

**Mala Chakraborty, Ph.D.**  
**Staff Scientist**  
**Molecular and Cellular Toxicology Section**  
**Immunology Center, NHLBI, NIH**  
[chakrabi@nhlbi.nih.gov](mailto:chakrabi@nhlbi.nih.gov)



### **Biosketch**

2008 - 2015 **Staff scientist**, Molecular and Cellular Toxicology Section, Immunology Center, NHLBI, NIH, Bethesda, MD  
2002 - 2008 **Research Fellow**, Laboratory of Tumor Immunology and Biology, NCI, NIH, Bethesda, MD  
1999- 2001 **Post doctoral Fellow**, Radiation Medicine, University of Kentucky, Lexington, KY  
1994- 1999 **Pre-doctoral Fellow**, Markey Cancer Center, University of Kentucky, Lexington, KY

### **Brief Summary of Overall Research Experience**

1. Developed methods to increase the efficacy of immunotherapeutic vaccines using low dose of radiation.
2. Elucidated the role of CTLA-4 antibody in combination with vaccine in tumor therapy and toxicological study after treatment.
3. Studied the role of immune tolerance in the development of idiosyncratic Drug-Induced Liver Injury (DILI) in a murine model using Halothane, an inhalation anesthetic that causes allergic hepatitis in humans.

### **Abstract: Allergic DILI from Suppression of Myeloid Cells**

Clinical evidence suggests that many cases of serious idiosyncratic drug-induced liver injury are mediated by the adaptive immune system in response to hepatic drug-protein adducts, also referred to as “drug-induced allergic hepatitis”; but detailed mechanistic proof has remained elusive due to the lack of animal models. We have hypothesized that drug-induced allergic hepatitis is as rare in animals as it is in humans due at least in part to the tolerogenic nature of the liver. We provide evidence that immune tolerance can be overcome in a murine model of halothane-induced liver injury initiated by trifluoroacetylated protein adducts of halothane formed in the liver. Twenty-four hours after female Balb/cJ mice were initially treated with halothane, perivenous necrosis and an infiltration of CD11b<sup>+</sup>Gr1<sup>high</sup> cells were observed in the liver. Further study revealed a subpopulation of myeloid-derived suppressor cells within the CD11b<sup>+</sup>Gr1<sup>high</sup> cell fraction that inhibited the proliferation of both CD4<sup>+</sup> and CD8<sup>+</sup> T cells. When CD11b<sup>+</sup>Gr1<sup>high</sup> cells were depleted from the liver with Gr-1 antibody treatment, enhanced liver injury was observed at 9 days after halothane rechallenge. Toxicity was associated with increased serum levels of interleukin-4 and immunoglobulins G1 and E directed against hepatic trifluoroacetylated protein adducts, as well as increased hepatic infiltration of eosinophils and CD4<sup>+</sup> T cells, all features of an allergic reaction. When hepatic CD4<sup>+</sup> T cells were depleted 5 days after halothane rechallenge, trifluoroacetylated protein adduct-specific serum immunoglobulin and hepatotoxicity were reduced. Our data provide a rational approach for developing animal models of drug-induced allergic hepatitis mediated by the adaptive immune system and suggest that impaired liver tolerance may predispose patients to this disease.