Discovery of Antibodies that inhibit primary steps of SOD1 misfolding

Dr. Stanislav Engel, the Department of Clinical biochemistry and pharmacology, Faculty of Health Sciences, Ben-Gurion University of the Negev, Israel

Technology

Dr. Engel's group characterized the backbone dynamics landscape of misfolded SOD1 to pinpoint surface areas predisposed to aberrant protein-protein interactions (PPIs). This analysis enabled to formulate a working hypothesis for the mechanism of the gain-of-function of misfolded SOD1, according to which an abnormal PPI potential results from the increased mobility of certain regions of the SOD1 surface backbone. These structural changes result in the exposure of a hidden β6/β7 loop epitope that possesses amylogenic properties. The exposure of this epitope appears to be the earliest manifestation of the SOD1 misfolding process and it is entirely reversible by the addition of metals (Cu2+ and Zn2+). Monoclonal antibodies (mAB) generated against this epitope recognize misfolded SOD1 (fALS SOD1 mutants and apo-SOD1-WT) but not the properly folded metallated holo-SOD1-WT. The use of this antibody is expected to inhibit disease onset and/or progression.

Application

ALS is a neurodegenerative disorder that leads to motor neurons' death. To date, Riluzole and Edaravone are the only approved drugs that only marginally slow down disease progression. Based on Global data analysis, global sales of ALS drugs are expected to grow from $287M in 2017 to $1.2B by 2027 at a CAGR of 19.4%. SOD1 is a pathogenic protein, initially link to fALS but more lately also to sALS. Biogen develop Tofersen; an antisense designed to reduce the production of SOD1. Tofersen is currently in the accelerated 212 patients phase III study; based on promising results of the interim analysis. **If when approved, it will pave the way to second-generation anti-SOD1 therapies.** "KOLs stated that Tofersen has a promising MoA and although it will be used in fALS patients initially, it can then be expanded to sALS patients.

Advantages

- Inhibiting Amyloid aggregation would not necessarily prevent the formation of disease-mediating epitopes on misfolded sSOD1 species. Only drugs that prevent the primary events of the noxious structural transformation of SOD1 are expected to block the pathogenic chain, thus constituting a more efficient anti- ALS strategy.
- Metal loss results in a reversible exposure of the putative noxious b6/b7 loop epitope.
- Compounds that stabilize SOD1 in its native conformation (by mimicking the stabilizing effect of metal) thus preventing/reversing the epitope exposure are expected to obliterate aberrant PPIs mediated by this epitope (including amyloid formation and prion-like propagation of the misfolding signal), and attenuate the disease onset and/or progression.

Patent WO2020/110122A1