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Rationale For Testing J-147 In SOD1 Murine Model

Summary

J-147 is a derivative/hybrid of curcumin and cyclohexyl-bisphenol (a molecule with neurotrophic activity which curcumin lacks), developed by Salk Institute for Biological Studies (Salk) and recently described as beneficial in the Alzheimer's Disease (AD) mouse model[1].

What differentiates this drug from the vast majority of other drugs targeted to AD and other neurodegenerative diseases like ALS is that Salk started at the pathologies of neurodegeneration and not pre-selected molecular targets, which makes this particular molecule potentially unique in its applications across the board in targeting the pathologies of neurodegeneration. Salk ran assays that included the loss of trophic support, oxidative stress, the reduction of energy metabolism (in vitro ischemia and glucose starvation) and amyloid toxicity. As potential lead drug candidates to screen in these assays, they chose a representative from the original pharmacopeia, plant-based polyphenolics. Natural products have a wide range of molecular targets because they resemble biosynthetic intermediates to a greater extent than synthetic drugs and are therefore able to compete with substrates for multiple enzymes.

The best compound in their initial library of compounds was CNB-001, a molecule that has improved stability over curcumin and that is neuroprotective in multiple neurotoxicity assays in which curcumin is inactive. They then generated a large number of derivatives of CNB-001 and selected the best compound on the basis of activity in their multiple toxicity assays. The result was a much more potent molecule called J-147. It was then asked if J-147 is effective in two paradigms of age-associated pathology, AD and memory. It is shown here that this broadly neuroprotective compound has the ability to enhance memory in normal animals as well as to prevent memory deficits in AD transgenic mice. The neurotrophic and memory-enhancing activities of J-147 are associated with an increase in Neural Growth Factor (NGF) and Brain Derived Neurotrophic Factor (BDNF) levels along with the expression of BDNF-responsive proteins which may be beneficial in ALS [5]. Other benefits include the enhancement of LTP, synaptic protein preservation, the reduction of markers for oxidative stress and inflammation, the reduction of amyloid plaques, and lower levels of soluble Aβ1–42 and Aβ1–40. These pleiotrophic effects of a single molecule suggest that J-147 has potential for the treatment of AD.

In a nutshell, instead of being directed at the usual AD target of amyloid-beta, J-147 acts in a number of common pathways that also make it attractive for neurodegenerative disease in general. Among these are neuroinflammatory[2] and oxidative stress[3] markers and heat shock protein expression[4]. J-147 also increases endogenous NGF and BDNF, neurotrophins which may be beneficial in ALS[5].

The drug is orally bioavailable, positively effects several biomarkers which may be relevant to ALS, is safe in mice and appears to cross the blood brain barrier in mice as well (based on the cognition/memory results). There are still questions about potential benefits in SOD1 mice, human safety and penetration of the human blood brain barrier but as a first step, utilizing the SOD1 mouse model may yield useful results and ultimately add an additional treatment option for ALS patients.

Achieving a positive result in the model would justify additional work to elucidate mechanism of action before advancing into human testing.

Neuronal cell death, Inflammation and Oxidative Stress

Inflammation has a prominent role in the progression of ALS[6]. A few promising experiments have been performed by the ALS Therapy Development Institute (TDI) using antibodies against CD40L showing efficacy in the murine model by diminishing the inflammatory attack on peripheral axons. A similar reaction was found in the FDA-approved MS drug Gilenya and TDI has started a Phase-2 trial of Gilenya in ALS patients. Another immunomodulation drug showing promise in Phase-2 is NP001 by Neuraltus Pharmaceuticals. This acts on macrophages/microglia, keeping them in a normal state or converting them back to normal from an inflammatory state. The available literature on J-147 uses anti-inflammatory markers which could be considered specific to AD. However, both diseases have many of the same hallmarks[7]. HO-1 upregulation in ALS is one result of increased ROS[8] and co-localizes with reactive astrocytes in mSOD1 transgenic rats[9]. Iba-1, a marker of macrophage/microglial activation upregulation versus controls, is useful as a measure of the inflammatory attack in the PNS/CNS[10]. 5-LOX inhibition is also shown to be neuroprotective by dampening pro-inflammatory signaling[11-12].

Heat Shock Proteins

Heat shock proteins (HSPs) are chaperones of protein folding and also participate in reactions to cellular stress[13]. Motor neurons have a high threshold for induction of HSPs[14] which may help explain their vulnerability to misfolded protein aggregates in ALS. The response of HSPs, once initiated, does not appear sufficient to handle the stress and may be subverted by the same stressing events[15-16]. Further, induction of HSPs in motor neurons is somewhat different than in other cells and can be contradictory[17-19]. Regardless, induction of HSPs clearly shows a high level of chronic stress. Treatment with J-147 lowers neuronal HSP levels to normal[1].

Neurotrophic Factors

Treatments to deliver neurotrophic factors (NTFs) have met with disappointment. Reasons include inability to penetrate the BBB and inability to deliver consistent long-term dosing[5]. Previous attempts to deliver NTFs via stem cells (specifically delivering GDNF) rescued cell bodies in G93A rats but did not rescue axonal projection to muscle[20]. A company named Brainstorm is using autologous mesenchymal stem cells (MSCs) engineered to produce multiple NTFs including GDNF and BDNF intended as treatment for neurodegenerative diseases[21]. Brainstorm is currently in Phase-1 in ALS using this MSC-as-NTF-factory approach. The trial is in Israel but Brainstorm is opening a trial in the USA. Although BDNF and other neurotrophins appear unable to rescue axonal projection, they do appear capable of rescuing neural cell bodies which is no doubt an important effect. Treatment with J-147 increases endogenous NGF and BDNF levels, along with several BDNF-responsive proteins[1]. J-147 also increases levels of drebrin, a cytoplasmic actin-binding protein thought to play a role in the process of neuronal growth[1][22].

Conclusion

Despite being distinct diseases, neurodegenerative diseases share many characteristics such as neuroinflammation, oxidative stress, and downregulation of NTFs. It follows that treatments acting on those shared pathways should show some efficacy in each (accounting for possible different dosage requirements). Although different markers might be preferable to measure between AD and ALS, from the J-147 report it appears to effectively dampen neuroinflammation and oxidative stress. A marker of such stress is upregulation of HSPs. Presumably just quelling such upregulation would not be beneficial, but if downregulation to normal levels is a reaction to a lessening or cessation of stressing stimulus it would suggest an improvement of cellular health. Increasing NTFs to provide a more nurturing environment would also be desirable. Techniques to supply exogenous NTFs have been and are being explored. Presumably a pharmaceutical method to boost endogenous NTFs would be preferable to any type of therapy involving surgery.

The common drug discovery and delivery paradigm is based on a single pathway focus which only recapitulates a single aspect of a particular disease. This approach has consistently and reliably failed in ALS where, by the time the disease is noticeable enough for diagnosis, a great many things are going wrong from an as yet unknown upstream pathological event. It is more logical to research and develop a potential therapeutic against multiple assays which recapitulate individual aspects relevant to a particular disease. J-147 was developed in this way[23].

Based on the potential action in pathways common to multiple neurodegenerative diseases and development against multiple assays relevant to pathological aspects of ALS, it seems logical and prudent to investigate J-147 in ALS. In particular, the data appear compelling enough to warrant careful analysis in the ALS murine model[24].

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