SPINAL MUSCULAR ATROPHY: Novel Disease Modifying Therapeutics

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Dr. Darras is the author of articles regarding neuromuscular diseases for UpToDate, Inc. UpToDate does not produce health-care related products or services.

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5q Proximal SMA is...

- An autosomal recessive disorder caused by loss or mutation of the \textit{SMN1} gene and retention of the \textit{SMN2} gene.

- \textit{SMN1} and \textit{SMN2} genes encode the "\textit{survival (of) motor neuron (SMN)}" protein.

- SMA is caused by decreased levels rather than complete loss of the SMN protein, leading to selective dysfunction of motor neurons in the spinal cord.
Full length SMN protein (294 AA)

Chromosome 5

Full length SMN protein (294 AA) Truncated protein SMNΔ7

c840 C>T transition

Creation of ESS

Exon 7

SMN2

~90-95%

~5-10%

100%

Truncated protein SMNΔ7

Full length SMN protein (294 AA)

The SMN2 Gene

An important gene

- A major phenotypic modifier
- It allowed the creation of animal models by introducing a number of SMN2 copies into mouse SMN knockouts (SMN Δ7 mouse)
  - Severe phenotype (death at 14-17 days)
  - Smn -/- Smn2 +/+ Smn delta7 +/+  
- Therapeutic target using SMN2 splicing modulators and upregulators

Hsieh-Li HM et al. Nature Genet 2000
Goal of most drug trials is to increase the full-length SMN protein production from $\textit{SMN2}$ gene.

Unique “translational” disease:
- Genetic defect same in all patients
- Clear target
Therapeutic Strategies for SMA

**Neuroprotection**
- Riluzole
- Gabapentin
- Thyrotropin-Releasing Hormone

**Amplification of SMN protein production**
- Phenylbutyrate
- Hydroxyurea
- Valproic Acid
- Trichostatin A
- Quinazoline (Repligen RG3039)

PNCR Network
Spinal Muscular Atrophy (SMA) Studies at Boston Children’s Hospital

Clinical Studies
- Natural History of SMA (PNCR)
- Biomaterials (PNCR)
- EIM and US in SMA (Rutkove / Darras)
- SMA Infant Biomarkers (NeuroNEXT)

Interventional Studies
- IONIS SMNRx (IONIS Pharmaceuticals)
- CK-2127107 (Cytokinetics/Astellas)
- R06885247 (Roche/PTC/SMAF) On hold
- chariSMA Gene AAV9 Rx (Avexis/OSU)
Natural History of SMA Study: Methods

- Clinical outcome measures include:
  - **Motor Function Measures**
    - Gross Motor Function Measure (GMFM-validated in SMA)
    - Hammersmith Functional Motor Scale (HFMS)
    - Expanded HFMS (HFMSE)
    - CHOP-INTEND
  - **Pulmonary Function Measures**
    - for cooperative children over 5 years of age, pulmonary function testing (forced expiratory vital capacity, FVC as percent predicted)

- Laboratory outcome measures include:
  - motor unit number estimation (**MUNE**) and CMAP
  - **SMN genetic testing**, various labs
SMA Natural History Study

PNCR Network

- 335 subjects enrolled over a 11-year period
  - NH study (4 years, 119 subjects)-3 publications
  - Minimal dataset study (5 years, 216 subjects)
- Developed/modified, validated or tested or just used 4 outcome measures in SMA
  - CHOP INTEND (Type I)
  - Hammersmith Functional Motor Scale-Expanded (HFMSE) (Types 2 and 3), RHS
  - 6 MWT (Type 3)
  - Upper Limb Module (Type 2 and 3)
- Created an extensive biomaterials repository
Therapeutic Strategies for SMA

1. Neuroprotection
   - Riluzole-F
   - Gabapentin-F
   - Thyrotropin-Releasing Hormone
   - Olesoxime (TRO19622) "Trophos" compound

2. Amplification of SMN protein production
   - Phenylbutyrate-F
   - Hydroxyurea-F
   - Valproic Acid-F
   - Trichostatin A
   - Quinazoline (Repligen RG3039)-T
   - RG7916 (PTC-Roche)

3. Muscle anabolism
   - Albuterol
   - Carnitine
   - Creatine
   - Anti-myostatin

4. Cell therapy (stem cells)

5. SMN2 exon 7 inclusion (antisense oligonucleotides)

6. Replacement of SMN1 (gene therapy)

F= failed, T=terminated, Green=ongoing strategies
Oligo Rx: SMN2 Exon 7 Inclusion

- Screening of oligos for exon 7 retention in SMN2 mRNA

- Long-term retention of exon 7 after ICV infusion in SMA mice

Hua et al 2008, 2010
IONIS-SMN<sub>Rx</sub>: Modulating Splicing of SMN2 to Increase Normal SMN Protein

- Uniformly 2’-O-methoxyethyl modified (MOE) antisense drug
- Corrects the splicing disorder in SMN2, resulting in the production of fully functional SMN protein in model systems
- In mild and severe mouse models of SMA provides a phenotypic and pathological benefit when delivered centrally*
- Distributes broadly to spinal cord motor neurons after intrathecal delivery in monkeys*
- Has a long half life in CNS tissue (>6 months in animal models)

Results of an Open-Label, Escalating Dose Study to Assess the Safety, Tolerability, and Dose Range Finding of a \textit{Single Intrathecal Dose} of ISIS-SMN_{Rx} in Patients with Spinal Muscular Atrophy (CS1)

1 – Boston Children’s Hospital; 2 – Columbia University Medical Center; 3 – University of Utah; 4 – UT Southwestern Medical Center; 5 – Ionis Pharmaceuticals, Inc.

No safety or tolerability issues (1,3,6,9 mg)

No serious adverse events or dose-limiting toxicities were reported in 28 patients
Mean change in HFMSE scores through 9-14 months post-dose

Ionis Pharmaceuticals, Inc.
Phase 2 *Multiple-Ascending Dose, Open-Label Study in Medically Stable SMA Patients 2-15 Years of Age*

- **Objectives:**
  - Evaluate the safety and tolerability of multiple intrathecal doses of ISIS-SMNRx
  - Evaluate CSF, plasma PK, and clinical outcomes related to SMA (including HMFSE)

- **Status:**
  - 3 mg, 6 mg, and 9 mg cohorts completed; 12 mg cohort was added

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<table>
<thead>
<tr>
<th>Cohort</th>
<th>Total Dose</th>
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<tbody>
<tr>
<td>3 mg</td>
<td>9 mg</td>
<td>8</td>
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<td>6 mg</td>
<td>18 mg</td>
<td>8</td>
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<tr>
<td>9 mg</td>
<td>18 mg</td>
<td>9</td>
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<tr>
<td>12 mg</td>
<td>36 mg</td>
<td>9</td>
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</table>

**SUBJECT DEMOGRAPHICS**

- **N=25**
  - SMA Type: Type 2 = 10; Type 3 = 15
  - Ambulatory/Non-ambulatory: 9/16
  - Mean age (range): 7.5 years (2-15)
  - SMN2 Copy #: 2 copies = 1; 3 copies = 20; 4 copies = 4
Interim Results of a Phase 2 Study of ISIS-SMN$_{Rx}$ in Children with Spinal Muscular Atrophy

Darras, B$^1$; Chiriboga, C$^2$; Swoboda, K$^3$; Iannaccone, S$^4$; Montes, J$^2$; Castro, D$^4$; Holuba, N$^2$; Rausch, N$^3$; Ramos, C$^3$; Visyak, N$^1$; Dunaway, S$^2$; Trussell D$^3$; Pasternak, A$^1$; Neilson, L$^4$; De Vivo, D$^2$; Norris, D$^5$; Bennett, F$^5$; Bishop, K$^5$

1 – Boston Children’s Hospital; 2 – Columbia University Medical Center; 3 – University of Utah; 4 – UT Southwestern Medical Center; 5 – Ionis Pharmaceuticals, Inc.

World Muscle Society Meeting, Berlin, 2014
IONIS-SMN$_{Rx}$ has been well tolerated when given as multiple doses up to 12 mg - no safety or tolerability concerns have been identified.

CSF and drug concentrations are dose-dependent and consistent with predictions; CSF half-life is about 4-6 months. Observations support infrequent administration.

- Dose and time dependent SS increase in HFMSE scores observed (even 9-14 months after last dose).
- Additional secondary endpoints (6 MWT, ULM) supportive, although open-label study and small numbers limit interpretation.

These data informed the design of a planned Phase 3 registration-enabling studies in infants and children with SMA.
IONIS (ISIS) SMNRx

- ASO* drug administered intrathecally (IT) to children with SMA
- Completed initial phase I/II single dose trial and open label extension trial (CS1 and CS10)
- Completed CS2 (multiple dose) and started open label extension trial, CS12 and now CS11
- Initiated phase III registration Type I trial (CS3B) and will start Type II trial (CS4) which are ongoing

*ASO: antisense oligonucleotide
ISIS-\textit{SMN}_{Rx} (Nusinersen) Phase CS3B Study in SMA Infants - ENDEAR

A Phase 3, randomized, double-blind, sham-procedure controlled study in infants with SMA Type I

- Global study in \sim 120 SMA infants \leq 7 months old with 2 copies of \textit{SMN2}
- 13-month study duration
- Evaluate the efficacy and safety of IONIS-\textit{SMN}_{Rx}
  - Primary efficacy endpoint is time to death/permanent ventilation
  - Additional efficacy endpoints include CHOP INTEND and motor milestones

Study initiated August 2014 – Promising results August 2016

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<tr>
<td>Sham control</td>
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<td>12 mg ISIS-\textit{SMN}_{Rx}</td>
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</table>

Ionis Pharmaceuticals, Inc.
Achievement of New Motor Milestones Observed in Some ISIS-SMN$_{Rx}$-treated SMA Infants

| Head control       | Unable to maintain upright | Wobbles | All the time upright |  |
|--------------------|----------------------------|---------|----------------------|  |
| Sitting            | Cannot sit                 | Sit with support at hips | Props | Stable sit | Pivots (rotates) |
| Voluntary grasp   | No grasp                   | Uses whole hand | Index finger and thumb but immature grasp | Pincer grasp |
| Ability to kick (in supine) | No kicking | Kicks horizontally; legs do not lift | Upward (vertically) | Touches leg | Touches toes |
| Rolling            | No rolling                 | Rolling to side | Prone to supine | Supine to prone |
| Crawling           | Does not lift head         | On elbow | On outstretched hand | Crawling flat on abdomen | On hands and knees |
| Standing           | Does not support weight    | Supports weight | Stands with support | Stands unaided |
| Walking            | No walking                 | Bouncing | Cruising (holding on) | Walking independently |

Incremental milestones achieved consistent with CHOP-INTEND score increases
(14/16 subjects exhibited improvements - 3/4 at 6 mg; 11/12 at 12 mg)
Achievement of New Motor Milestones Observed in Some ISIS-SMN$_{Rx}$-treated SMA Infants

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Incremental milestones achieved consistent with CHOP-INTEND score increases.
(14/16 subjects exhibited improvements - 3/4 at 6 mg; 11/12 at 12 mg)
SMA Type 1 infants in the PNCR study had a CHOP INTEND decline of 1.27 points/study year.

Majority of ISIS-SMN$_{Rx}$-treated infants saw increases in CHOP INTEND scores:
- Mean change from baseline = 9.3 points (p=0.005)
- 14/16 patients had increases.

At the 12 mg dose level, increases were observed in most of patients at 3-6 months:
- Mean change from baseline = 11.7 points (p=0.001)
- 11/12 patients had increases.
**ISIS-SMN_{Rx} (Nusinersen) Phase 3 Study in SMA Type II - CHERISH (ongoing)**

- A Phase 3, Randomized, Double-blind, Sham-Procedure Controlled Study in Children with SMA
- Global study in ~120 SMA children with SMA Type II
- 15 month study duration
- Determine the efficacy and safety of IONIS-SMN_{Rx}
  - Primary endpoint is change in Hammersmith motor function score

2014 initiation-still ongoing

**Cohorts**
- Sham control
- 12 mg IONIS-SMN_{Rx}

Ionis Pharmaceuticals, Inc.
SMNRx (Nusinersen) Studies

- **CS3B.** Infant SMA (Type 1) Phase 3, multiple-dose, RPCT study, 12 mg IT per dose, conducted at many centers.

- **CS4.** Phase 3, RSPCT for older children with Type 2 SMA

- **CS11.** Open label extension, 12 mg dose every six months for patients who participated in CS1, CS2, CS12, CS3A, CS3B and CS4.

- **Nurture.** Presymptomatic, for patients with 2 or 3 copies of SMN2

- Open access program (EAP)
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- R06885247 (Roche/PTC/SMAF) On hold
- chariSMA Gene AAV9 Rx (Avexis/OSU)
RO6885247: a new molecule to treat SMA by altering SMN splicing
- Extends life of SMNΔ7 mice from 14-17 days to more than 150 days
- Single dose study in Europe on adult healthy volunteers was completed and SMA trial was initiated.
- Phase 1 (Moonfish) study is on hold (retinal toxicity)
- A second SMN2 splicing modifier (RG7916), currently in a Single Ascending Dose (SAD) study in healthy volunteers, is progressing into Phase 2 studies in SMA patients SUNFISH (Type II) and FIREFISH (Type I)
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- R06885247 (Roche/PTC/SMAF) On hold
- chariSMA Gene AAV9 Rx (Avexis/OSU)
Adenovirus & Adeno-associated Virus

Adenovirus (childhood cold) 1999 Jesse Gelsinger

Adeno Associated Virus (non-pathogenic) >25 clinical trials Remarkable safety Long-term expression

Courtesy of Brian Kaspar, PhD
Gene Replacement by Early I.V. Delivery of scAAV9

Foust KD et al
Nature Biotech
February 2010

D1: good effect
D5: partial effect
D10: no effect
Gene Replacement by Delivery of SMN via scAAV9

- In 2013, NINDS award to Brian Kaspar, PhD, and Jerry Mendell, MD, in collaboration with FSMA to advance a CNS-directed gene therapy to IND

- Results on the treated 15 SMA Type I infants very encouraging:
  - Prolonged survival
  - Acquisition of milestones

- A Type II gene therapy study will start at various sites in the US in the near future (AveXis Inc.)
2016: SMA Drug Development Programs

<table>
<thead>
<tr>
<th>Drug Development</th>
<th>Lead Optimization</th>
<th>Preclinical</th>
<th>Clinical Trials</th>
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<tr>
<td>Nusinersen (Ionis/Biogen)</td>
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<td>ENDEAR (Type I)</td>
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<td>Olesoxime (Roche, formerly Trophos)</td>
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<td>CHERISH (Type II)</td>
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<td>CK-2127107 (Cytokinetics/Astellas)</td>
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<td>LMI070 (Novartis)</td>
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<td>AVXS-101 (AveXis/OSU)</td>
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<td>SUNFISH (Type II)</td>
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<td>SMN Gene Therapy (Genzyme/Sanofi)</td>
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<td>SMN Gene Therapy (Genethon/INSERM)</td>
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<td>Antisense Oligonucleotides (RaNA)</td>
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Based on publicly disclosed timelines, September 2016

Courtesy of Dr. Karen Chen, SMA Foundation
Spinal Muscular Atrophy: 125 years later and on the verge of a treatment(s)... but can SMA be prevented?

Postnatal Requirements for the SMN protein

Conclusions from animal studies

- Restoring SMN protein early during the course of the disease is more effective than restoring it late but can be effective after onset of disease.

- The requirements for the SMN protein change profoundly with age:
  - Very high early on (perhaps 1-2 years in humans)
  - Highest during neonatal life
  - Very low later in life
Postnatal Requirements for the SMN protein

Conclusions from human studies

- In normal infants, motor units continue to be established postnatally. They are lost early and precipitously in patients with SMA.

- CMAPs increase 1-2 mV to 6-8 mV in normal infants by 15-24 months, a critical age for motor unit development and maturation.

- We postulate that humans also need very high SMN protein levels during the first and most probably the second year of life.
Can SMA be prevented?

- If a therapeutic is partially effective in symptomatic patients, it will probably be even more effective or **preventive** of the disease, if the treatment is started early in life before the onset of symptoms.
- Pilot newborn screening program in NY, approved in MA
- Patients with 2, 3 or even 4 copies of SMN2 may need to be treated presymptomatically ASAP after the dx is made with NB screening, particularly patients with 2 or 3 copies of SMN2
- Nusinersen, NURTURE, **Presymptomatic**, for patients with 2 or 3 copies of SMN2
- Gene Therapy, before onset of symptoms
Thank you