

UC Davis researchers receive prestigious stimulus grant for stem-cell research on FXTAS

UC Davis researchers are among a handful of scientists nationwide to receive a highly coveted challenge grant from the National Institutes of Health, funded by the American Recovery and Reinvestment Act. The award is one of only 200 selected from among 22,000 challenge grant applications.

The research is being led by Paul Hagerman, a professor in the Department of Biochemistry and Molecular Medicine in the School of Medicine at UC Davis and the director of the UC Davis Neurotherapeutics Research Institute.

The two-year, \$787,300 grant allows Hagerman and his team to use stem cell technology to examine the disease mechanism in a neurodegenerative condition called fragile X-associated tremor/ataxia syndrome, or FXTAS. He anticipates the project will provide insights into other brain disorders, such as Parkinson's and Alzheimer's diseases.

The study uses induced pluripotent stem cells (iPSC), a type of stem cell typically derived from adult somatic cells by the temporary expression of certain genes that have the ability to become almost any cell in the body.

“Induced pluripotent stem cell technology is very new and not a lot of people have actually used it to address fundamental questions in neurodegeneration,” said Hagerman, who is also affiliated with the UC Davis MIND Institute. “So, we’re proposing to set up a model for neurodegeneration with FXTAS that we think can be a model for other neurodegenerative disease.

“In this study we will take skin cells, or fibroblasts, from patients with FXTAS and individuals who have the condition and induce them to become neurons that will develop the cellular features of FXTAS. We then will have in culture the cell type that has gone wrong in disease,” Hagerman said.

Joining Hagerman in the project are Jan Nolta, the director of the UC Davis Stem Cell Program, who will transform the skin cells into neuronal cells, and Isaac Pessah, a UC Davis professor of molecular biosciences, who will explore ways of converting the cells into active neurons. Pessah and Hagerman will then work together to study the cellular and molecular abnormalities.

“This funding is incredibly exciting on many levels,” Nolta said. “The development of iPSC technology allows scientists to examine for the first time large numbers of neurons that have been developed from a particular patient. This is a cutting-edge project can lead us to cures for debilitating neurodevelopmental and neurodegenerative diseases.”

FXTAS is an age-related disorder that is associated with debilitating balance problems, tremors and dementia in older adults. It was co-discovered in 2001 by Hagerman and Randi Hagerman, who is the medical director of the UC Davis MIND Institute.

"Never before have we been in a position to study neuronal development with cells derived from patients who already have been clinically evaluated in detail," said Pessah, who is also the

director of the UC Davis Children's Center for Environmental Health and Disease Prevention and a MIND Institute researcher.

"It's like sending the patient's cells back in developmental time and asking them to reveal where and how they went astray, and how best to intervene to put them back on track."

FXTAS is the result of a small mutation on the X chromosome — also called a premutation — in the same gene that causes fragile X syndrome, the most common cause of inherited mental impairment and the leading single-gene cause of autism in children. Prior to its discovery, FXTAS was often misdiagnosed as Alzheimer's disease, Parkinson's disease or the rarer Charcot-Marie-Tooth syndrome. Hagerman said that the skin cells from individuals with FXTAS will be provided by patients being treated by Randi Hagerman.

Paul Hagerman said that the study of the FXTAS mechanism could lead to insights into the origins of Alzheimer's, Parkinson's and Huntington's diseases, because the underlying mechanisms of these disorders are similar.

"With neurodegenerative diseases, one of the issues is to identify what causes them. With most cases of Alzheimer's disease and Parkinson's disease, we don't know what causes them. That presents a real challenge in trying to develop a treatment or cure. With FXTAS, we know exactly what causes it (an abnormal RNA from the fragile X gene), so that we can study the cellular abnormalities and the clinical problems," Hagerman said.

The ultimate goal of the research is to seek treatments and cures for people with FXTAS and, potentially, other types of neurodegenerative and neurodevelopmental disorders, including autism, on which the Pessah group focuses, and Huntington's disease, on which the Nolte laboratory works, in addition to Parkinson's disease, Alzheimer's and others.

"What we hope to get out of this is one or more therapeutic approaches that would then move us downstream to start looking at clinical efficacy. This is a stepping stone," Hagerman said. "Our ultimate goal is treatment."

The UC Davis M.I.N.D. Institute, in Sacramento, Calif., was founded in 1998 as a unique interdisciplinary research center where parents, community leaders, researchers, clinicians and volunteers collaborate to study and treat autism and other neurodevelopmental disorders. More information about the institute is available on the Web at <http://www.ucdmc.ucdavis.edu/mindinstitute>