CONCEPT REVIEW

Contract Title: **Potential for Environmental and Therapeutic Agents to Induce Immunotoxicity**

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Objective: To continue to screen environmental agents, therapeutic drugs and biological materials for their potential immunomodulatory effects.

The importance of immune parameters as a potential target for toxicant-induced injury was brought to the forefront through the investigations in previous contracts and these studies have significantly contributed to the risk assessment process. Effects on the immune system will be assessed using a defined and validated panel in rodent models. For most immunotoxic therapeutics, rodent data on immunotoxicity and comparability of doses have been generally predictive of what was later observed in the clinic. Statistical analyses of the database generated from previous contracts have provided models for the relationship between alterations in immune function and resistance to infectious disease and neoplasia. These studies will: (1) improve our ability to predict the types of environmental agents that could affect the human immune system and their potential impact on human disease; (2) provide relevant and quantitative data that can be used in risk assessment and regulatory processes; and (3) increase our basic understanding of immune-mediated disease.

Concept Statement

Chemicals will be examined for their ability to induce hypersensitivity responses (allergic contact dermatitis), immunosuppression, and/or initiate or potentiate autoimmune disease. A tiered panel (Luster et al., 1988) will be employed to identify agents that may produce immunosuppression and include measures of general toxicity, hematology, immunopathology, cell- and humoral-mediated immune function, immune cell phenotyping. Chemicals that are positive in an initial screen will be assessed for their ability to alter resistance to disease or neoplasia in models specific for the altered immune parameter. Hypersensitivity testing will be conducted in mice using the local lymph node assay (LLNA: ICCVAM, 1999) and the mouse ear-swelling test (MEST: Gad et al., 1986). Immune cell phenotyping in the draining lymph node and assessment of antigen-specific IgEs will be performed for chemicals positive in the MEST or LLNA. In addition, selected environmental agents will be examined for their ability to initiate or exacerbate autoimmune disease. Rodent models of chemical-induction, genetic predisposition and immunization with self-antigens will be used. The research and development component of this contract will focus on specific mechanisms and cellular targets of chemicals that induce immunsuppression or hypersensitivity, improving the sensitivity of disease resistance models and the validation of biological endpoints for the detection of autoimmune disease.

Changes in Statement of Work

The revised statement of work includes a new task to assess the effects of test articles on the developing immune system. These studies will contribute information on the effects and persistence of immunomodulation associated with perinatal exposure to chemical or therapeutic agents. In addition, the contract laboratory will routinely collect tissues for immunotoxicogenomic studies so that changes in gene expression in the spleen and thymus can be directly correlated with alterations in functional immune tests.

References

Gad, S.C., Dunn, B.J., Dobbs, D.W., Reilly, C., and Walsh, R.D.: Development and validation of an alternative dermal sensitization test: the mouse ear swelling test (MEST). Toxicol. Appl. Pharmacol. 84:93-114, 1986.

ICCVAM (Interagency Coordinating Committee on the Validation of Alternative Methods). The murine local lymph node assay: A test method for assessing the allergic contact dermatitis potential of chemicals/compounds. NIH Publication No. 99-4494, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina, 1999.

Luster, M.I., Munson, A.E., Thomas, P., Holsapple, M.P., Fenters, J., White, K., Lauer, L.D., and Dean, J.H.: Development of a testing battery to assess chemical-induced immunotoxicity. Fund. Appl. Toxicol. 10:2-19, 1988.