STUDY AND CHARACTERIZATION OF XENOESTROGEN EFFECTS ON T-CELL MEDIATED IMMUNITY

Kenneth Ndebele¹, Robert McMurray² Barbara Graham¹ and Paul B. Tchounwou¹

¹Molecular Toxicology Research Laboratory, NIH-Center for Environmental Health, College of Science, Engineering and Technology, Jackson State University, 1400 Lynch Street, P.O. Box 18540, Jackson, Mississippi, USA.
²University of Mississippi Medical Center Department of Rheumatology 2500 North State Street Jackson MS 39206, USA

Abstract: Endogenous estrogens and androgens contribute to the sexual dichotomy of immune responses and the female preponderance of autoimmune diseases such as systemic lupus erythematosus (SLE), multiple sclerosis (MS), and rheumatoid arthritis (RA). Several environmental, hormonally active endocrine-disrupting compounds exist, are superimposed upon the endogenous pituitary-gonadal axis, and may contribute to the incidence or development of immune disease. Xenoestrogenic compounds such as coumestrol (a phytoestrogen), bisphenol A (BPA – a plastic monomer), and o, p’-dichlorodiphenyltrichloroethane (DDT – an organochlorine) are representative environmental endocrine disrupters from different categories that can be classified as xenoestrogens and are known to have some immunoenocrine actions. Investigation of xenoestrogen immunomodulation may be critical to understanding potential low dose adverse/no adverse effects on development of immune or autoimmune disorders, resistance to infection, cancer immune surveillance, or cell cycle/cell survival abnormalities that could lead to lymphoid malignancies. In this application, we propose to further develop and characterize in vitro immunobiological systems for studying the nature of the dose and exposure time relationship to low dose adverse effects on T-cell mediated immunity. We hypothesize that xenoestrogens suppress lymphoproliferation and increase lymphocyte apoptosis through suppression of bcl-2 and cyclin A and stimulation of p53; suppress IL-2 and stimulate IL-4 or IL-10 through effects on nuclear transcription. The overall goal of this proposal is to characterize the effects and delineate xenoestrogen mechanisms of action on T lymphocyte immune responses. Its specific aims are: (i) To characterize the effects of xenoestrogens on cell cycle regulatory and survival proteins (bcl-2, p53, p21, and cyclin D and A) in T cell lines and peripheral blood lymphocytes (PBLs) as associated with proliferative and cell cycle transition abnormalities; (ii) To examine the effects of xenoestrogens on CD4+ and CD8+ T lymphokine production and CD4+ IL-2 transcriptional regulatory mechanisms; and Completion of these specific aims will elucidate several potential effects of environmental immunoenocrine disrupters that may have roles in the pathogenesis of human immune or autoimmune disease.

Keywords: Xenoestrogen, Cell Cycle, Apoptosis,

Acknowledgements: This research supported by a grant from the National Institutes of Health (Grant N0.1G12RR13459), through the NCRR-RCMI Center for Environmental Health at Jackson State University (JSU).