THE HARTWELL FOUNDATION

2011 Individual Biomedical Research Award

Review of Proposed Research

Investigator: **Frederic L. Chedin, Ph.D.**
Associate Professor
Department of Molecular and Cellular Biology

Institution: **University of California, Davis**

Proposal: **Genetic and Epigenetic Abnormalities in Childhood Auto-immune Disease: Role of DNA Methylation and Excessive R-loop Formation**

Human genes retain the ability to express themselves despite the fact that most of the human genome is regulated under heavy silencing ("switched off"). Silencing is linked to a mechanism that does not occur through genetic alteration of DNA, but through chemical modification of DNA referred to as an epigenetic perturbation. These modifications are known to be critical for both proper gene regulation and chromosome stability. The epigenetic silencing is thought to have evolved in response to the presence of the "junk" DNA that comprises at least half of our genome, which does not code for genes but represents a clear threat to our cells if it becomes expressed. Frederic proposes that subtle defects in epigenetic modification of DNA can result in its accumulation in the circulation, which can give rise to autoimmune disease (when the body attacks its own cells). More than 80 autoimmune diseases have been described, impacting about 10 percent of the US population, including 1 in 10,000 children. The most common pediatric manifestation of autoimmunity is early onset Systemic Lupus Erythematosus (SLE), a disease characterized by severe multi-organ adverse effects. SLE is a lifelong, incurable condition and children with SLE have only limited treatment options: most prescribed drugs are only moderately effective and have not changed in decades. This lack of effective therapy is primarily due to the fact that the molecular pathways underlying the autoimmune reaction are not understood. To address this unmet need, Frederick proposes exploit a unique childhood disease to piece together the molecular pathways that underlie the cause of SLE and provide a framework for new therapeutic efforts aimed at correcting the faulty steps. His research is based upon his innovative idea that explains how genes manage to remain turned on when most of our genome is switched off. He will test his hypothesis by focusing on Aicardi-Goutières syndrome (AGS), a severe autoimmune disorder and mimic of early onset SLE that is genetically well characterized, affects children in early infancy and in the majority of cases leads to premature death by age 10-15. Understanding the biological mechanisms that underlie AGS will generate critical insights into how the innate immune system can be triggered to recognize self-DNA. If Frederic is successful, the development of diagnostic assays and model systems suitable for screening drug therapies for AGS will lead to novel therapeutic interventions for children affected with early onset SLE and related autoimmune diseases.