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\$21.8 Million NIH Grant for Fragile X Research

Five-year study to focus on most common cause of inherited mental impairment and Parkinson-like syndrome

September 6—A team of researchers at the University of California, Davis, School of Medicine and the M.I.N.D. Institute, in collaboration with four allied institutions, has been awarded a five-year, \$21.8 million Interdisciplinary Research Consortium grant from the National Institutes of Health, the largest single federal award to date in support of research related to the Fragile X (*FMR1*) gene. Paul Hagerman, MD, PhD, is the principal investigator of the consortium, with Randi Hagerman, MD, and Cameron Carter, MD, the co-principal investigators. The Hagerman team has long been supported in Fragile X research by The National Fragile X Foundation (NFXF), whose funding of earlier research projects proved critical in setting the stage for the NIH award.

The award will support a broad interdisciplinary effort studying the mutation of the *FMR1* gene responsible for fragile X-associated tremor/ataxia syndrome (FXTAS) and fragile X syndrome (FXS). It will help develop targeted treatments for FXTAS, a neurodegenerative disorder, its closely related conditions of Alzheimer's and Parkinson's disease, and for FXS, a neurodevelopmental disorder. The award will result in the creation of the NeuroTherapeutics Research Institute (NTRI) at UC Davis.

According to Paul Hagerman, "Fundamental research on neuronal function in both human and mouse cultured cells, as well as work in whole animals, will expand our knowledge of the processes that underlie both fragile X syndrome and FXTAS. This research should inform our treatments for both disorders, providing a nice economy of scale."

FXTAS is one of the most common late-onset, neurodegenerative disorders known to be associated with a single gene. Its core features include progressive tremor and difficulty with balance and walking, with associated features of memory loss and dementia, parkinsonism, and peripheral neuropathy.

FXS is the leading heritable form of intellectual disability and the neurodevelopmental problems related to both full mutation and premutation forms of the *fragile X* gene. The full mutation is responsible for FXS and is the leading known single-gene cause of autism. The smaller, premutation form of the gene is the leading known cause of fragile X-associated premature ovarian failure (POF) in adult women, and can also cause ADHD and autism spectrum disorders.

The award is of particular importance to the NFXF and the families it serves. Besides the foundation's pilot funding of the Hagerman team's research, it is also impacted in the following ways:

- The award adds to the hope of families touched by FXS, POF, and FXTAS, and confirms that the pace of research is accelerating. It also demonstrates the power of donations to organizations like the NFXF, which fund pilot studies of scientists such as the Hagermans.
- NFXF parent advocates played a critical role in securing the Congressional directives which resulted in funding this consortium grant.
- The award advances the mission of the NFXF in providing a significant boost for research across the family of Fragile X-related disorders (FXS/autism, FXTAS, POF).

According to Paul Hagerman, “The National Fragile X Foundation has been the most powerful voice for a broad approach to Fragile X research, which is so critical if we are to develop integrated treatments for children with fragile X syndrome—and their grandfathers.”

Several aspects of the consortium research will involve both molecular/cellular and animal models for the developmental problems that accompany both the premutation and full mutation of the Fragile X gene. Thus, it is hoped that treatments for FXTAS, Alzheimer’s and Parkinson’s disease, FXS and autism may flow from the consortium’s work.

While the hub of the consortium is at UC Davis, the group includes investigators at Erasmus Medical Center, Rotterdam, the Netherlands; the University of Washington, Seattle; the University of Colorado Health Sciences Center, Denver; and Scripps Research Institute, Florida. All research sites will share the common objectives of developing therapeutic interventions and quantitative means for assessing their efficacy.

The award underscores the growing commitment at the NIH to disorders related to the Fragile X gene. The current award will be administered across four institutes: the National Center for Research Resources (NCRR), the National Institute on Aging (NIA), the National Institute of Neurological Disorders and Stroke (NINDS), and the National Institute on Drug Abuse (NIDA).

The research projects will use state-of-the-art measures to both assess features of the clinical presentation of FXTAS and to study FXS. The development of novel transgenic mouse models to evaluate candidate therapeutic drugs and the potential for reversing the neurodegenerative process will be a particular focus of the consortium.

A postdoctoral training component will enhance the power of the consortium through education of postdoctoral trainees in translational (bench-to-bedside) research. The experience provided to the postdoctoral scholars will be a unique opportunity to advance translational research in the broader Fragile X field, thereby creating a new generation of talented Fragile X researchers.

A unique feature of the consortium is its *Community Advisory Board (CAB)*. This board will connect the consortium to those who stand to benefit from its efforts. “Families affected by one of the Fragile X-related disorders provide the most powerful motivating force for translational research,” says Robert Miller, a CAB member and executive director of the NFXF. “They deserve to have both a voice in support of research efforts, and a means of monitoring progress. The CAB will serve both functions.”

Of the eight CAB members, four—Jeffrey and Arlene Cohen, Stephanie Jacob, and John Harrigan—are parents of children with fragile X syndrome, and have been members of The National Fragile X Foundation Board of Directors. The CAB and the NFXF will thus provide a powerful link between the Fragile X community and the consortium.

To learn more about all three Fragile X conditions, visit www.FragileX.org.