



Medical Education and Research Grant Outcome Report

Name: Mechanisms of CREB regulation and function in response to DNA damage

Principal Investigator: Randal S. Tibbetts, PhD

Phone/Email: 608-262-0332/rstibbetts@wisc.edu

Department: Pharmacology

Program: New Investigator Program

Grant Duration: 02-01-2006 to 1-31-09 (36 months)

Expenditures: \$100,000 (100%)

Use of Funds (Taxonomy): Basic Research

Research Keywords: neurodegeneration, cancer, ataxia-telangiectasia, genomic instability, phosphorylation

► **Description:** Genomic instability resulting from unrepaired DNA damage is a root cause of human cancer development. The ATM gene plays a critical role in suppressing genomic instability. This project studied ATM function with the aim of yielding new insights into how cells respond to DNA damage and how cancer arises.

► **Contributions/Results:** The goal of the project was to test whether ATM controls the DNA damage response by regulating a crucial transcription factor CREB, which modulates gene expression. The first experimental aim of the project was to compare gene expression profiles between mouse embryo fibroblasts (MEFs) that contain wild type CREB versus MEFs that express a mutant CREB gene that is not recognized by ATM. An analysis of gene expression changes in CREB targets, however, yielded no significant expression differences between the cell lines.

The investigators also fulfilled their second aim, generating a mouse strain with a CREB mutant knock-in gene that produces a CREB protein that is not recognized by ATM. Experiments using this system are deemed the most important aspect of the study and are underway. The mice can mature and reproduce, but may be abnormally resistant to DNA damage. Completion of this project will allow the investigators to test whether deregulation of the CREB pathway contributes to neurodegeneration and other phenotypes associated human A-T.

These studies defined an elaborate mechanism of CREB regulation by DNA damage. This may be

translated into a deeper understanding of cancer mechanisms and neurodegeneration. Unexpected findings pertaining to the phosphorylation of CREB in the absence of DNA damage may have broader implications for understanding how human cells interpret DNA damage in the context of other extracellular signals.

► **Met Objectives:** Project completed.

► **Timeline for Application of Results:** Unknown

► **New Partnerships or Collaborations:** The investigators collaborated with Dr. Jay Chung of the National Institutes of Health to explore possible metabolic disease in CREB S111A/S111A mice.

► **Matched Dollars (cash or in-kind):** None

► **Dissemination:**

- Publications: *Journal of Biological Chemistry* (two publications); *Biochemistry and Molecular Biology Reports*

► **Additional Funding:** Using the preliminary data from this project, Tibbetts has obtained a National Institutes of Health R01 grant to continue this work (R01 CA 124722-01; 12/01/07-11/30/11; \$760,000 total award)