

Spinal Muscular Atrophy & ISIS-SMN_{Rx}

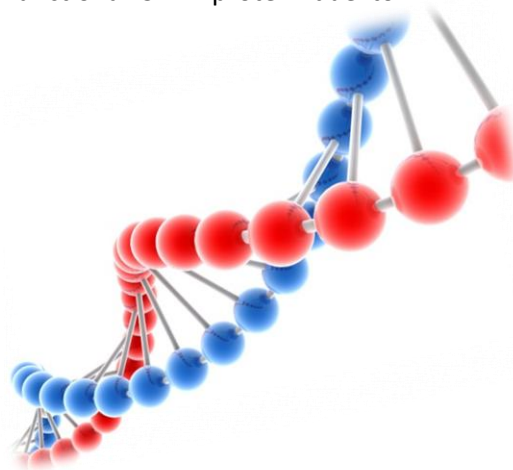
Understanding SMA

Spinal muscular atrophy (SMA) is a genetic neuromuscular disease characterized by muscle atrophy and weakness. SMA is a leading genetic cause of infant mortality. According to the National Institutes of Health, most infants born with SMA Type I, the most severe form of SMA, usually die within their first two years of life. One child out of approximately every 6,000 to 10,000 births is born with SMA. There are approximately 30,000 – 35,000 patients with SMA in the United States, Europe and Japan. Currently, there are no marketed treatments available for patients with SMA.

SMA is caused by a loss of, or defect in, the survival motor neuron 1 (SMN1) gene. The SMN1 gene produces most of the SMN protein, which is critical to the health and survival of the nerve cells in the spinal cord responsible for muscle contractions. The severity of SMA is correlated with the amount of SMN protein in the cell. Humans also have one or more copies of a related gene, SMN2, which produces a small fraction of functional SMN protein due to alternative RNA splicing.

Splicing & Its Role in Disease

Alternative splicing is a normal mechanism that the cell uses to produce different, but closely related proteins from a single gene by varying the processing of the RNA. It is estimated that of the approximately 25,000 genes in the human genome, approximately 90 percent have alternatively spliced forms. In some cases, alternative splicing results in diseases, such as SMA, where errant splicing inhibits the production of a functional protein



Antisense Therapeutics

Antisense drugs are small (12-21 nucleotides) DNA- or RNA-like compounds that are chemically modified to engineer good drug properties. Isis' antisense drugs have been evaluated extensively in both animals and man with more than 5,000 subjects dosed with Isis' antisense drugs. Isis has conducted approximately 80 clinical trials in more than a dozen different patient populations from cardiovascular to cancer. The most advanced antisense drug, mipomersen, completed a broad Phase 3 program in patients with high cholesterol and is currently being evaluated for marketing approval in Europe.



ISIS-SMN_{Rx}

Isis' drug, ISIS-SMN_{Rx}, is designed to modulate the alternative splicing of the SMN2 gene to significantly increase the production of functional SMN protein. In previously published results, researchers showed that ISIS-SMN_{Rx} increased production of functional SMN protein in mouse models of severe SMA. The increase in SMN production correlated with an increase in the number of motor neurons and improvements in behavior and survival.

Isis Pharmaceuticals is a leader in antisense technology to discover and develop novel drugs. Isis' broad drug pipeline consists of 24 drugs in development designed to treat a wide variety of diseases with an emphasis on cardiovascular, metabolic, severe and rare/neurodegenerative diseases and cancer.

For more information on Isis, ISIS-SMN_{Rx} and antisense therapeutics, please visit: www.isispharm.com

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Clinical Trials

Clinical trials are studies conducted using human participants designed to assess the safety and activity of new therapies in development. Clinical trials can be categorized into distinct Phases (Phase 1 – 4) depending upon the stage of clinical development of the drug. Phase 1 studies are the initial studies conducted in humans designed to primarily evaluate the safety and pharmacokinetics of the drugs in humans. Phase 2 and 3 studies are larger, longer studies in patients that continue to evaluate the safety of the drug and the activity of the drug prior to requesting regulatory agencies for marketing approval. Phase 4 studies are studies designed to provide additional information for a drug that has been approved for marketing and is already available to qualified patients.

More information on clinical trials can be found at: www.clinicaltrials.gov

More information on ISIS-SMN_{Rx} and clinical study please contact:

Isis Pharmaceuticals @ info@isisph.com

Intrathecal Delivery

Antisense drugs do not cross the blood-brain barrier, but do distribute to peripheral tissues and organs within the body, such as the liver and kidney when administered systemically (e.g. subcutaneously). This type of drug distribution is very beneficial for developing drugs toward gene targets that are expressed in these organs, such as drugs for treating metabolic diseases. However for neurodegenerative diseases like SMA, antisense drugs need to distribute broadly within the central nervous system (CNS). Intrathecal delivery refers to the administration of a drug directly into the cerebral spinal fluid, a fluid that surrounds the brain and spinal cord tissue. The drug is administered through an injection in the lower back into a fluid-filled space below the end of the spinal cord, resulting in broad distribution of the drug in various brain regions and the spinal cord. Isis has successfully been able to deliver antisense drugs intrathecally into the CNS in patients with ALS and plans to use intrathecal delivery for ISIS-SMN_{Rx}.

Related Publications

- 1: *Peripheral SMN restoration is essential for long-term rescue of a severe spinal muscular atrophy mouse model.* Hua Y, Sahashi K, Rigo F, Hung G, Horev G, Bennett CF, Krainer AR. *Nature*. 2011 Oct; 478: 123-126.
- 2: *Antisense oligonucleotides delivered to the mouse CNS ameliorate symptoms of severe spinal muscular atrophy.* Passini MA, Bu J, Richards AM, Kinnecom C, Sardi SP, Stanek LM, Hua Y, Rigo F, Matson J, Hung G, Kaye EM, Shihabuddin LS, Krainer AR, Bennett CF, Cheng SH. *Sci Transl Med*. 2011 Mar 2;3(72):72ra18.
- 3: *Antisense correction of SMN2 splicing in the CNS rescues necrosis in a type III SMA mouse model.* Hua Y, Sahashi K, Hung G, Rigo F, Passini MA, Bennett CF, Krainer AR. *Genes Dev*. 2010 Aug 1;24(15):1634-44.
- 4: *Antisense masking of an hnRNP A1/A2 intronic splicing silencer corrects SMN2 splicing in transgenic mice.* Hua Y, Vickers TA, Okunola HL, Bennett CF, Krainer AR. *Am J Hum Genet*. 2008 Apr;82(4):834-48.
- 5: *Enhancement of SMN2 exon 7 inclusion by antisense oligonucleotides targeting the exon.* Hua Y, Vickers TA, Baker BF, Bennett CF, Krainer AR. *PLoS Biol*. 2007 Apr;5(4):e73.



More information on SMA visit

Families of SMA
www.fsma.org

SMA Foundation
www.smafoundation.org