IL-1 receptor antagonists in ALS

By Lauren Martz, Staff Writer

Researchers at the **Max Planck Institute for Infection Biology** have shown that inhibiting the IL-1 receptor improves survival in a mouse model of familial amyotrophic lateral sclerosis.[1] Although efficacy results in mouse models of the disease have a notoriously poor record for translating into human efficacy, the path should be open to human clinical testing: 1 IL-1 receptor antagonist is on the market and at least 10 other companies have IL-1 receptor antagonists or antibodies against its ligand, IL-1β, in development.

In amyotrophic lateral sclerosis (ALS), motor neurons in the CNS degenerate, leading to muscle weakness, paralysis and death. The most common form of the disease, nonfamilial, sporadic ALS, has no clear genetic basis. Familial ALS occurs in 5%–10% of patients, and about one-quarter of those cases are linked to mutations in the gene coding for superoxide dismutase 1 (SOD1) that lead to pathogenic misfolded forms of the protein in neurons and glial cells.

Previous studies have shown that IL-1β levels are higher in the CNS of mice or human ALS patients with mutant SOD1 than in the CNS of healthy controls, suggesting that inhibiting IL-1 or its receptor would curb the neuroinflammatory aspect of the disease.[2]

In a paper published in the *Proceedings of the National Academy of Sciences*, Arturo Zychlinsky and two colleagues at Max Planck showed that antagonizing the IL-1 receptor indeed had a disease-modifying effect in ALS. Zychlinsky is a professor at the Max Planck Institute for Infection Biology.

The team's first step was to show a concrete link between SOD1 mutants and downstream neuroinflammation. In cultured microglia and macrophages, stimulation with a SOD1 mutant produced dose-dependent activation of caspase-1 compared with stimulation using wild-type SOD1. Caspase-1 is a protease that induces the maturation of IL-1β.[3]

Zychlinsky's group also showed that the degree of protein misfolding correlated with the level of activated caspase-1 and IL-1β secretion, suggesting that the inflammatory reaction is linked to the SOD1 mutation.

In a mutant SOD1 mouse model of ALS, animals with knockout of *caspase-1* or *IL-1*β had longer survival than ALS mice expressing both genes. Also, ALS mice treated with the IL-1 receptor antagonist Kineret anakinra had longer survival and better motor function than animals given placebo.

Swedish Orphan Biovitrum AB markets Kineret to treat rheumatoid arthritis (RA). The company exclusively licensed the biologic from **Amgen Inc.**

At least 10 other companies have IL-1 receptor antagonists and antibodies against its IL-1β ligand in clinical and preclinical testing for various other conditions including gout, diabetes and heart disease.

The only disease-modifying treatment on the market for ALS is **sanofi-aventis Group**'s Rilutek riluzole, a sodium channel blocker. "There is no doubt that it works, but it doesn't work well. It slows down the progression of the disease by about 10%, but there are a number of side effects. Only about half of the patients offered the medication choose to take it," noted Neil Cashman, CSO and cofounder of **Amorfix Life Sciences Ltd.** "We're left with symptomatic treatments, but they don't get to the root of disease."

Amorfix has mAbs against SOD1 in preclinical testing to treat ALS.

SOD1 model

Researchers contacted by *SciBX* said the mutant SOD1 mice used by the Max Planck team, which models the familial form of ALS, is a good screening tool because it represents a severe form of the disease. Thus, any compound that shows efficacy has overcome a significant disease burden. However, efficacy in the model has not consistently translated to the human disease.

> **"The fact that IL-1 is elevated in ALS patients' cerebrospinal fluid speaks in favor of this molecule having a role not only in the SOD1 mutant patients, but also in patients with sporadic ALS."**
>
> ***—Anders Haegerstrand, NeuroNova AB***

"The animal model isn't 100% the same as human ALS," noted Alan Solinger, VP of clinical immunology at **Xoma Ltd.** "It reproduces the lesions and symptoms, though, so it is a good screening model of pathways for disease intervention."

Xoma's XOMA 052, a humanized antibody against IL-1β, is in Phase II testing to treat diabetes and in preclinical testing for several other conditions.

Although the Max Planck group only tested Kineret in a model of familial ALS, Anders Haegerstrand, VP and CSO of **NeuroNova AB**, noted that the results suggest IL-1 antagonists also might have utility in the nonfamilial form of the disease as well.

"The fact that IL-1 is elevated in ALS patients' cerebrospinal fluid speaks in favor of this molecule having a role not only in the SOD1 mutant patients, but also in patients with sporadic ALS," he said.

Thus, according to Haegerstrand, increased IL-1 could be a shared characteristic among the different forms of ALS, and blocking the receptor might help treat both forms of the disease.

NeuroNova is developing sNN0029, a VEGF protein delivered directly to the brain through an intracerebroventricular pump. The compound is in Phase I/II testing to treat ALS.

For either form of ALS, an IL-1 receptor antagonist would need to cross the blood brain barrier (BBB) and enter the cerebrospinal fluid.

"It is not clear, at least to me, whether IL-1 antibodies would be able to pass the BBB to allow sufficient concentrations in the CNS. If not, direct delivery into the brain would be required. This presents a more challenging, but feasible, therapeutic development perspective," said Haegerstrand.

Thus, he told *SciBX*, "investigation of CNS penetration of IL-1 antibodies seems a logical first step. If the CNS penetration is good, a straightforward approach would be to simply initiate a clinical trial using Kineret."

"There have been studies of Kineret's CNS cerebrospinal fluid penetration, and it has been shown that a very small concentration of the drug does cross the BBB," Cashman noted. "Ordinarily, a treatment like this is first tried with peripheral administration, possibly with modifications to increase the penetration of the CNS. Then, if unsuccessful, delivery directly to the brain will be tested."

Finding a better IL-1 modulator

In addition to increasing BBB penetration, researchers think Kineret's half-life and side-effect profile both leave room for improvement.

Kineret "is not the best of all IL-1 modulators. It has a very short lifespan and is gone within three to four hours," said Solinger.

The drug's short half-life may have dampened its efficacy in the preclinical ALS study reported by Zychlinsky's group. Sylvain Chemtob, CSO and cofounder of **Allostera Pharma Inc.**, noted in particular that the effects on motor performance were rather modest.

Allostera's APG101.10, an oral IL-1 receptor inhibitor, is in preclinical testing to treat autoimmune diseases.

Solinger said Kineret served as a good tool to show the importance of IL-1 in the disease, but the daily administration required for the indication would make it expensive and inconvenient.

In addition to frequent dosing, side effects associated with chronic use of Kineret include flu-like symptoms and increased risk for serious infection, according to the drug's label.

Solinger told *SciBX* that "someone has to get the guts to test this strategy in ALS. Companies can be adverse to going into an unusual disease, which could waste a lot of money if unsuccessful. But if it's a good enough strategy with a lot of confidence behind it, it could be well worth it."

Xoma, however, does not have plans to test its IL-1 receptor antagonist in ALS.

The authors of the *PNAS* paper did not respond to interview requests.

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COMPANIES AND INSTITUTIONS MENTIONED

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