"Development of Structural Neurobiology and Genomics Programs in the Neurogenetic Institute"
Principal Investigator: Brian E. Henderson, M.D.

The purpose of the DOE equipment-only grant was to purchase instrumentation in support of structural biology and genomics core facilities in the Zilkha Neurogenetic Institute (ZNI). The ZNI, a new laboratory facility (125,000 GSF) and a center of excellence at the Keck School of Medicine of USC, was opened in 2003. The goal of the ZNI is to recruit upwards of 30 new faculty investigators engaged in interdisciplinary research programs that will add breadth and depth to existing school strengths in neuroscience, epidemiology and genetics. For the duration of the grant project period, and continuing to the present day, recruitment at the ZNI has been highly successful. Ten new neuroscience faculty have joined the ZNI since 2003, with an additional recruit joining the faculty by January 1, 2007. The ZNI will continue to search for quality faculty investigators over the next five year period, or until such time as the laboratory facility is fully occupied.

A key component to the success of the ZNI recruitment efforts is the availability of myriad core laboratory facilities that support various faculty investigators' research programs. Two such core laboratories are the structural biology and genomics core facilities, and for which the DOE provided resources to purchase equipment.

Structural Biology. The structural biology facility will house equipment necessary to determine three-dimensional structure of proteins and nucleic acid and will aid in understanding structure-function relationships. The structural biology group will focus on the elucidation of structural and molecular mechanisms in neurodegenerative diseases, and in particular, to attempt to uncover the molecular mechanisms by which protein deposits form in diseases such as Alzheimer's and Parkinson's.

The DOE grant purchased the following equipment in support of the structural biology core facility:

Bruker Biospin: Elexsys Spectrometer (partial)

This new technology allows the analysis of spin labeled proteins using pulsed EPR spectroscopy. This technology allows significant improvements over the conventional continuous wave EPR spectroscopy. One of the main improvements is the ability to measure long-range distances using DEER or multi quantum coherence measurements. These methodologies extend the sensitivity from 25 Å (conventional continuous wave methodology) to 70 Å. One of the main drawbacks of distance measurements using conventional methods has been the fact that only close distances could be measured. Thus, it often required a good first guess to be able to place two probes in close proximity. Many experiments in which probes were not close enough have been uninformative. In addition, it has been very difficult to obtain long-range distance constraints to refine the structures of multi-domain proteins using conventional methods. Another significant new advance lies in the fact that multiple distances can be

measured at the same time. This feature is particularly important in large molecular complexes such as the protein aggregates that form in diseases such as Parkinson's and Alzheimer's disease. In these diseases, multiple identical subunits come together to form toxic assemblies giving rise to multiple distances. In addition to these applications, the use of pulsed EPR has also some more general applications since different relaxation times (T1 and T2) can be measured directly. This feature should be useful structural analysis of all proteins, but membrane proteins in particular.

Genomics. The genomics facility is being developed to provide large-scale sequencing and genotyping for research groups in the ZNI, to other USC research programs, and to the broader scientific community. Scientists throughout USC who are working on defining candidate genes of inherited neurological diseases, as well as those who are examining regions of natural variation that occur among the genomes of diseased compared to non-diseased populations, will continue to utilize this core facility.

The DOE grant purchased the following equipment in support of the genomics core facility:

Applied Biosystems: Geneamp PCR System 9700
Applied Biosystems: DNA Analyzer
Illumina, Inc.: Beadarray Genotyping System (partial)

This system is a production SNP genotyping system that includes automation equipment (including two Tecan Genesis workstations), LIMS, BeadArray Readers, BeadStudio data analysis software, hardware and accessories for the generation of millions of genotypes per day. In addition to genotyping, the Illumina BeadLab platform has chemistry solutions for the analysis of DNA methylation (96 samples by 1536 sites), gene expression profiling (6 samples by ~48,000 genes), and analysis of DNA copy number changes and Loss of Heterozygosity (LOH, 1 sample by 550,000 genomic loci). The genomics core has been operating near 100% capacity for the past four months with interdisciplinary projects planned that will keep the capacity at 100% for at least 1.5 years. In the next year we will complete a total of 17 interdisciplinary projects with charges totaling over $2M. In addition, within the last year USC has been awarded three federal grants that make extensive use of this core and indeed, may not have been funded without the presence and expertise of the genomics facility.