Optimization of Compounds that Stabilize the SMN Protein for Treatment of SMA

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USA

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Optimization of Compounds that Stabilize the SMN Protein for Treatment of SMA

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1

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Research Abstract

? DESCRIPTION (provided by applicant): Spinal muscular atrophy (SMA) is an inherited disease of motor neuron degeneration that results from inadequately low levels of the SMN protein produced from the SMN2 mRNA, which undergoes alternative splicing and skipping of exon 7. We successfully implemented a high throughput chemical diversity screen for compounds that increase cellular levels of the functional, authentic SMN protein. Following a synthetic chemistry program, we identified a series of unique compounds with a shared

chemical scaffold that increase SMN protein levels in cultured cells. These compounds act by stabilization of the SMN protein yet are not proteasome inhibitors. After performing partial pharmacokinetic analyses, we selected one compound for proof of principle in vivo studies. This compound significantly extended mean survival and gross motor function in both severe and moderate murine models of SMA, and induced increased levels of SMN protein in brain and spinal cord. These data confirm the validity of our screening assay and the biological activity of this chemotype. The R21 portion of this grant proposal describes key steps in drug development. We will first complete characterization of the pharmacologic properties of the most active and potent chemotypes we have recently identified within this series. Second, we will develop a medically suitable formulation for in vivo administration, preferably by oral dosing. The toxicity profiles for compounds that fulfill our pre-established criteria will be ascertained i SMA mice. A comprehensive set of milestones are described for selection of the best compounds for advancement into the R33 phase. The R33 phase utilizes the results from the R21 year to instruct administration of the most potent and active analogs in several commonly used SMA mouse models. Investigator blinded compounds will be tested by two highly experienced SMA research labs for clinically significant outcomes including extension of lifespan and increased motor skills. Furthermore, because the mechanism of action of this series of compounds differs from the exon 7 splicing stimulatory modalities currently in human trials, we will test combinations of these agents with our SMN protein stabilizers for ability to cooperatively increase SMN protein levels and therapeutic responses in SMA mice. There is no FDA approved drug treatment for SMA. While new therapeutic strategies are in clinical trials, clinical efficacy and absence of prohibitive side effects remain to be determined. Success in this project would accelerate the pre-clinical optimization of our novel lead compounds and facilitate the prospects for NIH and/or industry investment to support entry into human clinical trials.

Further information available at:

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