The SMA Research Landscape: Today and Tomorrow

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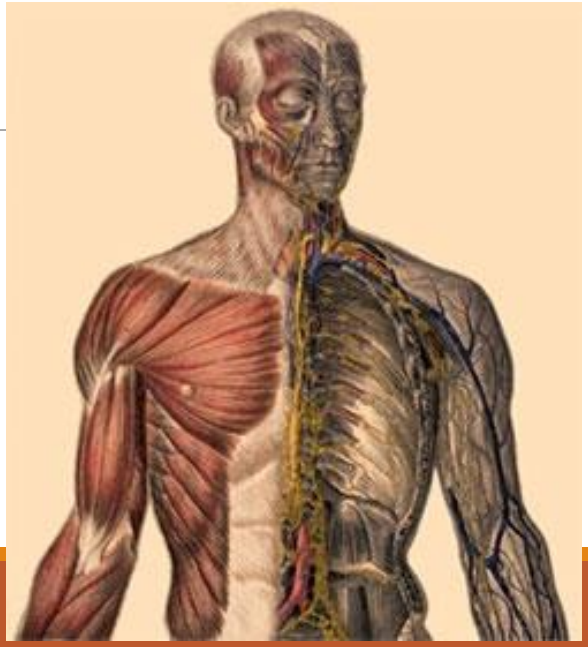
MDA Engage – Princeton, NJ
2023



Disclosures

Site PI or subinvestigator for industry-sponsored protocols

- Alexion, Astellas, AveXis/Novartis, Biogen, Catabasis, CSL Behring, Cytokinetics, Dyne, Fibrogen, Genentech, Ionis, Lilly, Pfizer, PTC Therapeutics, Sarepta, Summit, WaVe

Advisory Boards:

- PTC Therapeutics
- NS Pharma
- Fibrogen
- Dyne
- Alexion
- Momenta/ Janssen
- Cytokinetics
- AveXis/Novartis
- Scholar Rock
- Sarepta
- WaVE
- Pfizer
- Edgewise
- Audentes
- Takeda
- Biogen
- Genentech

AveXis and Biogen Expert on Demand

Overview

Spinal muscular atrophy natural history

Clinical trials in SMA

Targeting the genetic cause

- Nusinersen (Spinraza)
- Risdiplam and other small molecules
- Gene transfer therapy – Onasemnogene abeparvovec (Zolgensma)

Giving muscles a boost

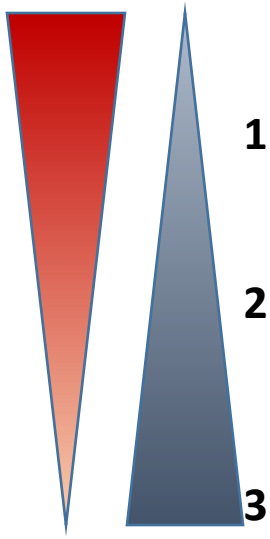
On the horizon

SMA and *SMN1/SMN2*

Healthy Person

Patients

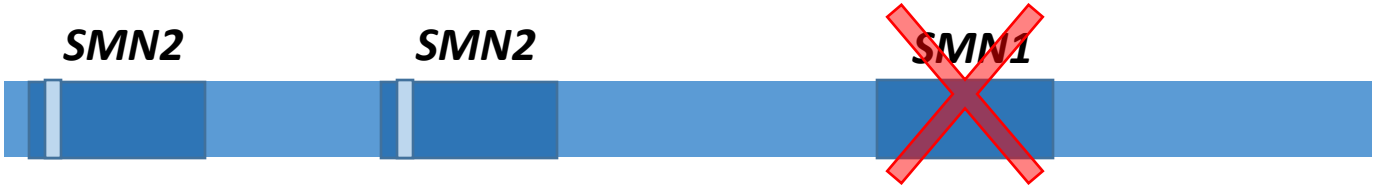
Severity



SMN2 Copy #

1 Copy

2 Copies



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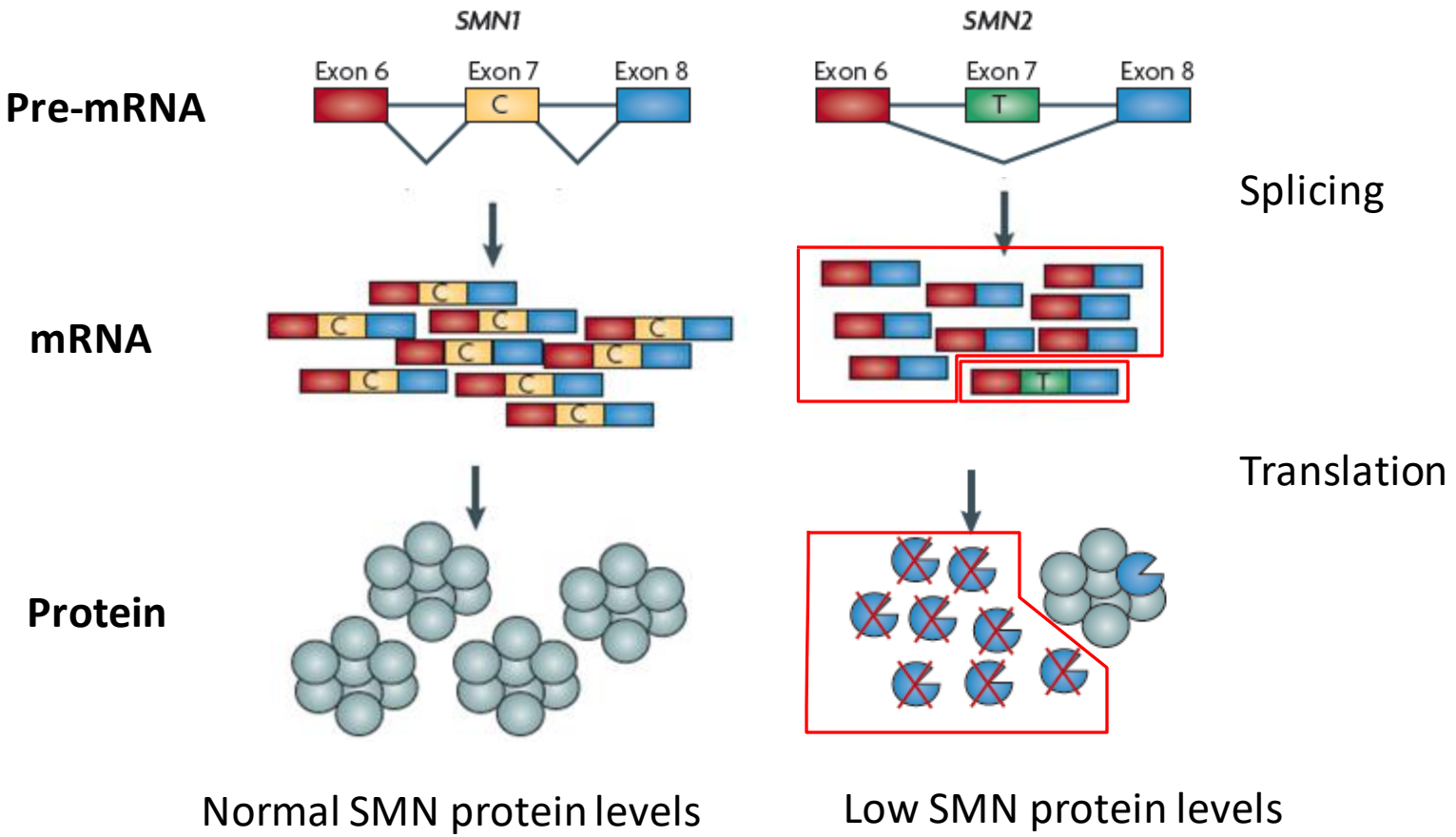
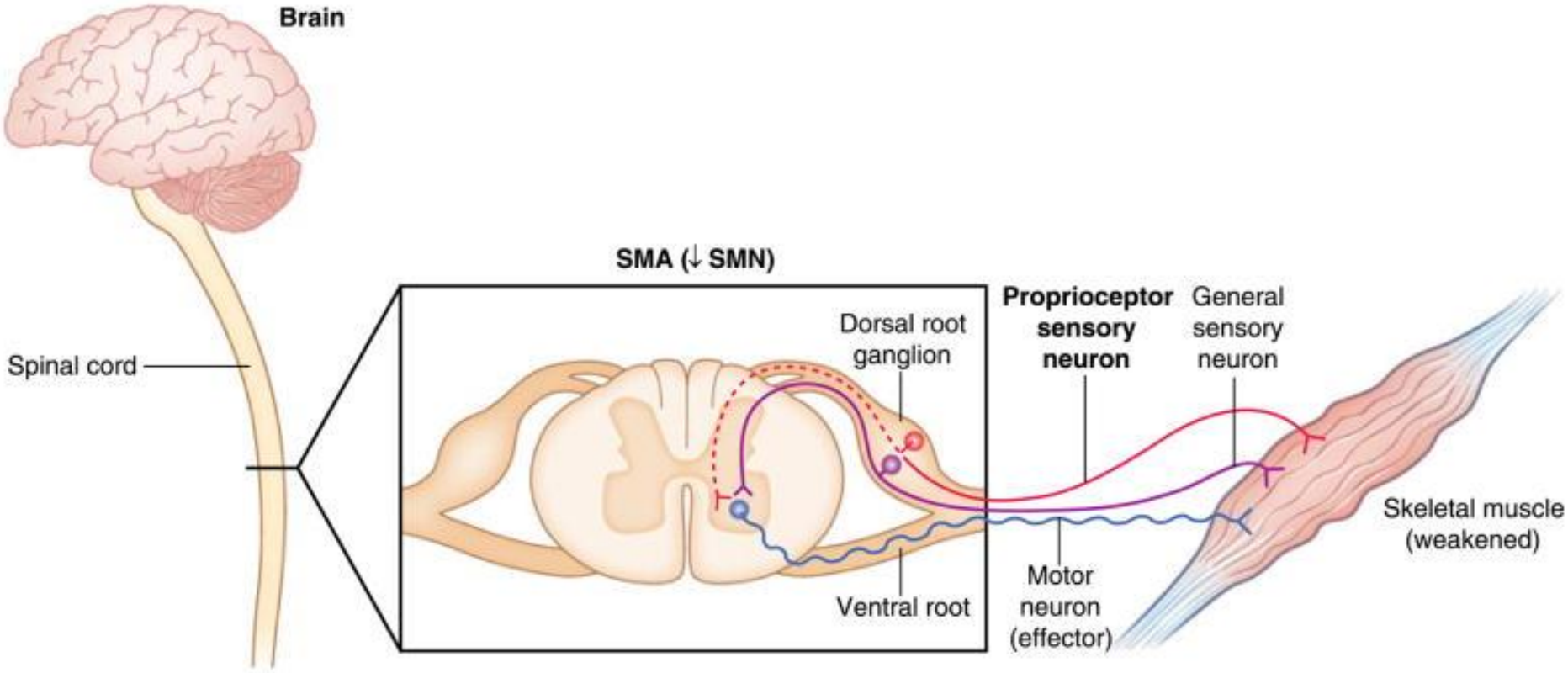
***SMN2* is a Disease Modifier**

SMN Stability

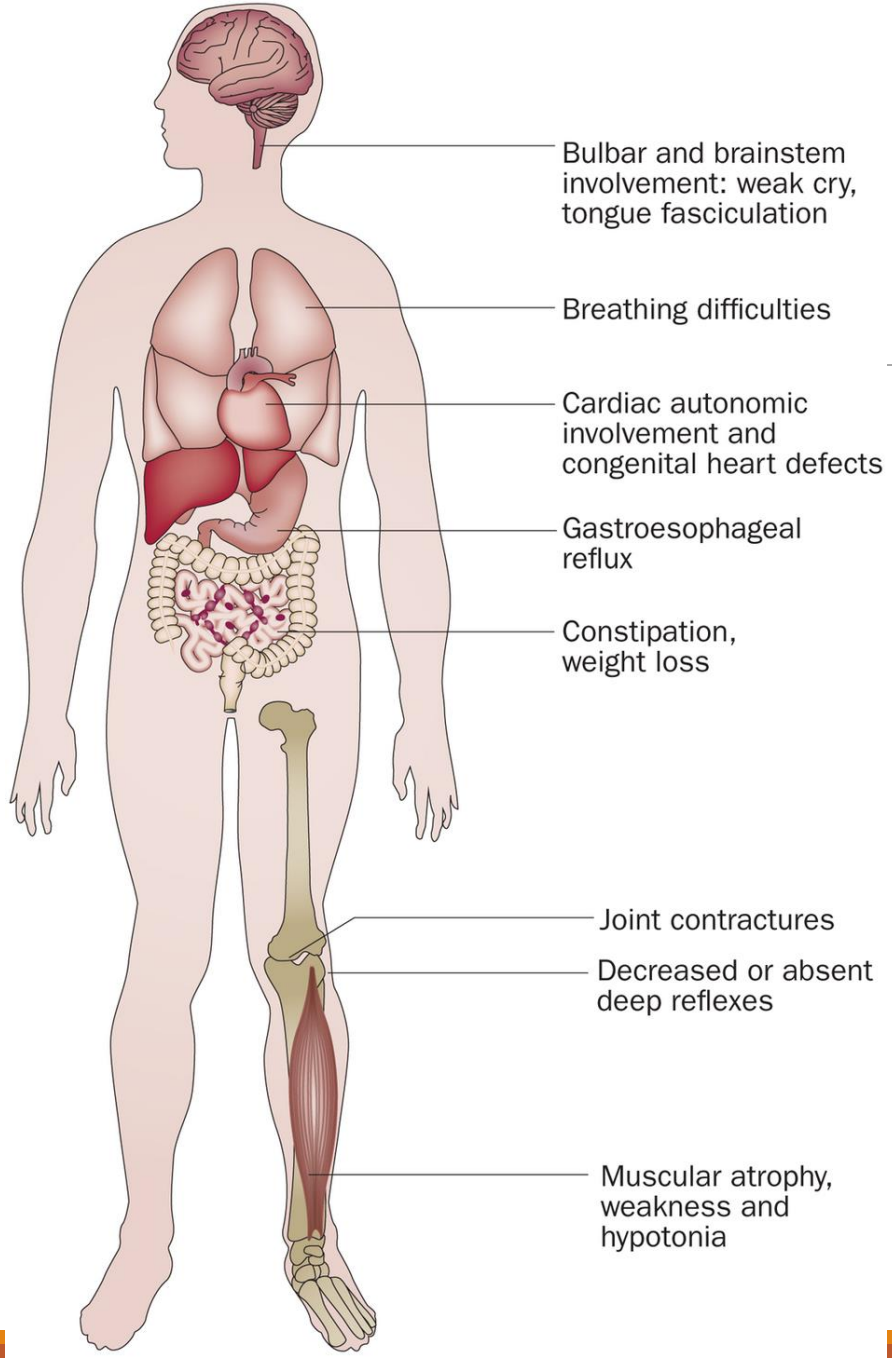




Sensory degeneration?
Autonomic involvement?
Neuromuscular junction dysfunction?
Muscle development and function?

Curr Neurol Neurosci Rep, 2012

Other Body Systems



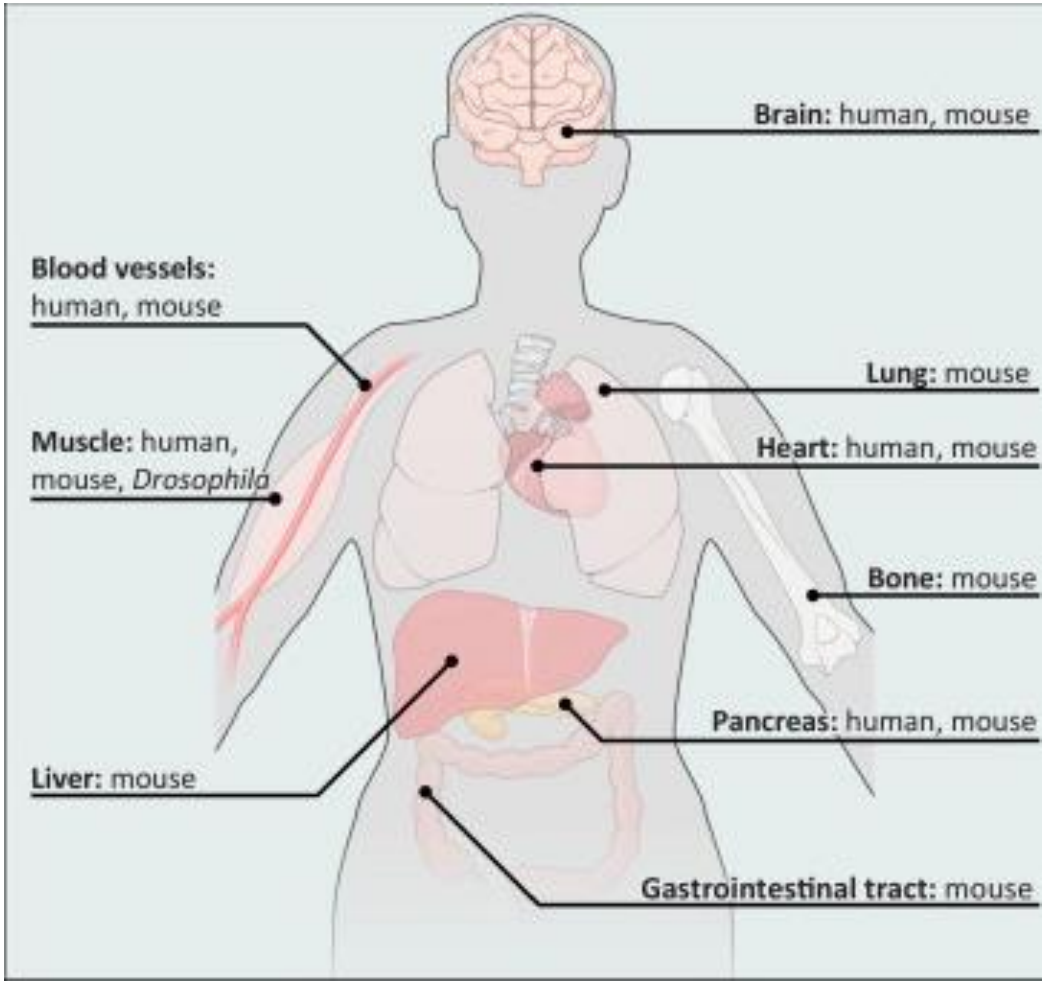
Nature Reviews Neurology, 2015

Multisystemic in severe SMA

- Heart/ vessels
  - Arrhythmias
  - Cardiomyopathy
  - Vasculopathy
- Liver
  - Low IGF-1
  - Iron overload
- Spleen/ thymus

Deguise, *Ann Clinic Transl Neurol*, 2017

- Cognitive/ brain
  - No IQ difference between SMA types or with controls
    - *Neuromusc Disord*, 2002
  - Migrational disorders
  - Thalamus
  - Hippocampus



Trends Mol Med, 2013

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On the horizon

Trial Design

Tremendous pressure on industry to produce results

Many therapies are “fast-tracked” for approval

Desire sensitive markers to show an effect quickly

Design Cont'd

Time

- Trial duration
- Age and functional level of participants at entry
- Natural history of disease

Potential Barriers to Participation

Time commitment
- Travel, missing work and school, finances

Long days of testing, sometimes invasive, painful or exhausting

Risk of unknown side effects

Cultural and social factors

More frustrations

What works in cells or animals or even in safety trials may not show an effect in a randomized trial

- Phase 1: Understanding the drug (safety and tolerability)
- Phase 2: Does it have a measurable effect, more safety evaluation
- Phase 3: Does it have a measurable effect in treated patients that is distinguishable from placebo or other commonly used treatments

www.clinicaltrials.gov

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Giving muscles a boost

On the horizon

Approved Disease-Modifying Treatments for SMA

Therapies	Approval	Strategy	Target	Indication
Onasemnogene abeparvovec-xioi	May 2019	Gene replacement	*SMN1*	Pediatric patients less than 2 years of age
Nusinersen	December 2016	Splicing modification (antisense oligonucleotide)	*SMN2*	Pediatric and adult patients
Risdiplam	August 2020	Splicing modification (small molecule)	*SMN2*	Pediatric and adult patients

Optimization of therapies

Nusinersen	Gene transfer	Risdiplam
Repetitive lumbar punctures and exposure to sedation/anesthesia	IV vs. intrathecal	Male fertility
Implanted device?	Safety of higher doses	Female pregnancy
Optimal dose and schedule?	Vector manufacturing, antibody titers in population	No retinal safety concerns with trial surveillance
	Long-term safety, population genome effects	Compliance/ Access
	Durability in different tissue types	

US Trials Currently Recruiting

Study of Nusinersen (BIIB058) in Participants With Spinal Muscular Atrophy: Phase 2, Phase 3

- Also Known By: DEVOTE
- ClinicalTrials.gov Identifier: NCT04089566
- General Criteria:
  - Part A: 2 to ≤ 15 years
  - Part B: 2 to < 10 years
  - Part C: ≥18 years (cohorts for ambulatory/nonambulatory)
- Primary Outcome: CHOP INTEND Part B / Safety SAEs and AEs, Parts A+C
  - Part A: Experimental: 28/28 Milligram (mg) Safety Group
  - Part B: Active Comparator: 12/12 mg Randomized Control Group OR Experimental: 50/28 mg Randomized Treatment Group
  - Part C: Experimental: 12/50/28 mg Titration Group

Courtesy of CureSMA

US Trials Currently Recruiting

A Study of Nusinersen Among Participants With Spinal Muscular Atrophy Who Received Onasemnogene Abeparvovec: Phase 4

- Also Known By: RESPOND
- ClinicalTrials.gov Identifier: NCT04488133
- General Criteria: 3 to 36 months of age, Must have previously received onasemnogene abeparvovec
- Primary Outcome: Total Hammersmith Infant Neurological Examination (HINE)

A Study to Evaluate Higher Dose (HD) Nusinersen (BIIB058) in Participants With Spinal Muscular Atrophy Previously Treated With Risdiplam: Phase 3

- Also Known By: ASCEND
- ClinicalTrials.gov Identifier: NCT05067790
- General Criteria:
  - ≥5 to ≤39 years nusinersen-naïve participants.
  - ≥18 to ≤39 years nusinersen-experienced participants
- Primary Outcome: Revised Upper Limb Module (RULM) Score

Courtesy of CureSMA

US Trials Currently Recruiting

Efficacy and Safety of Intrathecal OAV101 (AVXS-101) in Pediatric Patients With Type 2 Spinal Muscular Atrophy (SMA): Phase 3

- Also Known By: STEER
- ClinicalTrials.gov Identifier: NCT05089656
- General Criteria: ≥ 2 to < 18 years, treatment native, sitting, but never ambulatory
- Primary Outcome: Hammersmith

Safety and Efficacy of Intravenous OAV101 (AVXS-101) in Pediatric Patients With Spinal Muscular Atrophy (SMA): Phase 3

- Also Known By: SMART
- ClinicalTrials.gov Identifier: NCT04851873
- General Criteria: up to 17 Years, treatment native or discontinued *SMN2* modulator
- Primary Outcome: SAEs/AEs, Vital Sign Measurements

Courtesy of CureSMA

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Giving muscles a boost

On the horizon

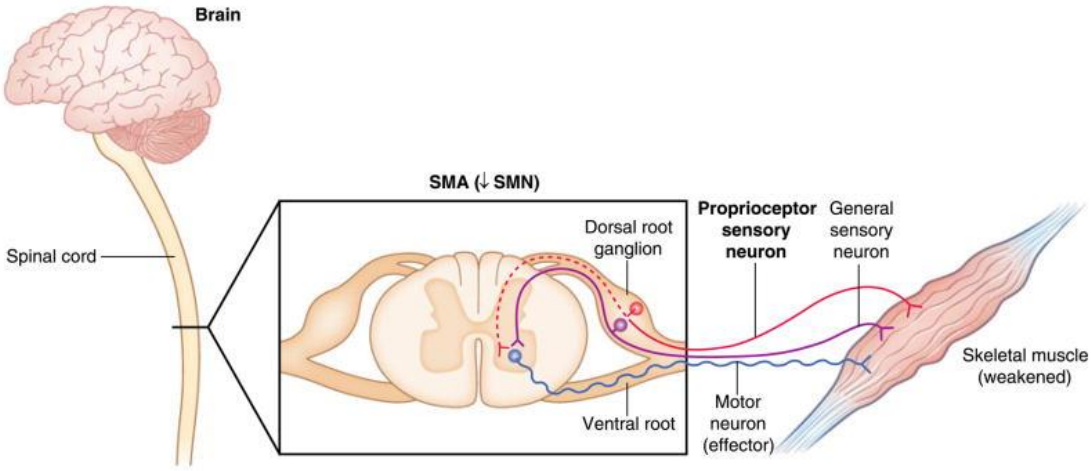
Other targets in the lower motor neuron

Albuterol (NMJ)

Investigational:

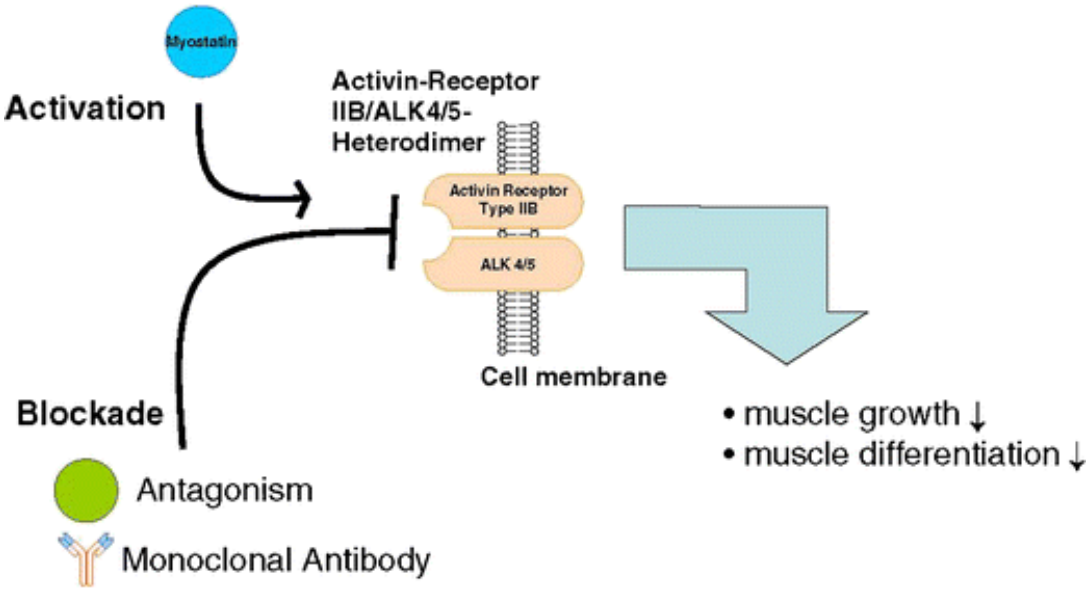
Troponin activation

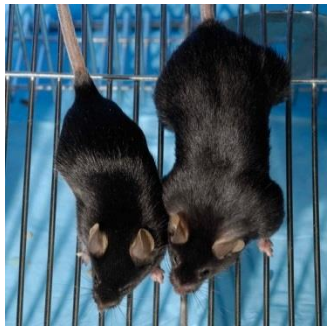
Myostatin inhibition

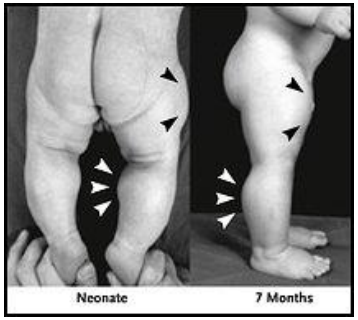


Curr Neurol Neurosci Rep, 2012

Myostatin Inhibition (Scholar Rock, Roche and Biohaven)







Promising phase 2 interim results from Scholar Rock presented at recent meetings

US Trials Currently Recruiting

A Study to Investigate the Safety and Efficacy of RO7204239 in Combination With Risdiplam (RO7034067) in Ambulatory Children With Spinal Muscular Atrophy: Phase 2, Phase 3

- Also Known By: MANATEE
- ClinicalTrials.gov Identifier: NCT05115110
- General Criteria: 2 to 10 years of age, Symptomatic
- Primary Outcome: Revised Hammersmith Scale (RHS) total score

Efficacy and Safety of Apitegromab in Patients With Later-Onset Spinal Muscular Atrophy Treated With Nusinersen or Risdiplam: Phase 3

- Also Known By: SAPPHIRE
- ClinicalTrials.gov Identifier: NCT05156320
- General Criteria: 2 through 21 years old, nonambulatory, receiving Nusinersen or Risdiplam
- Primary Outcome: Hammersmith Functional Motor Scale Expanded (HFMSE)

A Study to Evaluate the Efficacy and Safety of Taldefgrobep Alfa in Participants With Spinal Muscular Atrophy

- Also Known By: RESILIENT
- ClinicalTrials.gov Identifier: NCT05337553
- General Criteria: Ambulant or Non-Ambulant, nusinersen/ risdiplam, and/or history of onasemnogene abeparvovec; must weigh at least 15kg, no ventilation while awake
- Primary Outcome: Motor Function Measure (MFM-32)

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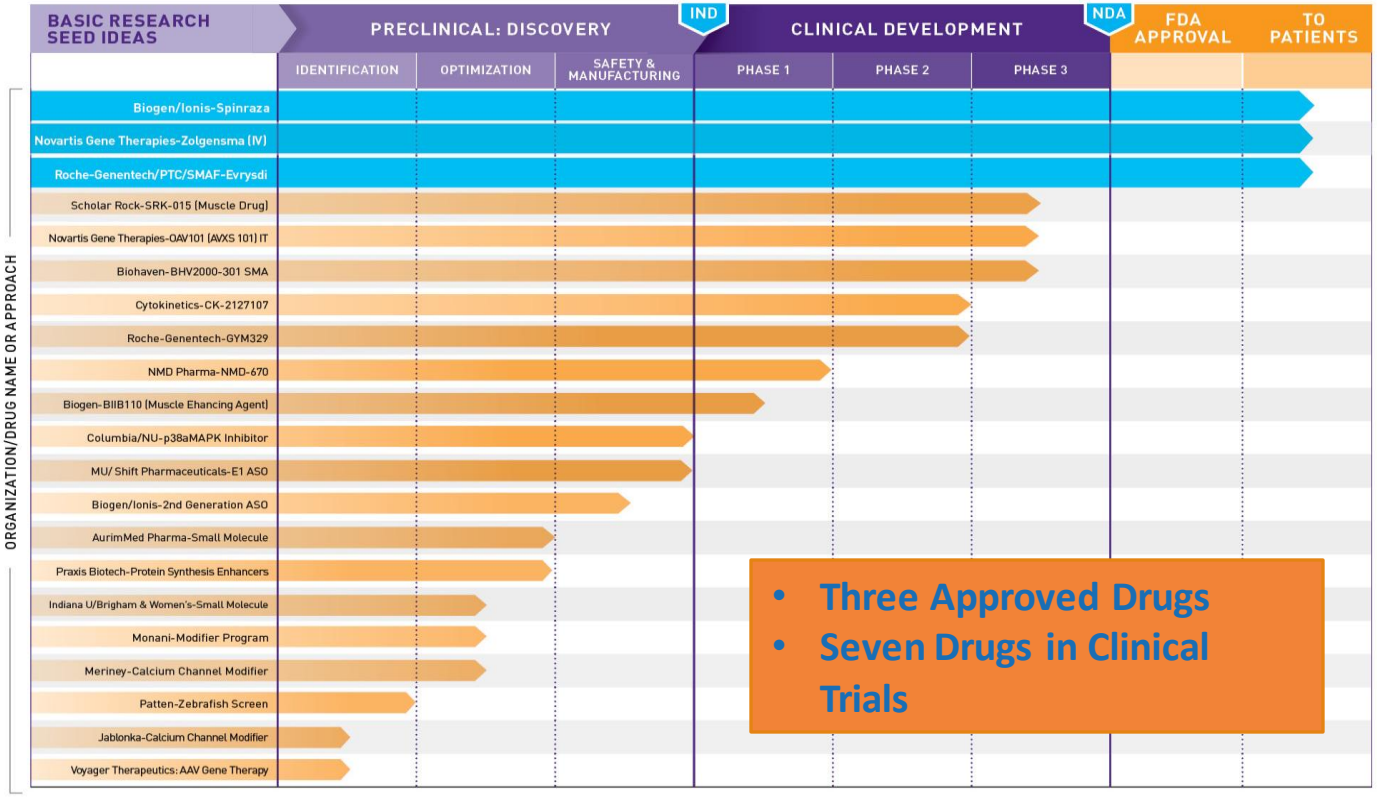
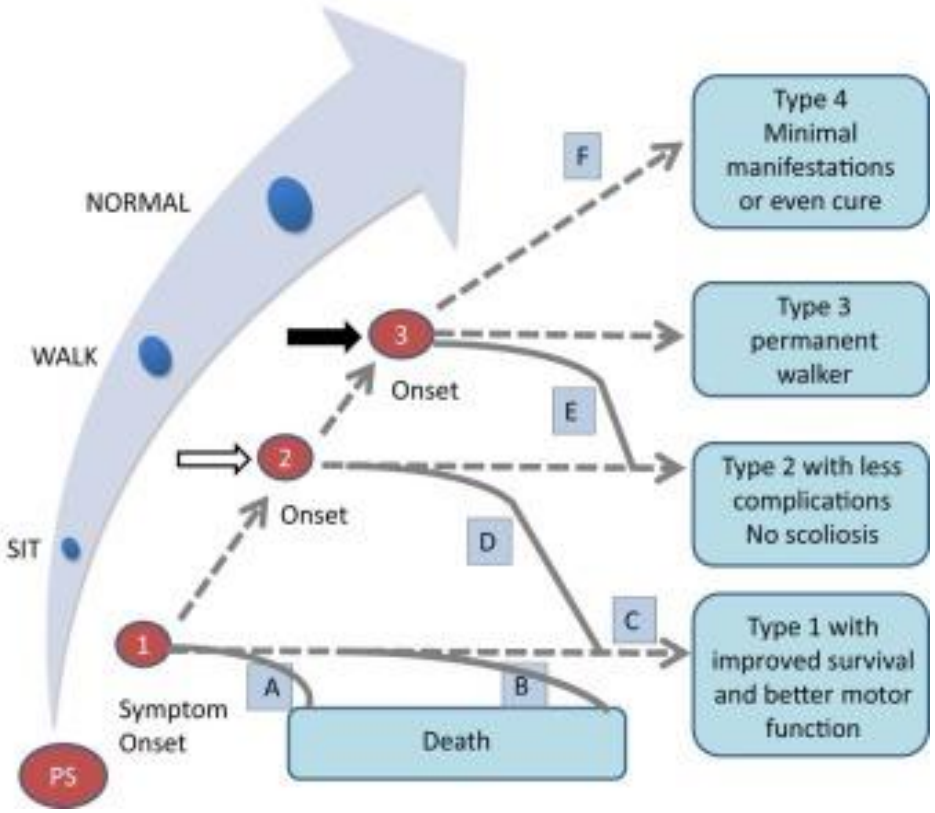
SMA DRUG PIPELINE

We're funding and directing research with more breadth and depth than ever before. We know what we need to do to develop and deliver new therapies, which could also work in combination, to reach our goal of treatments for all ages and types. And we're on the verge of further breakthroughs that will continue to change the course of SMA, and eventually lead to a cure.



IND = Investigational New Drug **NDA** = New Drug Application Last updated: June 2022

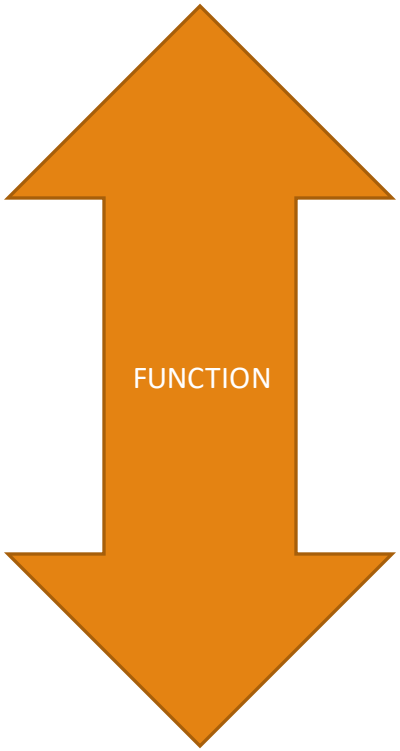
Impact on SMA by Novel Therapeutics



Tizzano and Finkel, *Neuromuscular Disorders*, 2017

SMA in the Era of Genetically Targeted Treatments

Prenatal and Newborn screening



Effect in patients with more denervation/weakness

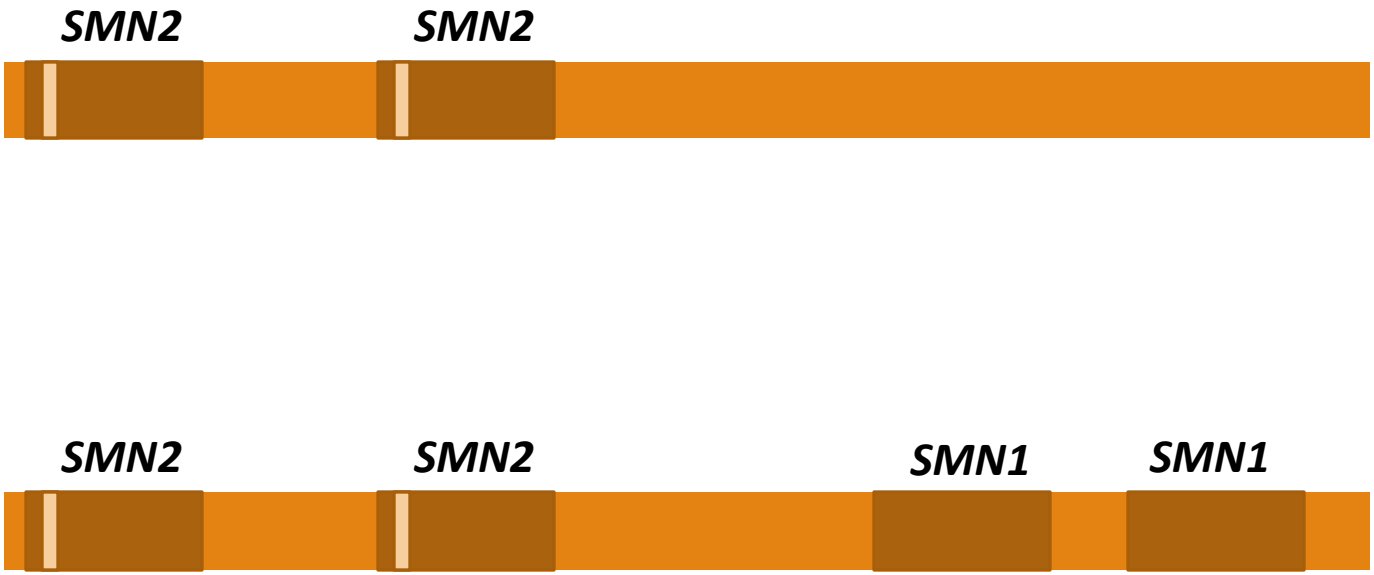
Presymptomatic Diagnosis of SMA

Prenatal parental carrier testing

Family History

Newborn screening

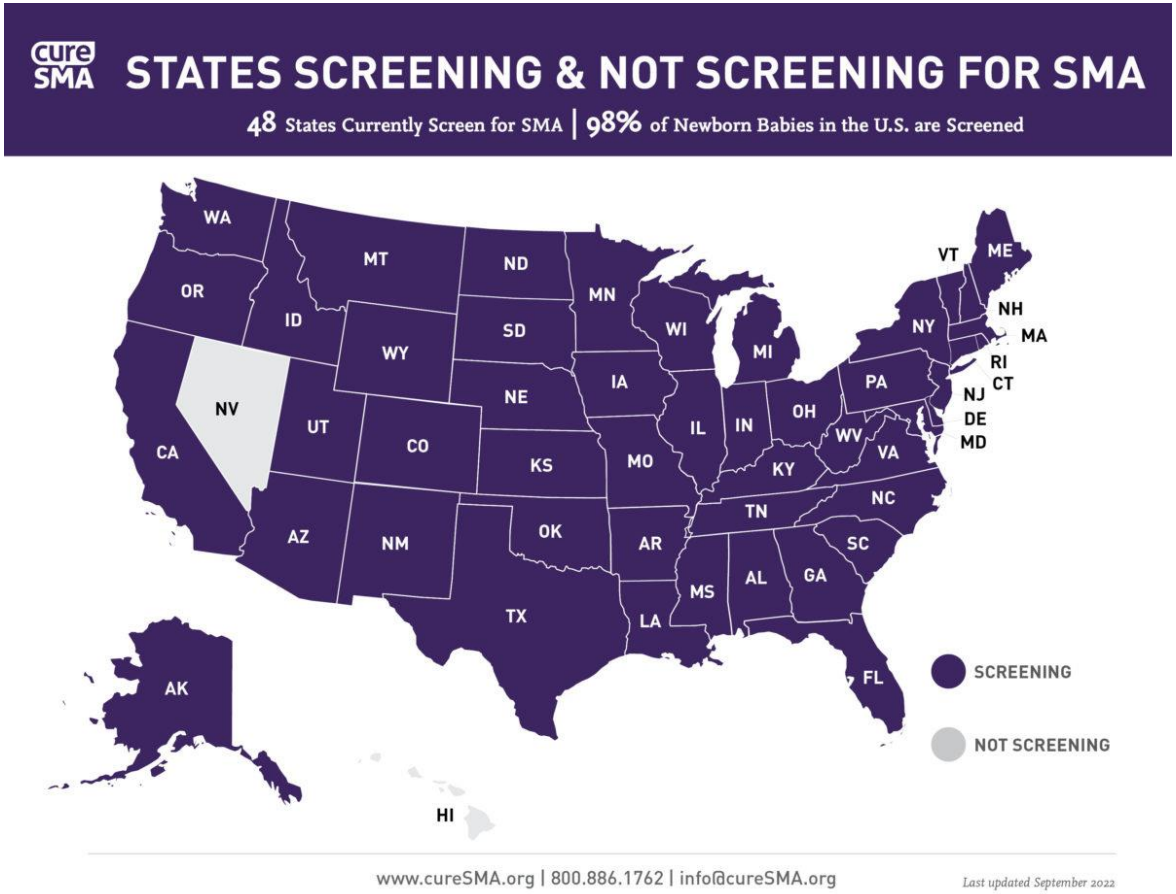
Carrier screening by qPCR – False negative risk (10%)



*Also will not detect carriers of a sequence change or other rare *SMN1* mutations

Prior, *Genet Med*, 2008

Presymptomatic Diagnosis of SMA



*Will not detect carriers of a sequence change or other rare *SMN1* mutations

Cocktail approach

Several combination trials, dual insurance approvals

Tailor combination therapies to the individual patient

-based on genotype and age of diagnosis/ symptoms

-prenatal therapies?

No therapy thus far is a complete cure

We will continue to have a smaller number of children present with symptoms based on current prenatal and newborn screening

0+2 carriers, Point mutations in *SMN1*

Many people are living with symptomatic SMA

Conclusions

New era of SMA

Research trials ongoing and starting

Even more on the horizon

Thank you!

- Questions?