An Orally Bioavailable Drug Candidate for Spinal Muscular Atrophy

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Principal Investigators

SCHULTZ, PETER G

Institution

CALIFORNIA INSTITUTE/BIOMEDICAL RESEARCH

Contact information of lead PI
Country

USA

Title of project or programme

An Orally Bioavailable Drug Candidate for Spinal Muscular Atrophy

Source of funding information

NIH (NINDS)

Total sum awarded (Euro)

€ 1,700,800.00

Start date of award

01/04/2016

Total duration of award in years

4

The project/programme is most relevant to:

Spinal muscular atrophy (SMA)

Keywords

Spinal Muscular Atrophy, Bioavailable, SMN1 gene, SMN2 gene, drug candidate

Research Abstract

? DESCRIPTION (provided by applicant): Spinal muscular atrophy is a genetic disease resulting from mutations in the SMN1 gene that results in impaired motor neuron function and can lead to death. Currently there are no approved drugs for this debilitating pediatric disease. Our goal is

to generate an orally bioavailable drug for the treatment of SMA that upregulates SMN2 gene expression to compensate for the loss of the wild type SMN1 gene. Such drugs can likely be used in combination with the splicing modulators or neuroprotective agents (if approved) that are currently in clinical development to provide increased patient benefit. In preliminary work we have identified a lead compound with excellent in vitro activity and good pharmacokinetics that upregulates SMN levels in the SMN?7 neonatal mouse model without obvious adverse effects. New analogs will be designed, synthesized and assessed for in vitro activity, cytotoxicity and in vitro ADME and safety profiles. Analogues with improved cellular activity (full-length SMN levels), low cytotoxicity and favorable in vitro safety profiles will be selected for PK studies in adult and neonatal mice. These analogs will also be studied in rat PK models (oral administration, plasma and brain levels at different time points) to assess their pharmacokinetics across different species. Analogs that exhibit favorable brain PK profiles at tolerated doses (without obvious adverse effects in neonatal mice) will be progressed to pharmacodynamic (full-length SMN levels in brain tissue) and efficacy studies in SMN?7 neonatal mice. In parallel the biological target of select potent compounds will be identified using affinity probes and the mechanism by which SMN levels are upregulated will be investigated. Finally, once a preclinical candidate is selected (a) the dosing regimen will be optimized including efficacious dose range determination and dosing frequency; (b) a comprehensive set of in vitro physicochemical, ADME and safety profiling studies (detailed in Table 2, vide infra) will be carried out; and (c) th PCC will be assessed in rat and dog pharmacokinetic and toxicology studies. Upon the completion of the proposed studies, we will be positioned to initiate IND-enabling studies for the selected PCC, and move the program forward into clinical studies with an appropriate commercial partner.

Lay Summary
PUBLIC HEALTH RELEVANCE: Spinal Muscular Atrophy (SMA) is a genetic neuromuscular disease characterized by muscle atrophy and weakness that generally manifests early in life and is one of the leading genetic causes of death in infants and toddlers. Currently, there are no approved drugs or other therapies available for the treatment of SMA. Our goal is to develop an orally bioavailable drug this debilitating disease that acts by increasing the expression of the SMN2 gene; in preliminary studies we have identified a lead compound that upregulates SMN levels in the transgenic SMN?7 model.

Further information available at:

Types:
Investments > €500k

Member States:
United States of America

Diseases:
Spinal muscular atrophy (SMA)

Years:
2016

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