials expected to begin in 2017

SUNFISH

- Clinical study in SMA type 2/3 patients initiated in November
  - Enrolling 36 patients for dose escalation phase, placebo controlled 2:1
  - Pivotal phase will enroll 150 patients, placebo controlled 1:1, 1º endpoint – change from baseline in the total score of the motor function measure (MFM-32) at 12 mos

FIREFISH

- Clinical study in SMA type 1 patients aged between 1 and 7 months old
  - Enrolling 8 patients for dose escalation phase
  - Pivotal phase will enroll 40 infants, open label, 1º endpoint – unsupported sitting after 12 months of treatment per Gross Motor Scale of the Bayley Scales (BSID-III)
IKBKAP splicing modifiers to treat familial dysautonomia
Familial dysautonomia

- Familial dysautonomia (FD) is caused by a splicing-altering mutation in the IKBKAP gene
- Low levels of IKAP protein negatively affect the development and survival of sensory and autonomic neurons
- AJ ancestry, carrier frequency 1/17 – 1/27
- No marketed therapies are currently available for FD, only supportive treatments
IKAP deficiency: aberrant development and function of autonomic and sensory neurons
Familial dysautonomia is caused by reduced levels of IKAP protein due to mutation and alternative splicing of exon 20 in its pre-mRNA.

Molecular genetics of FD is very similar to that of SMA.

Great fit to PTC’s Alternative Splicing technology.
IKBKAP exon 20 skipping is tissue-dependent; nervous system affected the most

Slaugenhaupt et al. AJHG (2001) 63:589
Cuajungco et al. AJHG (2003)
PTC and Massachusetts General Hospital are collaborating in finding the treatment of rare genetic disorders resulting from pre-mRNA splicing defects.
Compound modifies mutant IKBKAP splicing and increases IKAP protein in FD patient cells

- FD patient-derived fibroblasts treated for 20 hours

![Graphs showing mRNA and protein concentration](image)
Compound modifies mutant IKBKAP pre-mRNA splicing in vivo in all tissues

- Transgenic mice carrying human mutant IKBKAP gene
- Dosed for 8 days

The effect is lower in brain due to lower CNS exposure
Compound increases IKAP protein in vivo in all tissues

- Transgenic mice carrying human mutant IKBKAP gene
- Dosed for 8 days

Several active chemical series have been identified
Lead optimization is under way in partnership with key stakeholders
PTC’s splicing platform generates clinical and lead assets

- SMN splicing modifier for SMA is progressing in the clinic
  - Two pivotal studies are expected to begin in 2017

- IKBKAP splicing modifier for FD in progressing through lead optimization
  - In vivo activity has been achieved for several lead compounds

- Additional preclinical programs targeting alternative splicing in Huntington’s disease and oncology are ongoing
Acknowledgements

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- Dysautonomia Foundation
- NYU's Dysautonomia center
- Sue Slaugenhaupt and her lab (MGH)