The SMA Project

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The SMA Project

◆ What is it?
  • A NIH drug development program for SMA
  • A rare disease therapeutics experiment

◆ Goal:
  • At least 1 IND for testing a new drug in SMA patients
Rationale for SMA as a Pilot

- Defined cause = loss of SMN1 gene

- Defined strategy for treatment = SMN2: identical protein, low expression

- Compounds that increase SMN2 expression available as starting points
SMA Project Focus

Basic
- Target ID
- Assay
- Hit ID

Translational
- Proof of Concept
- Lead Optimization
- Candidate Selection
- Pre-clinical Safety

Clinical
- Clinical Trials

SMA Project

[Diagram showing flow from Basic to Clinical stages through various stages of scientific research]
Mouse Model Testing

Lead Development Team

SAIC Contract Monitors

Chemical Optimization
In vitro Testing
Pharm/Tox
Mouse Model Testing
Lead Development Team

◆ **Industry consultants:**
  - John McCall
  - Graham Johnson
  - Donna Romero
  - Paul Pearson
  - Tony Bannon

◆ **AMRI:**
  - Keith Barnes

◆ **NINDS:**
  - Jill Heemskerk
  - Amelie Gubitz

◆ **SAIC:**
  - Jim Romano
  - Sabina Robinson
Indoprofen: Starting Point for Medicinal Chemistry

- Indoprofen increases SMN protein in vitro:
  - SMN reporter assay
  - SMN protein in patient fibroblasts
- Indoprofen improves *in utero* survival of SMA mice

-B. Stockwell: Lunn et al, 2004
Customizing Indoprofen for SMA

Chemistry Goals
- Increase potency
- Eliminate toxicity
  - Cox Inhibition
- Improve BBB penetration

[Diagram showing structural substitutions and varied sites]

- Lactam: Varied heterocycle
- Phenyl: Substitutions: alkyl, halo, methoxy, aryl, heteroaryl
- Acetic Chain: Varied at methyl site, length of chain, and CO₂H

Substitutions:
- alkyl, halo, methoxy, cyano, amino, aryl, heteroaryl
Chemistry Improves Potency and Activity of Indoprofen

>1000 Indoprofen analogs synthesized and tested

![Graph showing concentration vs. luminescence for Indoprofen and P407923]
Optimized Indoprofen Analogs Increase the Number of Nuclear Gems in SMA Type I Patient Fibroblasts

-V. Mattis, M. Lorson, C. Lorson
Indoprofen Analogs Increase SMN Protein in Patient Fibroblasts: Western Blots

- Brenda Fung, CombinatoRx
Indoprofen Analogs Stimulate Translational Read-through

Interrupted Luciferase Construct:

- Compound

+ Compound

Luciferase Activity

-Courtesy Ellen Welch, PTC Therapeutics
Compounds Stabilize SMNΔ7 Protein via Translational Readthrough
Indoprofen Chemical Analogs are Drug-like

- Brain:Plasma as high as 10:1
- Orally bioavailable
- Well-tolerated in rodents
- Rodent half lives around 2 hours
- Excellent human microsome stability
- Favorable CYP, genotox, broad target profiles
- Abolished Cox inhibition
- 2 NIH patents
Timeline to Phase I Clinical Trial

1Q '10  |  2Q '10  |  3Q '10  |  4Q '10  |  1Q '11

- 200gm Synthesis
- GLP Synthesis
- Radio Synthesis
- Dose Ranging Tox

28-Day GLP Tox
14-Day GLP Tox
Safety Pharmacology
ADME

GMP Synthesis
Formulation Development
Regulatory Submission
First in Human Trial
Industry Engagement

- Industry experience on Steering Committee sets strategy (Robert Pacifici, Chair)
- Industry consultants on development team guide work flow (John McCall, Chair)
- Industry service providers conduct work
- Industry collaboration to identify drug mechanism of action

Goal: Industry licensing of NIH IP to commercialize compounds
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  - Jianhua Zhou
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  - Glenn Morris
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  - Jill Jarecki