Scientists identify first potentially effective therapy for human prion disease

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Corinne Lasmézas, Ph.D., The Scripps Research Institute, is a professor at the Florida campus. Credit: The Scripps Research Institute.

Human diseases caused by misfolded proteins known as prions are some of most rare yet terrifying on the planet—incurable with disturbing symptoms that include dementia, personality shifts, hallucinations and coordination problems. The most well-known of these is Creutzfeldt-

Jakob disease, which can be described as the naturally occurring human equivalent of mad cow disease.

Now, scientists from the Florida campus of The Scripps Research Institute (TSRI) have for the first time identified a pair of drugs already approved for human use that show anti-prion activity and, for one of them, great promise in treating these universally fatal disorders.

The study, led by TSRI Professor Corinne Lasmézas and performed in collaboration with TSRI Professor Emeritus Charles Weissmann and Director of Lead Identification Peter Hodder, was published this week online ahead of print by the journal *Proceedings of the National Academy of Sciences*.

The new study used an innovative high-throughput screening technique to uncover compounds that decrease the amount of the normal form of the prion protein (PrP, which becomes distorted by the disease) at the cell surface. The scientists found two compounds that reduced PrP on cell surfaces by approximately 70 percent in the screening and follow up tests.

The two compounds are already marketed as the drugs tacrolimus and astemizole.

Tacrolimus is an immune suppressant widely used in organ transplantation. Tacrolimus could prove problematic as an anti-prion drug, however, because of issues including possible neurotoxicity.

However, astemizole is an antihistamine that has potential for use as an anti-prion drug. While withdrawn voluntarily from the U.S. over-the-counter market in 1999 because of rare cardiac arrhythmias when used in high doses, it has been available in generic form in more than 30 countries and has a well-established safety profile. Astemizole not only

crosses the blood-brain barrier, but works effectively at a relatively low concentration.

Lasmézas noted that astemizole appears to stimulate autophagy, the process by which cells eliminate unwanted components. "Autophagy is involved in several protein misfolding neurodegenerative diseases such as Alzheimer's, Parkinson's and Huntington's diseases," she said. "So future studies on the mode of action of astemizole may uncover potentially new therapeutic targets for prion diseases and similar disorders."

The study noted that eliminating cell surface PrP expression could also be a potentially new approach to treat Alzheimer's disease, which is characterized by the build-up of amyloid β plaque in the brain. PrP is a cell surface receptor for Aβ peptides and helps mediate a number of critical deleterious processes in animal models of the disease.

More information: The first author of the study, "Unique Drug Screening Approach for Prion Diseases Identifies Tacrolimus and Astemizole as Antiprion Agents," is Yervand Eduard Karapetyan of The Scripps Research Institute. www.pnas.org/content/early/201 … /1303510110.abstract

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