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Researchers develop new drug approach that could lead to cures for wide range of diseases

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A team led by a longtime Oregon Health & Science University researcher has demonstrated in mice what could be a revolutionary new technique to cure a wide range of human diseases—from cystic fibrosis to cataracts to Alzheimer's disease—that are caused by "misfolded" protein molecules.

Misfolded protein molecules, caused by gene mutation, are capable of maintaining their function but are misrouted within the cell and can't work normally, thus causing disease. The OHSU team discovered a way to use small molecules that enter cells, fix the misfolded proteins and allow the proteins to move to the correct place and function normally again.

The researchers were led by P. Michael Conn, Ph.D., who was a senior scientist in reproductive sciences and neuroscience at OHSU's Oregon National Primate Research Center and professor of physiology and pharmacology, cell biology and development and obstetrics and gynecology at OHSU for the past 19 years. This month, Conn joined Texas Tech University Health Sciences Center as senior vice president for research and associate provost.

The team's work will be published this week in the early online edition of the *Proceedings of the National Academy of Sciences*. The work was the culmination of 13 years of work on the process by Conn and Jo Ann Janovick, former senior research associate at the ONPRC who is now also at TTUHSC. Richard R. Behringer, Ph.D., from the University of

Texas MD Anderson Cancer Center, M. David Stewart, from the University of Houston, and Douglas Stocco, Ph.D., and Pulak Manna, Ph.D., from the department of biochemistry/microbiology at TTUHSC, also contributed to the work.

Conn and his team perfected the process in mice, curing them of a form of disease that causes males to be unable to father offspring. The identical disease occurs in humans and Conn believes the same concept can work to cure human disease as well.

"The opportunity here is going to be enormous," said Conn, "because so many human diseases are caused by misfolded proteins. The ability of these drugs – called 'pharmacoperones' – to rescue misfolded proteins and return them to normalcy could someday be an underlying cure to a number of diseases. Drugs that act by regulating the trafficking of molecules within cells are a whole new way of thinking about treating disease."

Proteins must fold into three-dimensional shapes in precise ways to do their work within human cells. Before recent discoveries about misfolded proteins, scientists believed that proteins that were inactive were intrinsically non-functional. But work by Conn and others revealed that, when the proteins are misfolded, the cell's "quality control system" misroutes them within the cell and they cease to function only because of that misrouting. Pharmacoperones can fix misfolded proteins and thus make them functional again.

Scientists had in recent years observed this process in cells under a microscope. The work of Conn's team is the first time the process has worked in a living laboratory animal.

"These findings show how valuable laboratory animals are in identifying new treatments for human disease," said Conn. "We expect that these

studies will change the way drug companies look for drugs, since current screening procedures would have missed many useful pharmacoperone drugs."

A wide range of diseases are caused by an accumulation of misfolded proteins. Among the diseases are neurodegenerative diseases like Alzheimer's disease, Parkinson's disease and Huntington's disease. Other diseases include certain types of diabetes, inherited cataracts and cystic fibrosis.

Conn said the next steps will be clinical trials to see whether the same technique can work in humans.

More information: Restoration of testis function in hypogonadotropic hypogonadal mice harboring a misfolded GnRHR mutant by pharmacoperone drug therapy, www.pnas.org/cgi/doi/10.1073/pnas.1315194110

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