Cyclic EphA4 peptide antagonists for neuroprotection in ALS

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Principal Investigators

PASQUALE, ELENA B

Institution

SANFORD BURNHAM PREBYS MEDICAL DISCOVERY INSTITUTE

Contact information of lead PI
Country

USA

Title of project or programme

Cyclic EphA4 peptide antagonists for neuroprotection in ALS

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NIH (NINDS)

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3

The project/programme is most relevant to:

Motor neurone diseases

Keywords

Ephrins, Amyotrophic Lateral Sclerosis, neuroprotection, Eph Family Receptors, Ligand Binding Domain

Research Abstract

? DESCRIPTION (provided by applicant): The receptor tyrosine kinase EphA4 has been implicated in several neurodegenerative processes. Strikingly, a recent study has shown that

low EphA4 expression and loss-of-function mutations are linked to late onset and prolonged survival in amyotrophic lateral sclerosis (ALS), a devastating neurodegenerative illness for which there is no cure and the only FDA-approved therapy can increase survival by only several months. Even partial EphA4 gene inactivation has shown beneficial effects in animal models of ALS, making inhibition of EphA4 function an attractive strategy to counteract neurodegeneration. Accordingly, a peptide that we previously discovered as a selective EphA4 antagonist has shown promise in the classic rat SOD1 G93A ALS model, where it significantly dampened ALS pathogenesis demonstrating the therapeutic potential of EphA4 antagonistic agents. Despite these exciting results, our first generation EphA4 antagonists lack the required potency and stability in biological systems to make them suitable as leads for drug development. Thus, in this application we propose to develop and evaluate new potent EphA4 antagonists with pharmacological properties suitable to make them bona fide therapeutic leads for future treatment of ALS. In our preliminary work, we have developed a derivative of a cyclic dodecapeptide that specifically inhibits EphA4-ephrin binding with an IC50 value of ~25 nM. This prototype is a striking 80 fold more potent than any previously known EphA4 antagonist and has the potential for optimization to become a desired therapeutic lead. To develop related cyclic EphA4 antagonists towards this goal, we propose a highly integrated iterative strategy using peptide medicinal chemistry, structural biology and our long-standing expertise in EphA4 neurobiology. The activities of rationally designed new peptide antagonists will be evaluated using biochemical assays and neuronal cell culture models. Complementing these studies, our most promising new EphA4 antagonists will be profiled for their properties in plasma and cerebrospinal fluid and their propensity to cross the blood-brain barrier, as well as their half-lie in the blood circulation. Finally, in vivo studies in collaboration with renowned ALS expert Dr. Wim Robberecht will characterize the best antagonists in delaying disease onset and promoting survival in an ALS mouse model. We anticipate that the proposed studies will result in a potent EphA4 inhibitor with a pharmacologic profile suited for immediate development as a therapeutic agent alone or in combination with other treatments. They will also provide valuable insight into the mechanism underlying the benefits of EphA4 inhibition against neurodegeneration.

Lay Summary

PUBLIC HEALTH RELEVANCE: Several studies have implicated the EphA4 cell surface receptor in ALS and other neurological diseases. Recent work using first generation antagonistic agents we developed show that EphA4 is a new promising target whose decreased activity has beneficial effects in a classic animal model of ALS. Yet, currently available antagonists that inhibit the interaction of EphA4 with its natural ligands lack potency and other attributes necessary for development into future therapeutics. Overcoming this hindrance, we now have identified new EphA4 peptide antagonists as highly promising agents to achieve high potency for in vivo use, which we seek to advance towards a bona fide lead for the development of ALS therapies in this proposal. Our studies will additionally generate tools and insight to decipher the role of EphA4 in ALS and neurodegeneration.

Further information available at:

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United States of America

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Motor neurone diseases

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