

## **The National Institute of Environmental Health Sciences: Mouse Models To Study DNA Repair Following Environmental Exposures**

*The objective of this NIH supported project is to develop mouse models containing human genes. The mice are used to study the ability of cells to repair DNA damage in response to environmental exposures. DNA repair is a major component in diseases influenced by aging such as cancer.*

### **Lead Agency:**

The National Institute of Environmental Health Sciences (NIEHS)/  
National Institutes of Health (NIH)

### **Agency Mission:**

The mission of the NIEHS is to reduce the burden of human illness and disability by understanding how the environment influences the development and progression of human disease.

### **Principal Investigator:**

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### **Partner Agency:**

Fred Hutchinson Cancer Research Center

### **General Description:**

#### **Mouse Models To Study DNA Repair Following Environmental Exposures**

DNA repair is a major component in diseases influenced by aging such as cancer. The overall objective of this NIH supported project is to develop mouse models for studying the biological function of environmentally sensitive DNA repair/cell cycle control gene variants found in the human population. The capacity for DNA repair is a major influence in the sensitivity to carcinogenic stimuli, so genetic variants must be considered in risk assessment. The concept that common variants in the population contribute to genetic risk for common diseases has triggered intense interest in identifying DNA sequence variants known as single nucleotide polymorphisms (SNPs). However, the functional significance of SNP variants in relation to environmental carcinogens is largely unknown. This study is designed to establish a genetically engineered mouse system as a mammalian model for human functional genomics and SNP variant-environment interactions. The development of these mouse models will mirror specific human, environmentally responsive polymorphic gene variants found in the general

population, and provide a biological system for understanding the functional significance of these polymorphic variants.

***Excellence:*** What makes this project exceptional?

Mitochondria are organelles found in most cells that are responsible for chemical energy production. They are involved in a range of processes including cellular signaling, differentiation, cell cycle control, growth, and death. Mitochondria dysfunction has been implicated in several human disorders including neurological diseases, cardiac dysfunction, cancer, diabetes, and may play a role in the aging process.

Results from this research project contradict a widely-believed theory that mitochondrial mutations drive the aging process. In the study, mice with mitochondrial mutations 500 times higher than normal levels did not show signs of premature aging.

***Significance:*** How is this research relevant to older persons, populations and/or an aging society?

As organisms age, some cellular processes are perturbed and don't work as well as they do in younger organisms. Previous research led to the theory that accumulated mitochondrial mutations throughout life eventually cause the decline in tissue functioning associated with aging. However, this research shows that transgenic mice engineered to have a high degree of mitochondrial mutation age the same as normal mice.

***Effectiveness:*** What is the impact and/or application of this research to older persons?

This basic research may have future impacts on the prevention or treatment of diseases in aging populations. It provides knowledge on what is considered normal for cells in aging organisms.

***Innovativeness:*** Why is this research exciting or newsworthy?

This research opens new pathways for discovery in the aging process and questions what was previously accepted as normal. It could be the first step in developing new preventive methods or drugs and interventions that could stop or reverse declines in cellular function as an organism ages.