Optimization of a novel series of thiazolopyridines for the treatment of SMA

https://neurodegenerationresearch.eu/survey/optimization-of-a-novel-series-of-thiazolopyridines-for-the-treatment-of-sma/

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Country

USA

Title of project or programme

Optimization of a novel series of thiazolopyridines for the treatment of SMA

Source of funding information

NIH (NINDS)

Total sum awarded (Euro)

€ 796,709.17

Start date of award

01/04/2015

Total duration of award in years

1

The project/programme is most relevant to:

Spinal muscular atrophy (SMA)

Keywords

SMN2 gene, Spinal Muscular Atrophy, SMN protein , Motor Neurons, SMN1 gene

Research Abstract

? DESCRIPTION (provided by applicant): Spinal muscular atrophy (SMA) is a neurodegenerative disease that causes progressive muscle weakness. About 95% of SMA

cases are caused by the loss of both copies of the SMN1 gene. The SMN2 gene found in humans is a nearly identical copy of SMN1 and expresses only a small amount of the active SMN protein. While SMN2 cannot fully compensate for the loss of SMN1 in motor neurons, it provides an excellent target for therapeutic intervention. Increased expression of functional full-length SMN protein from the endogenous SMN2 gene should lessen disease severity. Previously, we developed innovative reporter cell assays for inducers of SMN expression, and hit compounds from these assays demonstrated positive effects in the SMN?7 mouse model. Very recently, an optimized analog (LDN-2014) demonstrated efficacy both in the very severe SMN?7 and moderately severe 2B/- model following intraperitoneal (IP) dosing, although LDN-2014 did not have suitable pharmacokinetic properties for further development. We now have applied this same in vitro assay to screen a novel library of compounds designed and synthesized at the LDDN and identified patentable leads; preliminary optimization has established tractable SAR. Furthermore, potent compounds with good plasma and brain exposures following oral administration have been discovered from this new series. Preliminary investigations indicate that the new series of compounds has a similar mechanism of action as LDN-2014, both of which act post-transcriptionally and stabilize the SMN-protein. The optimization of this novel series as activators of SMN2 protein is a unique approach, which we believe will lead to pre-clinical development candidates for the treatment of SMA. Project Goals: Aim 1 is to conduct medicinal chemistry optimization of the thiazolopyridine series with the objective of identifying 4-6 compounds that have pharmacokinetic properties suitable for pharmacological evaluation in two mouse models of SMA. Derivatives that selectively increase SMN2-luciferase expression without decreasing cell viability will be advanced for secondary screening in SMA derived human fibroblasts. Molecules that increase SMN protein levels by >1.5 fold, and with EC50 < 100 nM, will be advanced into in vitro drug-like property assays (e.g., solubility, microsomal stability, permeability). This iterative process will continue until compounds suitable for mouse oral PK experiments are discovered. Taken together, the in vitro and in vivo data then will be used to select the 4-6 compounds to evaluate in mouse models of SMA. Aim 2 is the characterization of advanced lead compounds in two mouse models of SMA. The 4-6 leading compounds that emerge from Aim 1 will be advanced into the severe (Li) mouse model of SMA. In year 2, the two analogs with the best overall features will be selected for profiling in the less severe SMNRT model. We believe that compounds that emerge from the stringent in vitro and in vivo evaluation we are proposing will be of suitable quality for final pr-clinical evaluation and advancement into clinical studies.

Lay Summary

PUBLIC HEALTH RELEVANCE: Spinal muscular atrophy (SMA) is a neurodegenerative disease with no known cure that causes progressive muscle weakness and primarily targets proximal muscles. We recently discovered a novel series of thiazolopyridines that: (i) promotes an increase in SMN2 protein in SMN2 luciferase reporter assay; (ii) increases SMN protein expression in patient-derived fibroblasts; (iii) acts post-transcriptionally and stabilizes the SMN protein; and (iv) demonstrates excellent plasma and brain exposure following oral administration. We propose to optimize this novel series, as activators of SMN2 protein, and we expect to identify preclinical candidates that give full lifespan and significant improvements in motor function in SMA mouse models.

Further information available at:

Types:

Investments > €500k

Member States:
United States of America

Diseases:
Spinal muscular atrophy (SMA)

Years:
2016

Database Categories:
N/A

Database Tags:
N/A