Innovative IGF-2 Receptor Agonists for Treating Neurodevelopmental Disorders and Neurodegenerative Diseases

Disease-modifying therapy with differentiated mechanisms of action to restore memory and motor function in neurodegenerative diseases and neurodevelopmental disorders.

Technology

The Alberini Lab at NYU has embarked on a drug development program to create novel small-molecule agonists of the insulin-like growth factor 2 receptor (IGF-2R) to treat neurodegenerative diseases and neurodevelopmental disorders by restoring protein metabolism homeostasis (proteostasis) in the brain. IGF-2R binds insulin-like growth factor 2 (IGF2) at the cell surface and mannose-6-phosphate (M6P)-labeled proteins in the trans-Golgi network and has been shown by the Alberini Lab (*Yu et al. eLife 2020; Pandey et al. 2020*) to regulate protein metabolism in neurons by controlling the activation of autophagy coupled to de novo protein synthesis (Figure 1). The developed IGF-2R agonists are natural ligands, or derivatives thereof, that include a prodrug of mannose-6-phosphate (M6P) (“lead candidate”) and non-prodrug derivatives of M6P (“backup candidates”). In unpublished work, the lead candidate (when administered subcutaneously) was shown to accelerate autophagic flux in the brain of a reporter mouse, and when administered orally or subcutaneously, demonstrated a significant enhancement of memory in normal, healthy mice and a reversal of memory impairments and motor deficits in an Angelman syndrome mouse model. In all, these IGF-2R agonists are promising candidates for further preclinical development and offer a differentiated, disease-modifying approach to treat neurodegenerative diseases and neurodevelopmental disorders.

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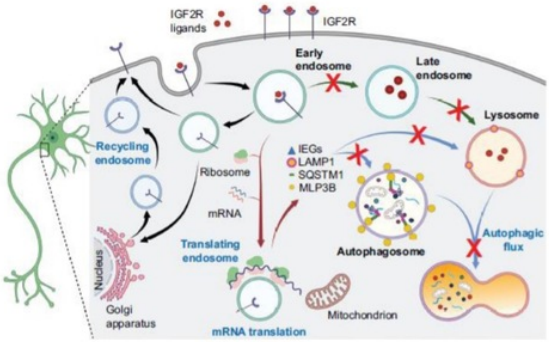

Figure 1. Schematic illustrating the mechanism of action of IGF-2R activation and potential defective mechanisms in diseases. Administration of an IGF-2R agonist is expected to restore or promote protein degradation pathways (endosomal acidification and autophagy) in diseases where defects (denoted by the red "X's" in the cartoon) impair those mechanisms and thereby reverse toxic protein accumulation in the brain.

Development Status

IGF-2R agonists showed efficacy in preclinical rodent models of neurodevelopmental disorders and preliminary *in vitro* DMPK results were generally positive: the lead candidate converted quickly in plasma; one of the backup candidates was stable in plasma; and there were no problematic toxicity alerts. Next steps include (1) binding assays to measure and validate the IGF-2R:agonist interactions and (2) additional *in-vitro* ADME tests to proceed to IND-enabling studies.

Background

Neurodegenerative diseases and neurodevelopmental disorders represent a significant and growing public health challenge worldwide. Alzheimer's disease, the most common neurodegenerative disorder and a leading cause of dementia, affects approximately 6.5 million people aged 65 and older in the U.S. alone, with prevalence expected to rise with population aging. Similarly, neurodevelopmental disorders such as Angelman syndrome and autism spectrum disorder (ASD) impact a substantial number of children, resulting in lifelong cognitive, behavioral, and social impairments. ASD affects about 1 in 36 children in the U.S., and Angelman syndrome, a rare genetic disorder, has a prevalence of approximately 1 in 12,000-20,000 individuals globally. Despite extensive research, current treatments for these diseases/disorders are limited and primarily focus on symptom management rather than addressing the underlying pathophysiology: accumulation of toxic proteins in the brain. Therefore, there is an urgent unmet need for innovative, disease-modifying therapeutic approaches to rebalance brain proteostasis in these diseases/disorders.

Applications

- For the treatment of neurodegenerative diseases, including:
  - Alzheimer's disease/dementia, Huntington's disease, Parkinson's disease, amyotrophic lateral sclerosis, and aging-related cognitive impairments
- For the treatment of neurodevelopmental disorders, including:
  - Angelman syndrome and autism spectrum disorder

Advantages

- Disease-modifying therapy: Rebalances proteostasis to combat toxic protein accumulation in the brain
- Granted FDA designations: Orphan Drug Designation and Rare Pediatric Disease Designation granted to the lead compound for Angelman Syndrome treatment
- Oral administration: The lead compound maintains efficacy in disease models when administered orally
- Extensively validated target: The Alberini Lab and others have extensively characterized the IGF-2R signaling pathway
- Simple and inexpensive synthesis: The IGF-2R agonists are based on natural ligands, so the chemistry is straightforward
- Favorable preliminary ADMET readouts for IGF-2R agonists

Intellectual Property

NYU holds multiple issued patents and pending patent applications in the U.S. and in major foreign markets covering the chemical compositions of IGF-2R agonists and methods of use thereof in treating neurodevelopmental disorders and neurodegenerative diseases

- Patent family 1 (NYU internal ref. ALB01-03): Issued and pending cases
- Patent family 2 (NYU internal ref. ALB01-04): Issued and pending cases
- Patent family 3 (NYU internal ref. ALB01-06): pending, unpublished U.S. provisional application

References

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