

ONLINE FIRST

Spinal Muscular Atrophy

A Timely Review

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Spinal muscular atrophy (SMA) is a neurodegenerative disease characterized by loss of motor neurons in the anterior horn of the spinal cord and resultant weakness. The most common form of SMA, accounting for 95% of cases, is autosomal recessive proximal SMA associated with mutations in the survival of motor neurons (*SMN1*) gene. Relentless progress during the past 15 years in the understanding of the molecular genetics and pathophysiology of SMA has resulted in a unique opportunity for rational, effective therapeutic trials. The goal of SMA therapy is to increase the expression levels of the SMN protein in the correct cells at the right time. With this target in sight, investigators can now effectively screen potential therapies in vitro, test them in accurate, reliable animal models, move promising agents forward to clinical trials, and accurately diagnose patients at an early or presymptomatic stage of disease. A major challenge for the SMA community will be to prioritize and develop the most promising therapies in an efficient, timely, and safe manner with the guidance of the appropriate regulatory agencies. This review will take a historical perspective to highlight important milestones on the road to developing effective therapies for SMA.

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The term spinal muscular atrophy (SMA) refers to a group of genetic disorders characterized by degeneration of anterior horn cells and resultant muscle atrophy and weakness. The most common SMA is caused by mutations in the 5q13 survival of the motor neuron (*SMN1*) gene. This disorder affects 1 in 6000 to 10 000 infants with a carrier frequency of 1 in 40. Cumulative advances during the past 15 years in the understanding of this disorder's unique molecular genetics and pathophysiology have provided the basis for pharmacologic and genetic therapies and have ushered in a new era of translational medicine. This review will take a historical perspective to highlight important milestones in developing treatments of SMA at a time when the convergence of basic, preclinical, and clinical efforts holds great promise to provide a cure for SMA (**Figure 1**).

EARLY DESCRIPTIONS AND CLINICAL MANIFESTATIONS: 1890 TO 1990

Spinal muscular atrophy was originally described in 2 infant brothers by Guido Werdnig in 1891 and in 7 additional cases by Johan Hoffmann from 1893 to 1900. Although the eponym Werdnig-Hoffmann disease eventually became affixed to the severe infantile form of SMA, their cases actually were of intermediate severity; the first descriptions of severe infantile SMA were made by Sylvestre in 1899 and Beevor in 1903.¹ A milder form of SMA in which patients retained the ability to stand and walk, with prolonged survival, was not formally described until the 1950s by Wohlfart, Fez, and Eliasson and then in more detail by Kugelberg and Welander.¹ All of these descriptions recognized and emphasized the seminal pathology as anterior horn cell degeneration as well as the

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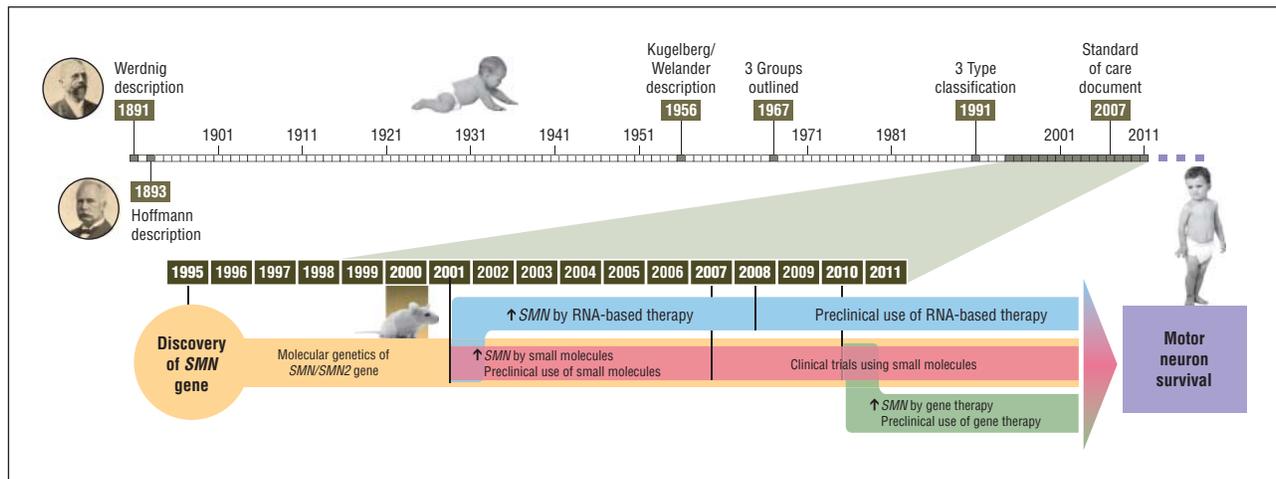


Figure 1. Spinal muscular atrophy (SMA) timeline. Spinal muscular atrophy was first reported by Werdnig in 1891 and then by others who recognized variability of muscle weakness severity. A century later, a consensus classification scheme outlining three SMA types was adopted, and in 2007 a Standard of Care document formalized the clinical treatment of patients with SMA. The *SMN* gene was identified as the causative gene in SMA in 1995, which has led to the development of SMA animal models and targeted therapeutic approaches to increase SMN protein levels. The increasingly successful preclinical testing of multiple therapeutic approaches during the last 10 years has led to great optimism that an era of successful clinical trials is fast approaching.

pertinent clinical features of symmetrical, proximal predominant extremity weakness that also affects axial, intercostal, and bulbar musculature.¹

During the next half century, the variability in severity was further defined and characterized and controversy arose regarding whether the infantile, juvenile, and adult forms of SMA represented one or multiple diseases. The multiple phenotypes were eventually formalized into a classification scheme at an International Consortium on Spinal Muscular Atrophy sponsored by the Muscular Dystrophy Association in 1991.² This classification highlighted 3 SMA types based on the highest level of motor function (ie, sitting or standing) and age of onset. Subsequent modifications divided the type 3 category by age of onset, added a type 4 for adult-onset cases, and included a type 0 for patients with prenatal onset and death within weeks. Although there are degrees of severity even within an individual type, and as many as 25% of patients elude precise classification, this scheme remains relevant in the genetic era and provides useful clinical and prognostic information (**Table 1**).

MOLECULAR GENETICS: 1990 TO 2000

The SMA classification presented a riddle regarding severity that was appreciated even at the time of its development: how can one gene defect result in such a wide range of clinical severity? The solution to this riddle began with the discovery by the Melki laboratory in 1995 that 95% of cases of SMA, irrespective of type, are caused by a homozygous deletion in the *SMN1* gene on chromosome 5q13.³ In humans, 2 forms of the *SMN* gene exist on each allele: a telomeric form (*SMN1*) and a centromeric form (*SMN2*) (**Figure 2**). Transcription of the *SMN1* gene produces full-length messenger RNA (mRNA) transcripts that encode the SMN protein. The *SMN2* gene is identical to the *SMN1* gene with the exception of a C to T substitution at position 840 that results in the exclusion of exon 7 during transcription. The resultant truncated protein is not functional and is rapidly degraded.

Critically, the exclusion of exon 7 from *SMN2* mRNAs is not complete, and so a small fraction of the total mRNA transcripts (approximately 10%-15%) arising from the *SMN2* gene contain exon 7, which encodes the normal SMN protein (Figure 2).

All patients with SMA lack a functioning *SMN1* gene and are thus dependent on their *SMN2* gene, however inefficient, to produce the SMN protein necessary for survival. Thus, SMA is caused by a deficiency in the SMN protein that, for reasons still unknown, results in selective motor neuron loss. The answer to the riddle of severity was found in the variability of *SMN2* gene copy number that was found in SMA patients. Several subsequent genotype/phenotype analyses confirmed a positive correlation between *SMN2* copy number and milder phenotype.⁴ Although *SMN2* copy number is now known to be the primary determinant of SMA severity, it is clearly not the only phenotypic modifier. Prior and colleagues described 3 adult patients with mild 3b phenotypes and only 2 copies of *SMN2*, a seemingly incongruous finding that was explained by the fact that these individuals had a c.859G>C exon 7 mutation that created an exon splice-enhancing element that resulted in increased full-length SMN protein production and a milder phenotype.⁵ Other modifiers have been described and more are expected as the understanding of the molecular pathogenesis of SMA is refined. Thus, the SMA phenotype cannot always be deduced solely from the *SMN2* copy number determination, a fact crucial when performing genetic counseling with patient families.

Within 5 years of the discovery of the *SMN* gene, animal models of SMA were developed that mimic many of the pathological and electrophysiological changes seen in patients and have formed the cornerstone for all therapeutic developments that followed. Mice have no native *SMN2* gene, and deletions in the murine *smn* gene are invariably lethal. However, in a seminal demonstration of genetic legerdemain, Burghes and colleagues⁶ found that mice with 2 copies of human *SMN2* on a null *smn*^{-/-} background are viable, with a severe SMA-like pheno-

Table 1. Spinal Muscular Atrophy Classification

Type	Age at Onset	Highest Function	Natural Age at Death	SMN2 No.
0	Prenatal	Respiratory support	<1 mo	1
1	0-6 mo	Never sit	<2 y	2
2	<18 mo	Never stand	>2 y	3, 4
3	>18 mo	Stand alone	Adult	
3a	18 mo-3 y	Stand alone	Adult	3, 4
3b	>3 y	Stand alone	Adult	4
4	>21 y	Stand alone	Adult	4-8

type, loss of motor neurons, and lifespan of 5 days, whereas mice with 8 copies of *SMN2* on the same background are normal. This and subsequent murine models, as well as the development of SMA models in zebrafish and *Drosophila*, have provided proof of principle that increasing expression of the full-length SMN protein is protective. These models also established superb preclinical model systems for screening potential therapies and permitted in-depth molecular and biochemical studies of disease pathogenesis.⁷ The stage was set for subsequent efforts to find therapies to increase the expression of SMN protein and prevent motor neuron loss.

MOLECULAR PATHOGENESIS

Although a detailed discussion of the pathogenesis of SMA is beyond the scope of this review, a few comments are in order. The SMN protein is found throughout the cytoplasm and nucleus where it functions as part of a multiprotein complex, the SMN complex, that plays an essential role in spliceosomal small nuclear ribonuclear protein biogenesis and pre-mRNA splicing.⁸ Small nuclear ribonuclear protein biogenesis is altered in the cells of mice with SMA. The SMN protein has also been detected in the axons of motor neurons. These observations have led to a central question: while the SMN protein influences RNA processing functions in all cells, does the protein have an additional, unique function in motor neurons?^{9,10} One parsimonious explanation may be that the downstream consequences of altered RNA processing that result from insufficient expression of SMN are not favorable for motor neuron development, survival, or both. In this sense, because the motor neuron transcriptome is unique, a global alteration in splicing, for example, could have a unique effect on the transcriptome of motor neurons. This hypothesis on the pathogenic role of RNA processing defects in motor neuron diseases is gaining momentum, in large part because of recent advances in the understanding of SMN biology.¹¹

Fortunately, on the basis of human genotype-phenotype studies and the preclinical studies performed in SMA animal models, a complete understanding of the molecular pathogenesis of the disease may not be an absolute necessity for the development of rational therapeutic strategies. Nevertheless, the molecular pathogenesis of SMA may provide a foothold and lead the way to an understanding of related diseases of the motor neuron such as the non-SMN spinal muscular atrophies and amyotrophic lateral sclerosis.

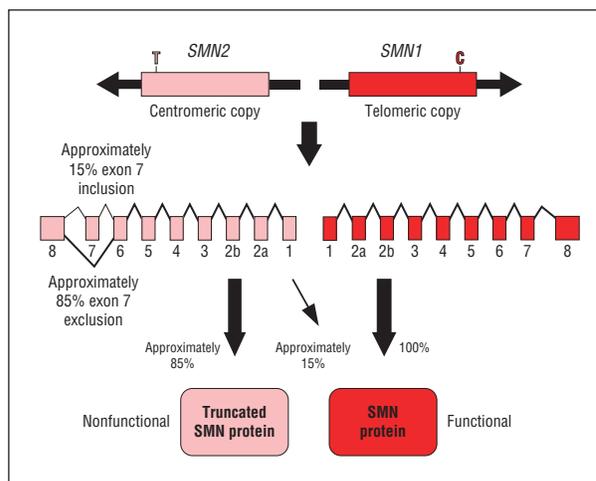


Figure 2. Schematic of *SMN* gene. Schematic diagram of the human *SMN1* and *SMN2* genes and the resultant pre-messenger RNAs. Patients with spinal muscular atrophy (SMA) have deletions or mutations in both copies of *SMN1*. The *SMN2* gene is expressed, however, most resultant *SMN2* pre-mRNA lacks exon 7 because of a C-to-T transition at position 6 of exon 7. The truncated SMN protein is unstable and nonfunctional. A small proportion of full-length messenger RNA containing exon 7 is produced by from the *SMN2* pre-messenger RNA, however, resulting in full-length SMN protein, which is functional.

EMERGING THERAPEUTICS: 2000 TO 2011

For more than 100 years since its initial description, therapy for SMA has mainly involved supportive and palliative care. During the past decade, there has been a marked improvement in the ability of clinicians to manage the multiple respiratory, nutritional, orthopedic, rehabilitative, emotional, and social problems that develop in most of these patients. A notable achievement in this regard was the development of a comprehensive standard of care document by Wang and a collaborating panel of experts that was published in 2007.¹² This document, which is currently being updated and made more comprehensive, established guidelines for managing the multiple expected clinical problems that develop in patients with SMA as they age.

Prior to the 1990s, there were relatively few clinical trials in SMA because there was no clear molecular target. Studies that were undertaken usually involved pharmacologic agents that were repurposed and had shown encouraging results in other diseases characterized by muscle weakness such as amyotrophic lateral sclerosis or muscular dystrophy. The elucidation of the genetic and molecular basis of SMA just described, however, sug-

Table 2. Spinal Muscular Atrophy Milestones

Source	Year	Milestone
Werdnig ¹³	1891	Initial description by Werdnig
Hoffmann ¹⁴	1893	Hoffmann description
Kugelberg and Welander ¹⁵	1956	Kugelberg/Welander description
Dubowitz ¹⁶	1967	3 Groups outlined
Munsat ²	1991	Consensus classification of 3 types of SMA
Lefebvre et al ³	1995	Discovery of <i>SMN</i> gene
Andreassi ¹⁷	2001	First demonstration of increased <i>SMN</i> expression resulting from a potential small molecule therapy in cell culture
Lim and Hertel ¹⁸	2001	First demonstration of increased <i>SMN</i> expression resulting from a potential antisense oligonucleotide therapy in cell culture
Change et al ¹⁹	2001	First preclinical study using small molecule therapy
Mercuri ²⁰	2007	First clinical trial using small molecule therapy
Wang et al ¹²	2007	Consensus statement for Standard of Care established
Hua et al, ²¹ Dickson et al, ²² and Coady et al ²³	2008	First preclinical studies using RNA-based therapy
Foust et al, ²⁴ Passini et al, ²⁵ and Dominguez et al ²⁶	2010	First preclinical studies using <i>SMN1</i> gene therapy

gested several possible therapeutic approaches based on the general principle of increasing the expression of the SMN protein. These strategies include pharmacologic or gene-based therapies to increase SMN2 expression (leading to more full-length SMN mRNA), antisense oligonucleotide-based therapies to favor incorporation of exon 7 into SMN2-derived mRNA transcripts, and virus-mediated therapies to replace the entire *SMN1* gene. The development of these approaches is now proceeding at a rapid rate, with human clinical trials using RNA-based and gene therapy approaches imminent (**Table 2**).

Small-Molecule Therapy

The past decade has witnessed several large SMA drug development projects coordinated by the National Institute of Neurological Disorders and Stroke, private foundations, and the pharmaceutical and biotechnology industries. These projects have focused on developing cell-based, high-throughput assays to screen for candidate small molecules that can increase SMN protein levels. Compounds that increase SMN levels in these assays have been tested in SMA animal models. Through this approach, a diverse set of compounds has been identified that include histone deacetylase inhibitors, aminoglycosides, and quinazoline derivatives. Histone deacetylase inhibitors such as valproic acid, sodium butyrate, phenylbutyrate, and trichostatin A activate the *SMN2* promoter, resulting in increased full-length SMN protein. Despite favorable results in mouse models, clinical trials with several of these agents, most notably phenylbutyrate, valproic acid, and hydroxyurea have been disappointing, with no substantial clinical benefit demonstrated. Despite multiple issues related to dosing, duration of therapy, and timing of therapy (ie, when in the course of the disease therapy is instituted), trials with several of these agents are currently under way.

RNA-Based Therapy

Alteration of *SMN2* splicing to favor inclusion of exon 7 into the final mRNA transcript, and therefore increased

expression of the full-length SMN protein, is a second promising strategy to treat SMA. These approaches target the elegant interactions between cis-acting sequence motifs found in the introns and exons of *SMN2* pre-mRNA and the various trans-acting splicing factors involved in the regulation of exon 7 splicing. Antisense oligonucleotides (ASOs) are therapeutic RNA molecules designed to bind to their complementary sequences within a targeted intron or exon that can either enhance or disrupt the targeted splicing event. Initial efforts to increase the inclusion of exon 7 from *SMN2* pre-mRNA used an ASO designed to inhibit a 3' splice site of exon 8.¹⁸ Since then, additional splice site regulators have been identified and refinements have been made to the chemical stability of ASOs. One such additional splice site regulator is the intron 7 intronic splicing silencer N1 in the *SMN2* gene.²⁷ ASO-induced blocking of the intronic splicing silencer N1 strongly enhances exon 7 inclusion in cultured fibroblasts and results in increased SMN1 protein. In vivo efficacy testing of these ASOs resulted in efficient inclusion of exon 7 and increased full-length SMN protein levels in mice.²¹ In this first preclinical ASO study, systemic administration failed to penetrate the blood brain barrier; however, this obstacle was quickly overcome by several groups, resulting in increased full-length SMN mRNA and protein in the mouse spinal cord when delivered by intracerebroventricular injection.^{28,29}

A number of variations on the theme of RNA-based therapies for SMA have since emerged. Bifunctional RNAs are ASOs that are either covalently linked to a peptide or to a sequence recognized by specific splicing modulators to enhance the stability and/or activity of the therapeutic RNA. Lorson and colleagues engineered a bifunctional RNA containing an ASO directed to the intron 7-exon 8 junction that also contained a sequence that recruited heterogenous nuclear ribonuclear protein A1, a splicing factor that prevents exon 8 inclusion, resulting in more exon 7 inclusion.²² Intracerebroventricular injections of this bifunctional RNA therapeutic molecule and other bifunctional RNAs have been shown to elevate full-length SMN levels in brain.^{22,30} Trans-splicing RNAs are a third RNA-based strategy that has

been applied to SMA mouse models. Therapeutic trans-splicing RNA for SMA is a synthetic RNA molecule that interacts with the endogenous *SMN2* pre-mRNA, resulting in a hybrid mRNA that has the endogenous mutation spliced out, resulting in more full-length *SMN* mRNA and protein. Preclinical studies with therapeutic trans-splicing RNA in SMA mouse models have also been successfully applied.^{23,31}

Gene Therapy

Perhaps the most direct approach to SMA therapy is to correct the fundamental cause of the disorder by replacing the missing *SMN1* gene. The recent successful rescue of a mouse model of severe SMA using a self-complementary adeno-associated viral vector, serotype 9 by Foust and colleagues²⁴ was a landmark first step in this direction. In this study, mouse pups were treated on postnatal day 1 with a single intravenous injection of 5×10^{11} viral adeno-associated virus, serotype 9, particles carrying the *SMN1* gene. This resulted in *SMN1* expression in 60% of spinal cord motor neurons and complete rescue of motor function and strength, muscle physiology, and life span, so that the treated mice had an average life span of more than 400 days compared with approximately 16 days in the untreated animals. This approach has been reproduced by other groups using both adeno-associated virus, serotypes 8 and 9 constructs to deliver *SMN1* to motor neurons.^{25,26,32} An important caveat to this approach is that injections done in the mice have their maximal effect on postnatal day 1; the effect falls off rapidly with advancing age so that injections on day 5 had only a partial effect, while injections on postnatal date 10 had no effect. This may mean that therapies designed to increase *SMN* expression in humans, via gene therapy or otherwise, will have to be coordinated with early disease detection and immediate institution of therapy, hopefully before clinically significant symptomatology develops. This requirement, in turn, provides a strong rationale for eventual newborn screening and other early detection programs.³³ This observation also suggests that there may be a critical period in development during which sufficient *SMN* protein is essential for the future health of motor neurons; further study of this aspect of motor neuron biology may yield great insight into the determinants of motor neuron viability.

THE FUTURE OF SMA CLINICAL TREATMENT TRIALS: 2011 AND BEYOND

The SMA community stands at the threshold of an exciting era of opportunity to translate the phenomenal success in treating SMA mouse models into effective therapy for patients with SMA. Owing to the remarkable progress made during the past 2 decades in understanding the molecular pathogenesis of this disease, investigators are now able to effectively screen potential therapies in vitro, test them in accurate animal models, and then move promising agents forward to clinical trials in patients identified in an early or possibly presymptomatic stage of disease. It will be a challenging responsibility to prioritize and advance the most promising therapies forward to clinical trials in an efficient, timely, and safe manner with the

guidance of the US Food and Drug Administration and other regulatory agencies. Testing any therapy will involve developing outcome measures, biomarkers, and an infrastructure to conduct meaningful clinical trials while providing optimal supportive care as these new therapies are being developed. Effectively meeting these challenges will be a necessary prerequisite to adding the final point on the timeline of SMA: the point at which SMA is no longer a fatal, incurable, debilitating disease.

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