

September 24, 2009

The Honorable Debbie Stabenow
United States Senate
133 Hart Senate Office Building
Washington, DC 20510

The Honorable Johnny Isakson
United States Senate
120 Russell Senate Office Building
Washington, DC 20510

Dear Senator Stabenow and Senator Isakson:

As scientific investigators and clinicians working to develop a treatment or cure for Spinal Muscular Atrophy (SMA) and to provide care for SMA patients, we write to express our strong support for your legislation, the SMA Treatment Acceleration Act of 2009 (S. 1158). This measure provides much needed additional federal support to complement ongoing research supported by substantial private funding from national non-profit organizations, as well as by the NIH under the model translational research project initiated by NINDS known as the "SMA Project". Passage of this landmark bill will ensure that these investments of both public and private resources reach their fullest potential by enabling the mounting of national clinical trials to demonstrate that potential treatments are safe and effective for SMA patients.

As you know, SMA is an autosomal recessive genetic disorder that causes motor neuron loss and childhood muscle weakness. It is a relatively common "rare" disorder that occurs in about 1 in every 6,000 live births. Approximately 1 in 40 individuals (7.5 million Americans) carry the mutated gene that causes the disease. Of genetic diseases in children, SMA is the leading killer of infants under two years of age. It destroys the nerves controlling voluntary muscle movement, which affects crawling, walking, head and neck control, swallowing, and breathing. Approximately 60 -70% of those affected suffer from Type I SMA, the most severe form. These children never are able to sit on their own and more than 95% die in infancy or require extensive respiratory support by the age of two.

While currently there is no treatment or cure for SMA, the underlying genetics of the disease and recent research breakthroughs make a treatment foreseeable. The single gene that is responsible for 95% of all SMA cases, Survival Motor Neuron 1 (SMN1), was discovered in 1995. The job of SMN1 is to produce SMN protein, which is vital to the health of motor neurons. Children with SMA are missing both copies of SMN1 and in the absence of SMN1 the body produces insufficient SMN protein, causing motor neurons to die and leading to profound muscular weakness, paralysis, and often to death.

The key to identifying a treatment for SMA has been the discovery of a nearly identical "back-up" gene known as SMN2. This gene differs from SMN1 by just one nucleotide, but this minor difference in the DNA causes the SMN2 gene to produce insufficient amounts of fully functional, full-length SMN protein. However, the number of copies of the SMN2 gene varies per person in the human population and the number of SMN2 gene copies a person possesses has been shown to modify SMA disease severity; those with more copies of SMN2 usually have a less severe form of the disease. Research has shown that SMA mice with eight copies of the SMN2 gene do not show any signs of the disease.

The broad correlation between SMN2 gene copy number and SMA severity seems to indicate that increasing the amount of SMN protein produced from the SMN2 gene might lead to an effective

treatment for SMA. Thus, SMN2 is an ideal target for pharmaceutical intervention. There are three methods currently being researched: (1) turning up the SMN2 “promoter” to produce more SMN2 mRNA and SMN protein; (2) correcting the defective splicing of SMN2 to make it act like SMN1 and produce fully functional, full-length SMN protein; and (3) stabilizing the SMN protein produced by SMN2 so that more of it is functional. Results from these studies are providing groundbreaking data with implications for therapeutics discovery in SMA and in other disorders of transcription and translation, including the muscular dystrophies, Friedreich’s Ataxia, Fragile X syndrome, and Huntington’s disease.

Due to the investments made in basic and translational research by national non-profit organizations, several compounds have been identified that are shown to increase SMN protein levels from the SMN2 gene in cellular and animal models of SMA. The next step towards developing a beneficial drug treatment for SMA is for these compounds to be tested in national clinical trials on SMA populations in order to demonstrate their safety and effectiveness so that they can secure approval by the U.S. Food and Drug Administration.

Success in any one of the potential treatment pathways for SMA is dependent upon a clear path forward in clinical development. Requirements include an experienced team of clinical investigators, a well-profiled patient population, ready access to patients, data collection and data management capabilities, and the resources to build a durable infrastructure and capacity to respond to opportunity. The non-profit sector has contributed to the development of individual pieces of this system, but greater sums are required to coordinate the elements into a productive research enterprise. Only the federal government can provide the necessary resources.

The national non-profit SMA patient organizations collectively devote nearly \$20 million each year towards SMA research and currently fund several clinical trials sites and networks, but the cost of upgrading and unifying these sites into a national network is prohibitively expensive for organizations that fundraise primarily from affected families. Several biotechnology firms work collaboratively with the non-profit patient organizations on SMA research, but they often do not possess the resources necessary to run national clinical trials. To date, “Big Pharma” has shown little interest in investing in human clinical testing for a small-sized therapeutic area like SMA, even though promising data exists demonstrating that these drugs may benefit SMA patients.

The national non-profit patient organizations have brought SMA research to the precipice of the development of a treatment. It is incumbent upon the federal government to ensure that this investment is brought to the finish line so that thousands of affected children and their families can be spared the devastation that is caused by SMA.

Sincerely,

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