Why might Gilenya be helpful for ALS?

Amyotrophic Lateral Sclerosis (ALS, Lou Gehrig's disease) is a complex neurodegenerative disorder for which there are currently no effective treatments. The cause of the disease is not known for upwards of 90% of cases; the others are linked to mutations in more than a dozen different genes.

One of the considerable challenges in developing a treatment for ALS is that over the course of the disease, the blood brain barrier breaks down and circulating white blood cells, called T-lymphocytes, infiltrate the central nervous system (CNS). This causes the immune cells of the CNS (microglia (purple) and astrocytes (light blue)) to become activated, which in turn triggers the inflammation of motor nerves, further fueling the progression of the disease.

In 2010, ALS TDI reported in *Nature Genetics* that a monoclonal antibody directed against CD40 ligand reduced the activation of these immune cells, slowed disease progression, and extended survival of an ALS mouse model. In December 2011, ALS TDI announced a partnership with Biogen Idec and UCB to further develop this strategy as a potential treatment for ALS in the clinic.

Subsequent ALS TDI studies suggested that reducing the trafficking and circulation of T-cell lymphocytes would in turn reduce their infiltration and the activation of microglia and astrocytes, thereby also providing potential therapeutic benefit by slowing the progression of disease.

To expedite the evaluation of such a treatment strategy in the clinic, ALS TDI tested several compounds known to reduce the infiltration of T-cell lymphocytes into the CNS. One such medicine was Novartis' Gilenya™ (fingolimod), also known as "TDI 132," currently used to treat multiple sclerosis. ALS TDI studies confirmed that this compound in fact reduced the trafficking and circulation of these immune cells in a mouse model of ALS. Further testing showed a significant benefit in treating disease in that model of ALS.

A comprehensive review and analysis of these results, in consultation with outside experts, gives ALS TDI the confidence to push this potential therapeutic for ALS forward into the clinic. The trial is anticipated to launch in early 2013.

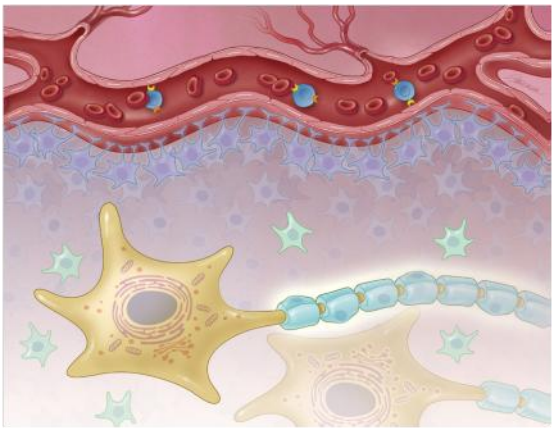

FIGURE 1. HEALTHY CENTRAL NERVOUS SYSTEM (CNS)

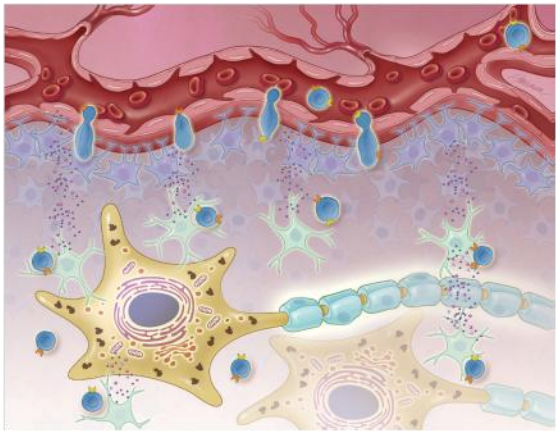

FIGURE 2. T-CELL INFILTRATION & IMMUNE SYSTEM ACTIVATION

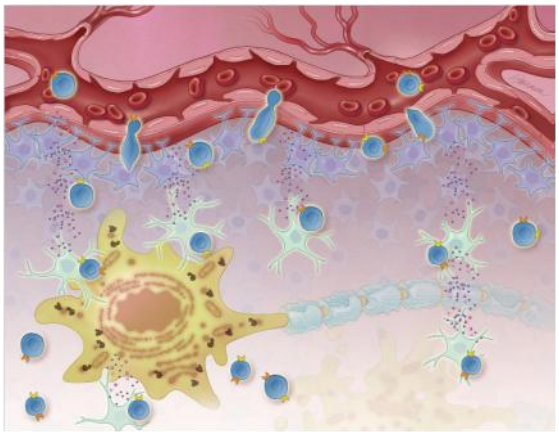

FIGURE 3. CNS DEGENERATION

300 Technology Square, Suite 400 Cambridge, MA 02139 t: 617.441.7200 f: 617.441.7299 web: www.als.net