Inhibition of Astrocyte-Derived Neurotoxic Lipid for Treatment of Neurological Injury and Diseases

Efficacious treatment for chronic neurological diseases and acute central nervous system (CNS) injury.

Technology

The Liddelow research group has identified and characterized a novel therapeutic approach with applicability across major chronic neurological diseases and acute CNS injuries. Central to this approach is the discovery made by the Liddelow group in preliminary studies published in *Nature*, of a specific reactive astrocyte subtype that drives the death of neurons and mature oligodendrocytes. The Liddelow group coined these cells 'neurotoxic reactive astrocytes' (NRAs) and through *in situ* hybridization and immunochemistry on post-mortem tissue from patients, revealed that these NRAs reactive astrocytes are abundant in Alzheimer's, Huntington's and Parkinson's disease, amyotrophic lateral sclerosis and multiple sclerosis. The pathology of these NRAs has been validated in animal models across all these diseases, as well as glaucoma, acute nerve trauma, and even prion infection. The neurotoxicity of these cells was demonstrated to be the result of their secretion of neurotoxic long chain free fatty acids (LCFAs) which cause lipoapoptosis of the neighboring neuronal cells. Eliminating the formation of these LCFAs by astrocyte-specific knockout of the saturated lipid synthesis enzyme ELOVL1 mitigated astrocyte-mediated neurotoxicity *in vitro* as well as *in vivo* in a model of either acute axonal injury or chronic Alzheimer's Disease. Moreover, a highly potent, CNS-penetrant ELOVL1 inhibitor with favorable *in vivo* pharmacokinetics is feasible. These findings validate a novel approach to treat an array of chronic neurological diseases and acute CNS injuries through the inhibition of NRAs reactive astrocyte production of long-chain saturated lipids.

Background

Astrocytes are critical regulators of CNS homeostasis, supporting synaptic formation/maintenance and neuronal survival. However, in response to CNS injury and disease, they undergo transformation into multiple reactive states. The detrimental NRA state has been shown to contribute to neuronal and oligodendrocyte death in several disease models. Current therapeutic approaches to neurodegenerative diseases do not target NRAs, limiting their efficacy in mitigating pathological neuroinflammation and cell death. To date, there is not a single astrocyte-specific targeting therapy available on the market. Targeting the NRA production of long-chain saturated lipids represents a promising therapeutic approach for halting disease progression and promoting CNS recovery for many neurological diseases.

Development Stage

Researchers have shown efficacy of inhibiting astrocyte-secreted neurotoxic lipids in both acute and chronic *in vivo* models of CNS injury and disease, and are currently exploring the generation

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of novel small molecule ELOVL1 inhibitors.

Applications

- Treatment of neurodegenerative diseases (Alzheimer's, Parkinson's, Huntington's).
- Acute CNS injuries, including traumatic brain and spinal cord injury.
- Multiple sclerosis and amyotrophic lateral sclerosis.
- Prevention of neuronal degeneration following ischemic stroke.

Advantages

- **Targeted mechanism of action:** Precisely reduces the neurotoxicity caused by NRA cells, directly addressing a root cause of neuronal and oligodendrocyte death.
- **Broad applicability:** This approach has demonstrated efficacy across a range of chronic neurological diseases and acute CNS injuries.
- **Reduction of neuroinflammation:** Reduces the inflammatory response driven by NRAs, potentially leading to better management of neuroinflammation and improved outcomes for patients.
- **Potential for disease modification:** Reduction in neurotoxic lipid production offers a novel approach that could modify the disease course, potentially slowing or halting the progression of neurodegenerative conditions.
- **Tractable target**: Preliminary small molecule inhibition of ELOVL1 within the CNS has already been achieved.

Intellectual Property

NYU has a pending US and EP patent application covering the method of targeting astrocyte-secreted neurotoxic lipids for the treatment of multiple CNS diseases and injuries.

References

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