IOM Workshop on Venture Philanthropy Strategies
Starting a Translational Research Program

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SMA: Leading Genetic Cause of Mortality in Infants and Toddlers

- Autosomal recessive inheritance
- 1 in 35 people (7 million Americans) are carriers
- 1 in 6,000-10,000 incidence
- Well-defined patient population: 50,000+ in US/EU/Japan
- **Common** rare disease: comparable to Cystic Fibrosis, Duchenne Muscular Dystrophy, Sickle Cell Anemia, ALS
- Affects all racial and ethnic groups

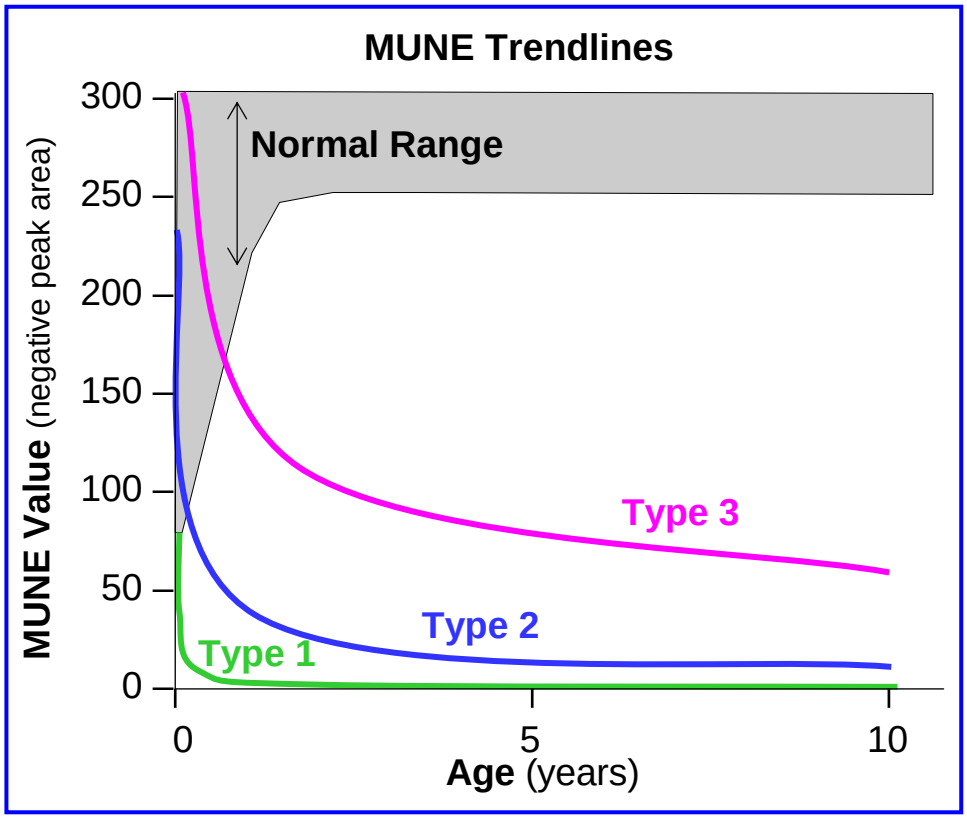
Urgent unmet need – no specific treatment available

Devastating, Progressive Disease Leading to Premature Death in >50% cases

- Progressive loss of motor neurons
  - Proximal muscles most severely affected
- Patients lack, or progressively lose, the ability to walk, stand, sit and move
- Skeletal deformities and fatal respiratory insufficiency
  - Repeated surgeries and respiratory support required
- Enormous cost for multidisciplinary care
- Cognition/intellect, emotional development and sensory nerves unaffected

Natural History of Disease Supports Accessible Therapeutic Window

- Motor neurons present and functional, even in the most severe disease form
  - Newborn screening plus early intervention may prevent loss
- Number of functional motor units (MUNE scores) correlates with disease severity: potential outcome measure
- Potential for regenerative strategies
  - Motor neurons persist after MUNE counts decline
  - Evidence for reinnervation in Type 2 and 3 disease

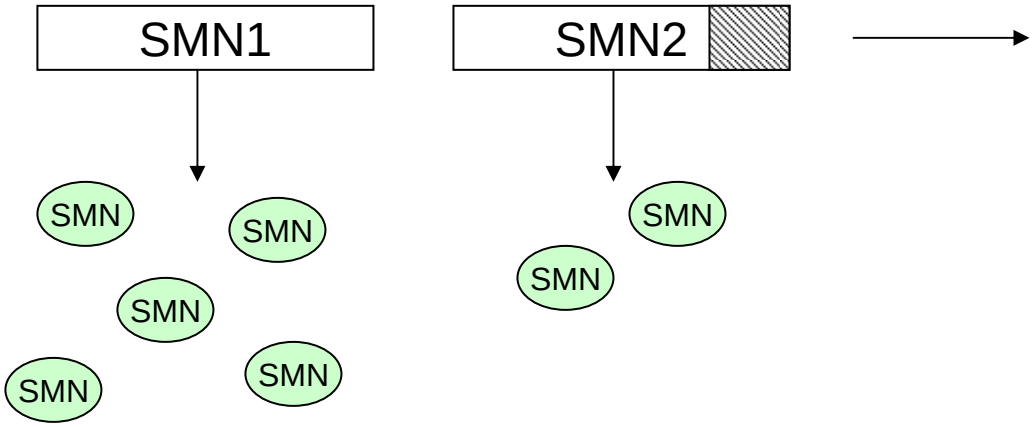


Based on Swoboda et al (2005) Ann Neurol 57:704-712

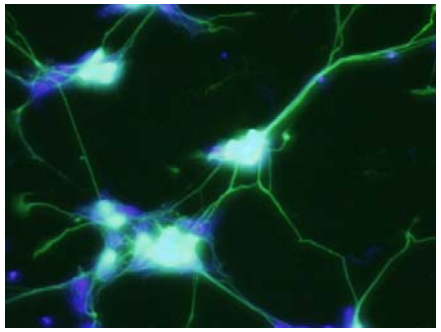
The Survival of Motor Neuron (*SMN*) is an Essential Protein for Neurons

- Humans normally carry SMN1 and SMN2 genes, which both result in production of SMN protein
- All cells require SMN protein, though different levels may be required
- SMN1 results in high level expression of SMN protein, while SMN2 results in low-level expression of SMN protein

Normal SMN Expression



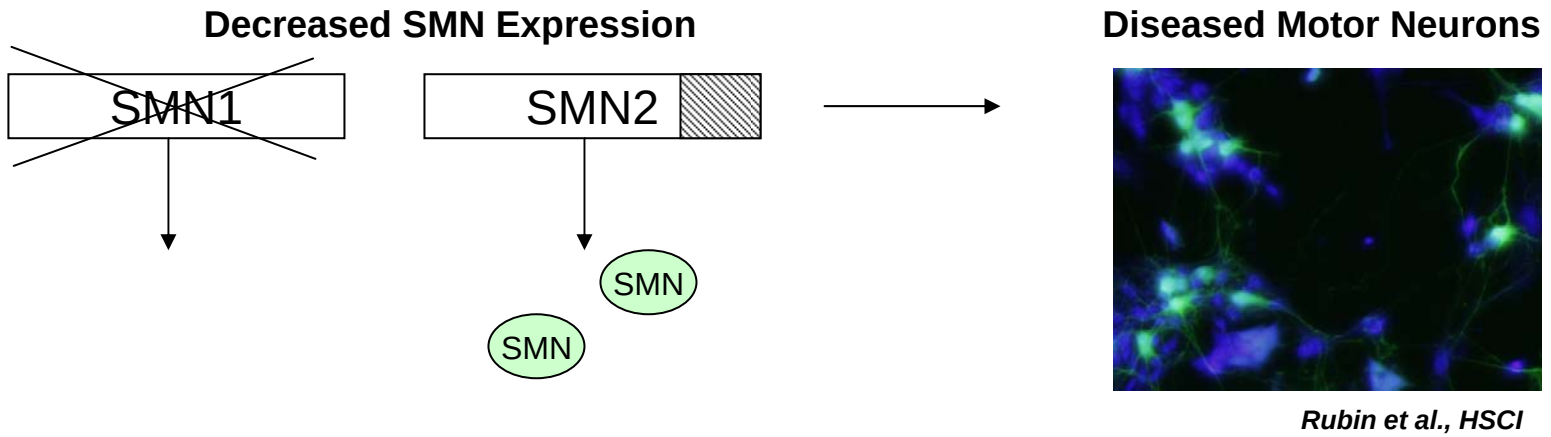
Healthy Motor Neurons



Rubin et al., HSCI

Spinal Muscular Atrophy is Caused by Defects in the *SMN* Gene

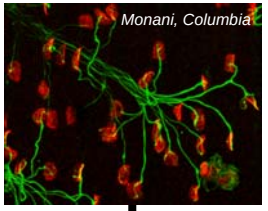
- Mutation in SMN1 leads to decreased levels of SMN protein, which is responsible for motor neuron degeneration and muscle atrophy characteristic of SMA



Rubin et al., HSCI

- Unlike most neurologic diseases, there is a single known cause
  - >98% of SMA cases are due to deletions or loss-of-function mutations in *SMN1* gene and deficiency of SMN protein [Lefebvre et al., (1995) *Cell*, **80**:155-165]

Diverse Approaches Increase Chances of Success

Targets in Patients	Treatment Strategy
GENE	SMN Gene Replacement
mRNA	Correct Splicing
PROTEIN	
	Increase / Stabilize Transcript
	Stabilize Protein
	Neuroprotection / Trophic Factors

SMA Foundation Goals

Founded in 2003 with a five year mission to:

"**accelerate the development of a treatment** or a cure for SMA, the number one genetic killer of infants and toddlers."

Goals:

- Increase the research commitment to SMA among academic, government and industry investigators
- Raise awareness among key decisionmakers and funders in government and industry
- Raise awareness among the general public
- **Bring a treatment into clinical trials - ASAP**

Acceleration Strategies

- Recruit supporters
  - Build a diverse Scientific Advisory Board
  - Increase recognition and awareness in NIH
  - Use non-profit platform to bridge between government, academia & industry
- Launch scientific awareness and recruitment efforts
  - Create virtual “centers” of expertise in academic communities
  - Establish standardized, reproducible assay platforms
  - Foster collaboration across the community
- Remove barriers to research for investigators and commercial drug developers
  - Distinguish between research tools and drug leads in IP discussions
  - Facilitate data sharing
  - Build and enhance ‘pre-competitive space’
- Invest in early-stage discovery efforts & create opportunity for industry to join

Mixed Model Program

- Sponsored Research: creativity matters
  - Basic pathology
  - Assay development
  - Clinical trial infrastructure
- Fee for Service: control and time matter most
  - Detection kits/Antibody Development
  - *In vivo* compound screening
- Industry Partnerships: full-scale drug programs
  - Project management

Sponsored Research Requirements

- Research Plan with timelines and deliverables
- Quarterly/weekly team meetings and/or reports
- Seat at the table for major decisions
- Non-exclusive license to inventions –including research tools
- Research tool sharing provisions
- 3rd party compound protections
- Step-in rights
- Key man clause

Foundation Research Tool Box: Ensuring Access to Research Tools

- License/sublicense for existing tools
  - Mouse models
  - Motor neuron protocols/assays
  - Gene sequences

- Research Agreement Terms ensure access to new tools "*umbrella agreements*"
  - Terms regarding access for academic and industry partners
  - Pre-negotiated MTA and sublicenses – risk deferred to commercialization of product
  - Protections for testing 3rd party compounds – risk-free compound characterization in battery of assays

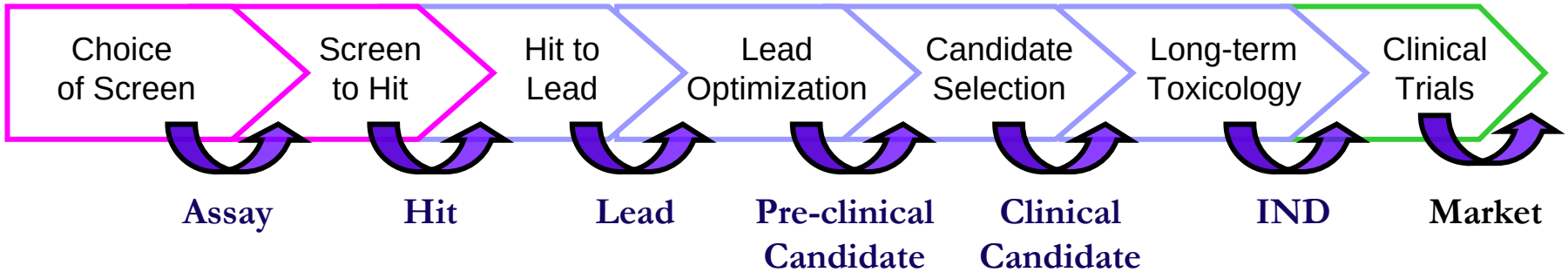
Standardization of Assays and Reagents

- Facilitate use of mouse models across the field
  - Available through central repository (Jackson Labs)
  - Secure sub-licenses for drug testing
- Standardize drug testing platform in animals
  - Large colony capacity for comparative studies
  - Moderate through-put assay of “hit list”
  - Resource for new discovery programs
- Support development of new *in vitro* assays
  - Academic and industry efforts
  - Focus on target tissues

Incentivizing Commitment & Investment in SMA

- Focus on urgent need and timeline driven activities
- Commitment to address issues that shorten timelines
  - "Umbrella licenses"
  - MOUs
- Recognize incentive structures among stakeholders
  - Career development/platform validation
  - Revenue structures
  - Public awareness
- Create opportunities to defer risk
  - Advance compounds through proof-of-concept, preclinical development
  - Shift licensing costs to marketed product
- Highlight "first mover" opportunity for industry
  - Development rewards for rare diseases
  - Market exclusivity

SMA Drug Discovery Landscape 2008: Community Resources



Discovery Tools

Cell reagents
- Fibroblasts
- Lymphoblasts
- Motorneurons

Antibodies
cDNAs & BACs
ELISA and PCR assays
HTS
Secondary assays

Optimization

Animal models
- Mice
- Zebrafish
- Invertebrates

Dev. Partners
•MedChem
•PK/PD/ADMET

Clinical Development

Clinical Trials Networks
Patient Registry
Natural History Studies
Biomarkers
Outcome Measures
ICC/TREAT-NMD

Research Program Considerations for Venture Philanthropists

- Clarity of goals and scope of work
  - Research objectives
  - Timeline
- Identifying resources required - Is there a match?
  - Funding
  - Research Needs
    - Academic
    - Industry
    - CRO
- Recruiting help
  - Advisors
  - Diligence
  - Oversight
  - STAFF

Investment Considerations for Venture Philanthropists

- Generally, early stage is less expensive

  Discovery efforts <<development<<<<clinical trials
- There is room for smaller key investments at strategic points:
  - Assay development
  - Proof-of-concept studies
  - Clinical trial tools (registries, natural history studies, repositories)
- Industry needs a significant investment to justify opportunity costs
- The barrier to collaboration is lower if the project is aligned with core research platforms….and strategic business plan

Lessons Learned

- Consistent and focused leadership required
- Prepare to be a change agent among constituents
  - Anticipate cultural barriers - eg tech transfer environment
  - Prepare for high commitment to legal issues
- Anticipate need to change directions
  - Parallel experiments shorten timelines – at higher cost
- Prepare to be a risk-taker with research dollars

Thanks to the SMA Foundation Advisory Board (p. 1 of 2)

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Dennis Choi, MD, PhD	Executive Director of Neuroscience Initiatives Emory University
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Many Thanks to Our Friends & Collaborators