Inhibition of ER stress-based cytotoxicity in Huntington's disease (Ramot)

code: 10-2013-549

Gerardo Z. (Zelmar) Lederkremer, T.A.U Tel Aviv University, Life Sciences, Cell Research and Immunology
Daniel OFFEN, T.A.U Tel Aviv University, Medicine-Sackler Faculty, Felsenstein Medical Res Center-Beilinson
Moshe Portnoy, T.A.U Tel Aviv University, Exact Sciences, School of Chemistry

There is currently no effective therapy for HD nor for most other neurodegenerative diseases. Some current approaches try to interfere with the aggregation of huntingtin (Htt), the misfolded protein that causes this disease. This may not be beneficial, as misfolded protein sequestration into large aggregates appears to be a last resource cell protective mechanism. Our strategy is instead to modulate a major cytotoxicity pathway that is induced, involving ER stress.
The global market for Huntington's disease therapeutics is projected to exceed US$ 1.3 billion by 2020, driven by growing awareness about the disease worldwide and the huge unmet patients needs. The United States represents the largest and the fastest growing market worldwide with a CAGR of 21.6 % over the analysis period.

TECHNOLOGY

The technology is based on modulators of PERK - eukaryotic translation initiation factor 2-alpha kinase 3, which phosphorylates the alpha subunit of eukaryotic translation-initiation factor 2 (EIF2), leading to its inactivation, and thus to a rapid reduction of translational initiation and repression of global protein synthesis. One of the new modulators, MK-28, was able to strongly reduce the toxicity of mutant huntingtin-induced stress and rescue striatal cells in culture. Using the R6/2 transgenic Huntington’s disease mouse model, MK-28 significantly improved cognitive and motor functions and extended survival.

POTENTIAL APPLICATION

This approach could rescue cells in other neurodegenerative disorders, which currently have no effective treatment: Alzheimer’s disease, Parkinson’s disease and amyotrophic lateral sclerosis (ALS), and other diseases involving aggregation-prone proteins, which likely cause cytotoxicity by mechanisms similar to that of pathogenic huntingtin.
PERK modulators have not been tried so far for other neurodegenerative diseases, but compounds of a different class than the ones described here, have been reported to have anti-tumor and anti-angiogenic activity. Therefore, this activity should also be tested in different cancer models.

STAGE OF DEVELOPMENT

We have evaluated our PERK modulator in 4 models:
1. In vitro- kinase activity of isolated PERK.
2. In vitro- striatal neurons expressing mutant Htt.
3. In vivo- R6/2 transgenic HD mouse model.
4. In vivo- wild type mice-Toxicity assessment.

In addition, the MK28 compound demonstrated:
1. A good PK profile in both blood and brain
2. Superiority over GSK pipeline PERK inhibitor and over a PERK activator (CCT020312) in rescue from Htt-induced apoptosis in vitro

The results are very encouraging for a potential HD therapy. Given the similar ER stress pathways involved, this approach could also hold a promise for therapy of many other neurodegenerative diseases for which there is currently no cure or effective treatment. This compound, MK-28 or some of its derivatives should also be tested in AD , Parkinson ALS models.

PATENTS

Provisional filed covering the composition of matter of MK-28

SUPPORTING PUBLICATIONS

Ogen-Shtern, N., Ben-David, T. and Lederkremer, GZ. Protein Aggregation and ER Stress. Brain Res. 2016: 1648, 658-666.

Marina Shenkman, Hagit Eiger, Gerardo Z. Lederkremer. Genesis of ER Stress in Huntington's Disease. Endoplasm. Reticul. Stress Dis. 2015; 2, 94–106.

Contact for more information:

Amichai Bar On ✉, VP BD LS,

Ramot at Tel Aviv University Ltd. P.O. Box 39296, Tel Aviv 61392 ISRAEL
Phone: +972-3-6406608
Fax: +972-3-6406675