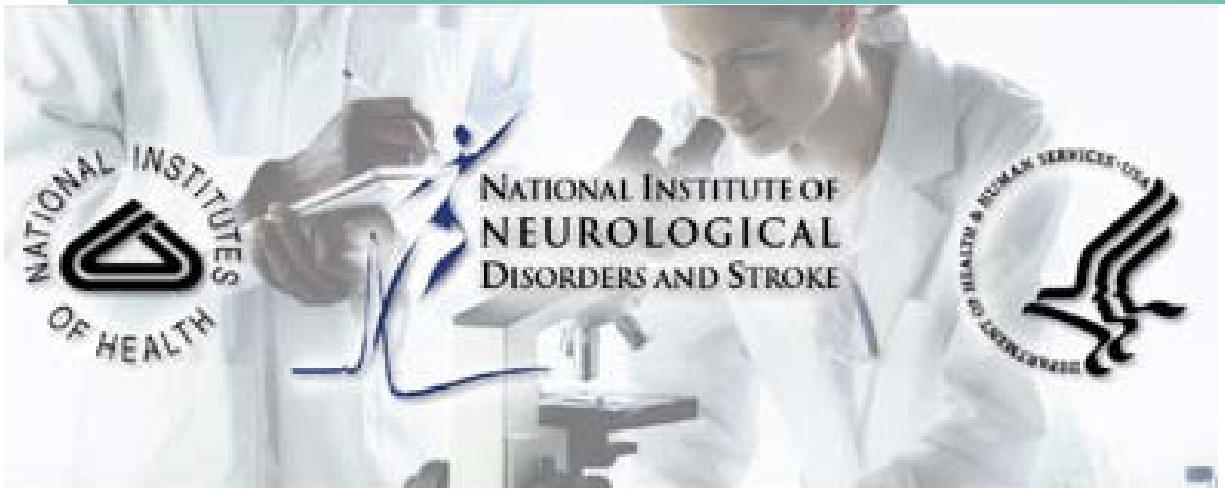
The SMA Project

Jill Heemskerk, PhD

NINDS Office of Translational Research

The Spinal Muscular Atrophy Project



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

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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

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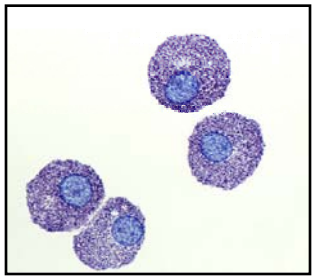
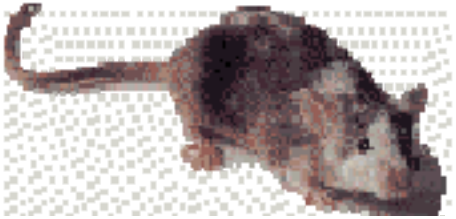
SMA Project Focus

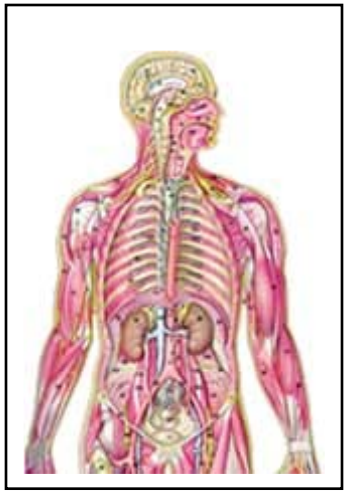
SMA Project

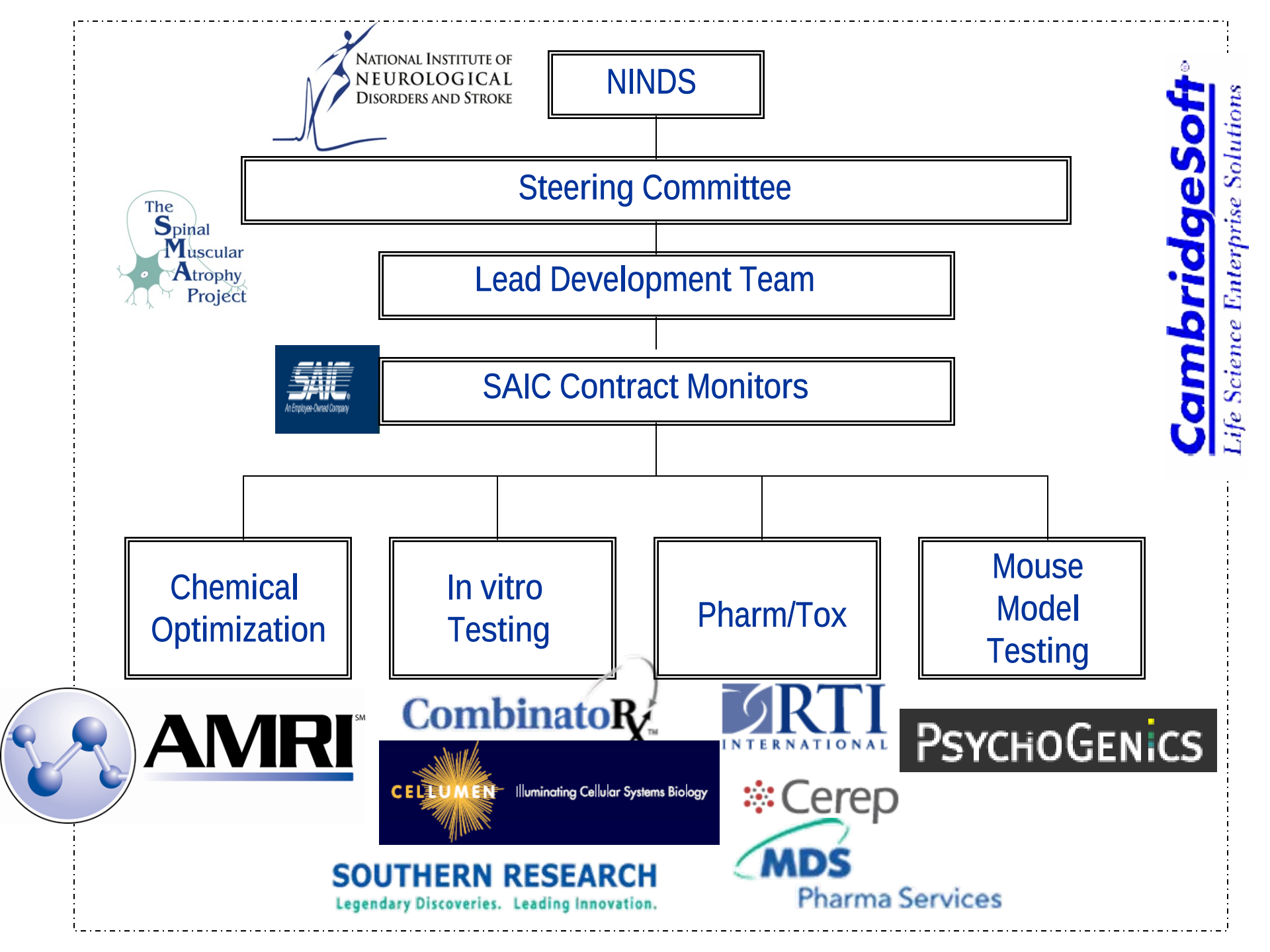
Basic | **Translational** | **Clinical**

Target ID → Assay → Hit ID → Proof of Concept → Lead Optimization → Candidate Selection → Pre-clinical Safety → Clinical Trials








National Institute of Neurological Disorders and Stroke
NINDS
Steering Committee
The Spinal Muscular Atrophy Project
Lead Development Team
SAIC
An Employee-Owned Company
SAIC Contract Monitors
CambridgeSoft
Life Science Enterprise Solutions
Chemical Optimization
In vitro Testing
Pharm/Tox
Mouse Model Testing
AMRI
CombinatoRx
RTI International
PsychoGenics
Cellumen
Illuminating Cellular Systems Biology
Cerep
MDS Pharma Services
Southern Research
Legendary Discoveries. Leading Innovation.

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

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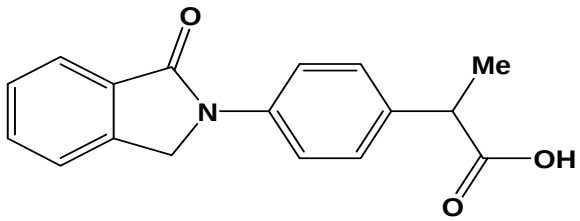
Indoprofen:
Starting Point for Medicinal Chemistry



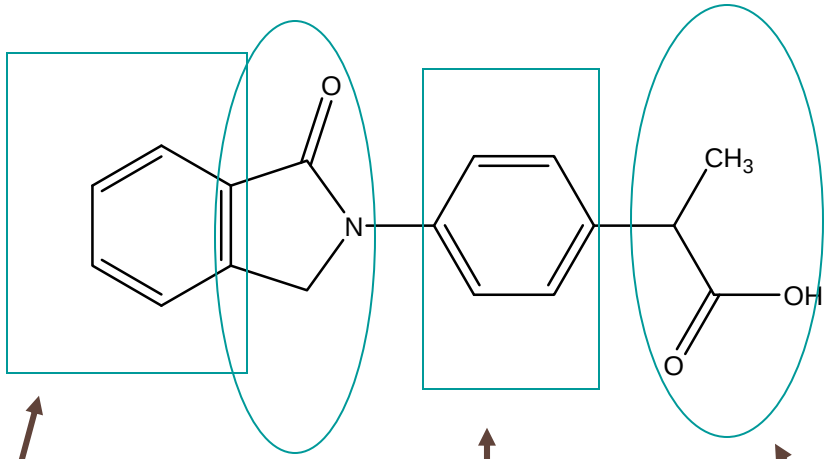
- Indoprofen increases SMN protein in vitro:
  - SMN reporter assay
  - SMN protein in patient fibroblasts
- Indoprofen improves *in utero* survival of SMA mice

-B. Stockwell: Lunn et al, 2004

Customizing Indoprofen for SMA

Chemistry Goals

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



Benzo
Substitutions: alkyl, halo, methoxy, cyano, amino, aryl, heteroaryl

Lactam
Varied heterocycle

Phenyl
Substitutions: alkyl, halo, methoxy, aryl, heteroaryl

Acetic Chain
Varied at methyl site, length of chain, and CO_2H

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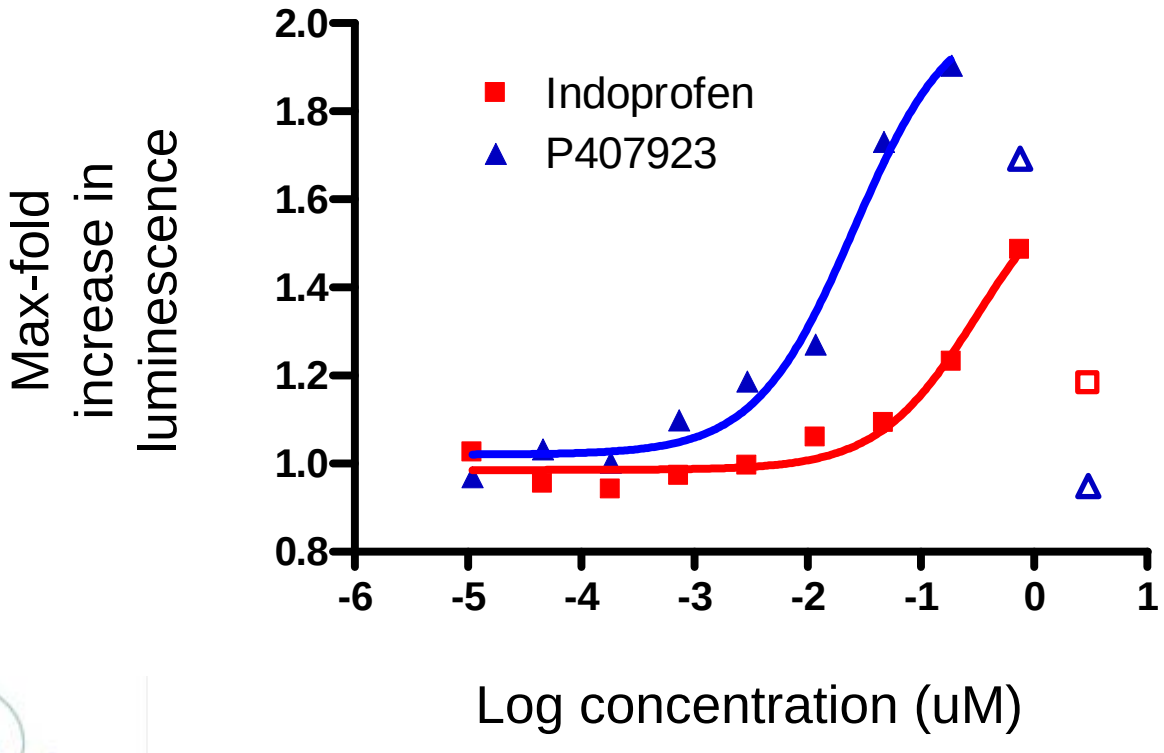
Chemistry Improves Potency and Activity of Indoprofen

>1000 Indoprofen analogs synthesized and tested



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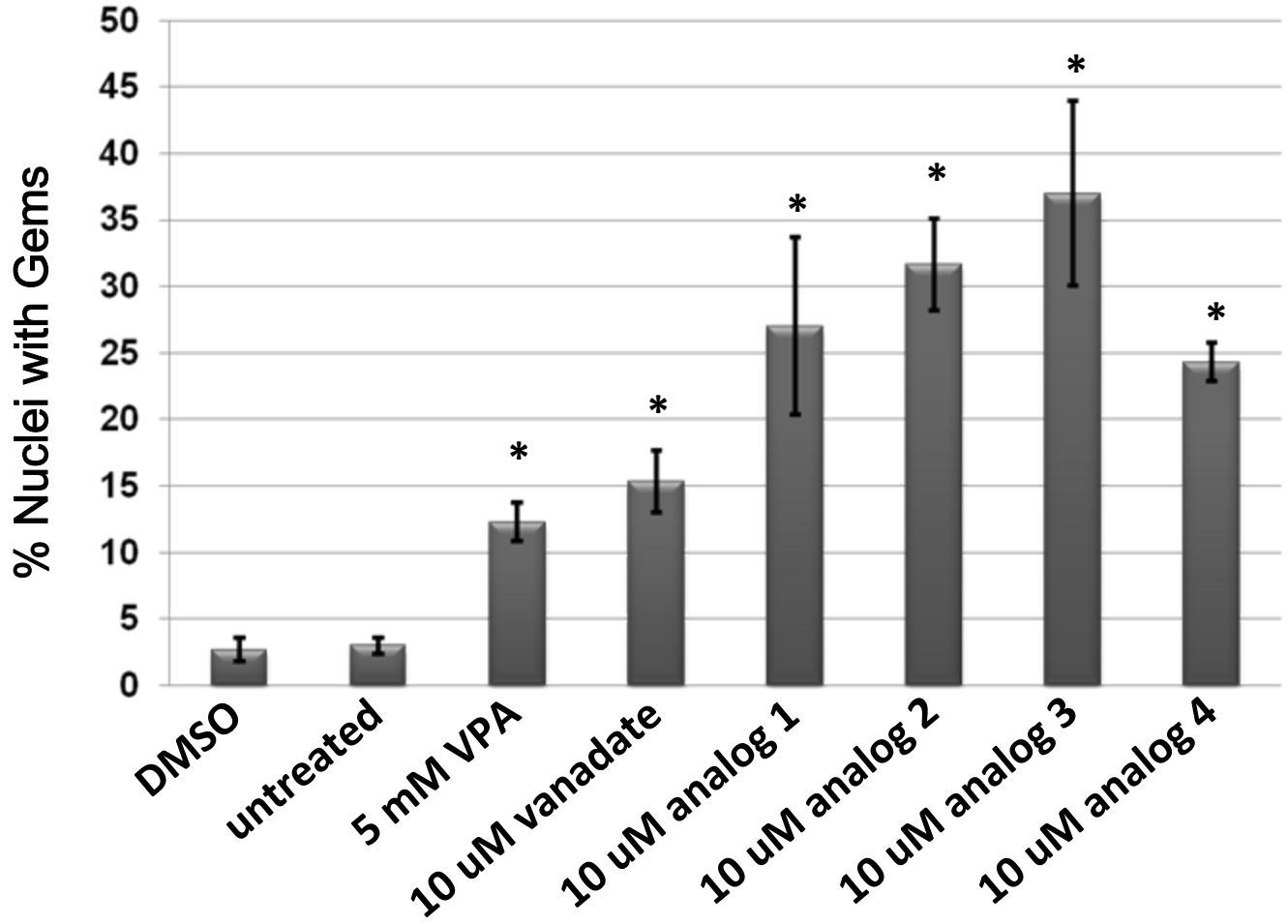
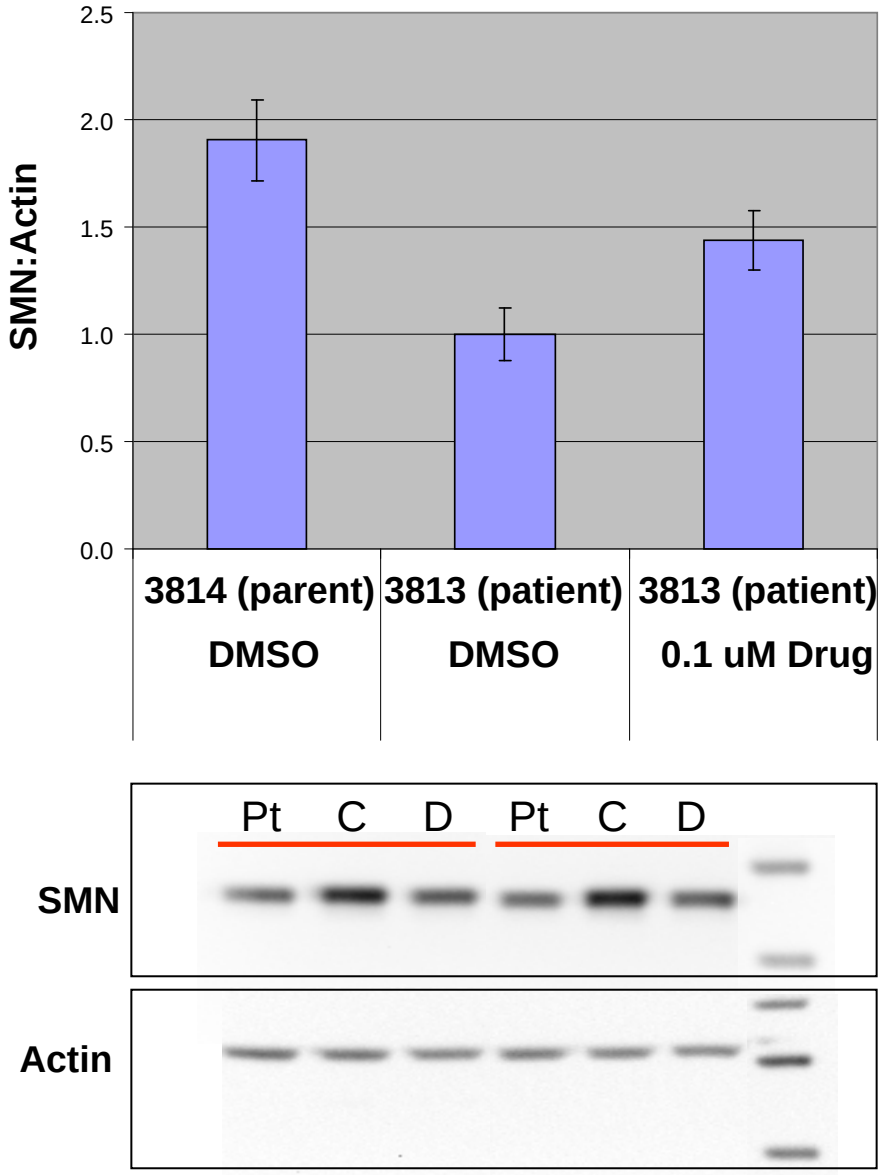
Optimized Indoprofen Analogs Increase the Number of Nuclear Gems in SMA Type I Patient Fibroblasts



-V. Mattis, M. Lorson, C. Lorson

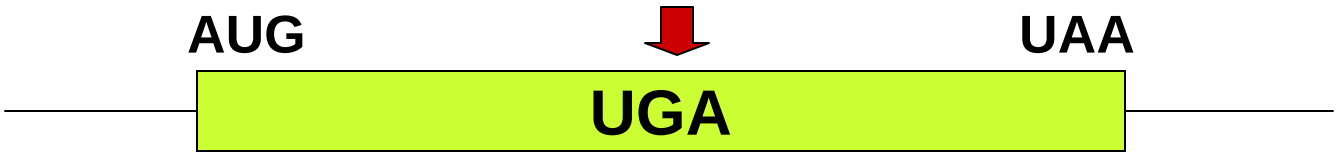
Indoprofen Analogs Increase SMN Protein in Patient Fibroblasts: Western Blots



-Brenda Fung, CombinatoRx

Indoprofen Analogs Stimulate Translational Read-through

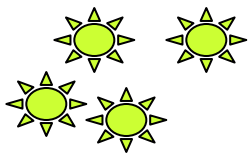
Interrupted Luciferase Construct:



Luciferase Activity

- Compound

+ Compound



-Courtesy Ellen Welch, PTC Therapeutics

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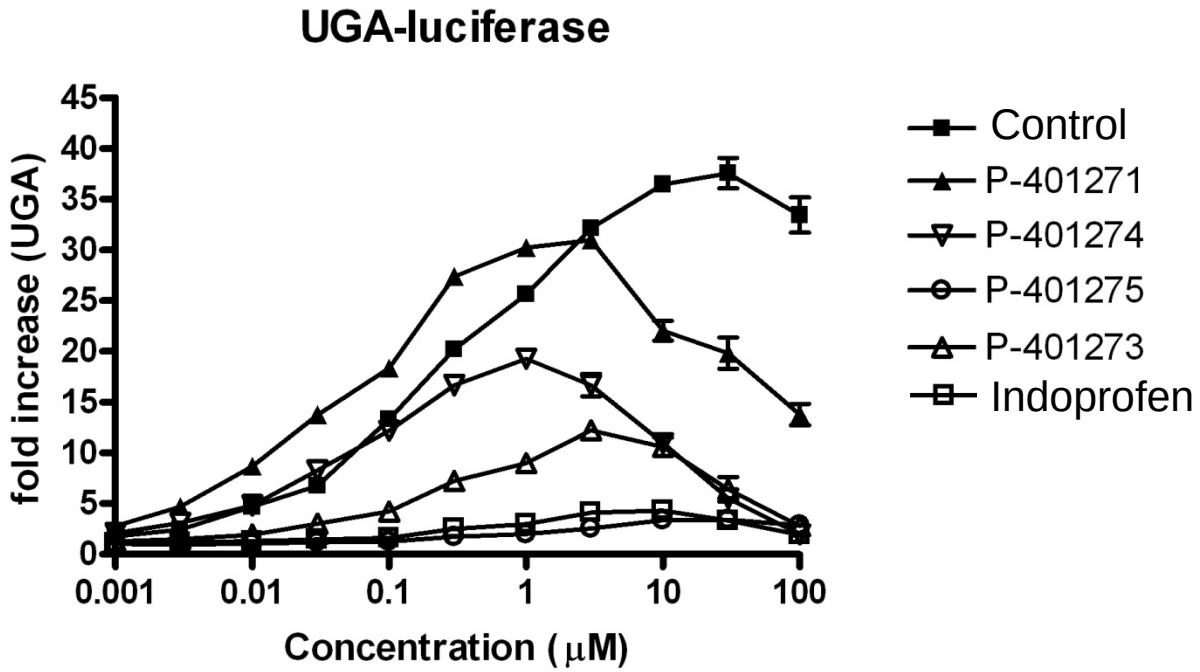
Compounds Stabilize SMNΔ7 Protein via Translational Readthrough



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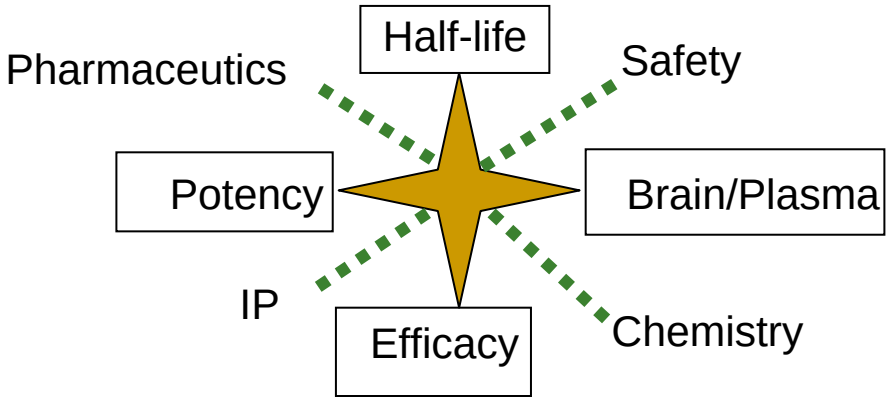
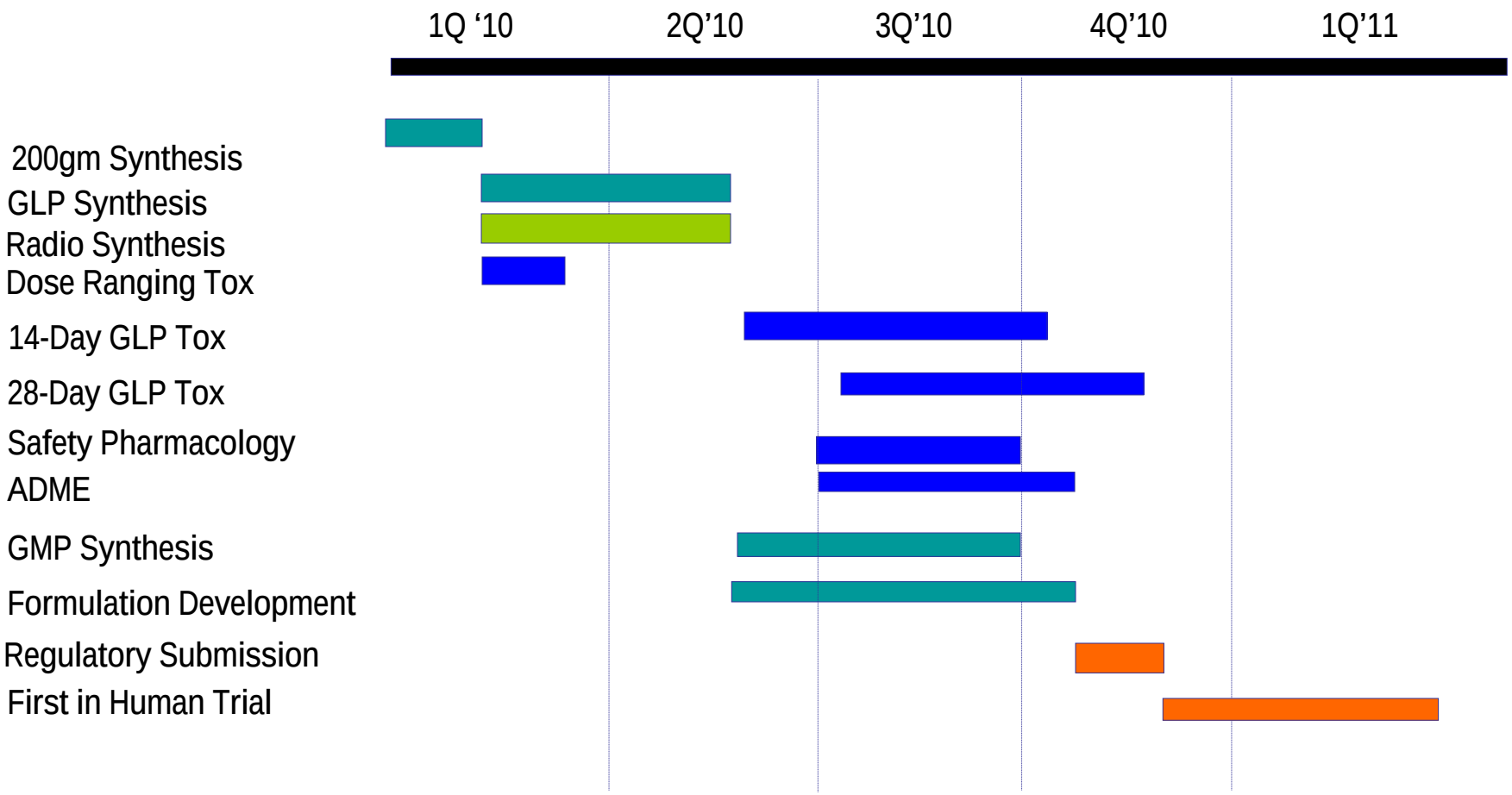
-E. Welch, A. Bhattacharyya, PTC

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



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**

- **<u>Goal:</u> Industry licensing of NIH IP to commercialize compounds**

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Acknowledgements

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  - Amelie Gubitz
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