

Immunotoxicology

The U.S. Food and Drug Administration requires that companies assess a new drug's potential for adverse effects on the immune system. There are five major areas of immunotoxicology defined by the FDA guidelines (1):

- Immunosuppression
- Immunogenicity
- Hypersensitivity/Allergy
- Autoimmunity
- Adverse Immunostimulation

IBT Reference Lab is a research-based, clinical lab that has been providing specialized immunology services to the pharmaceutical and biotech industry since 1983. The lab has experience developing custom assays for a variety of protein therapeutics, including monoclonal antibodies, chemically modified proteins and recombinant proteins. In addition, the lab has experience with special specimens, including BAL, blood, urine and sputum.

Immunosuppression: Immunosuppression can occur as an unintended consequence of drug administration. Experimental approaches to assess immunosuppression include:

- Quantifying specific and total IgG, IgM, IgA
- T&B Cell Enumeration
- T Cell Function Testing
- Antibody Response to Vaccines
- Response to Mitogens (e.g. PHA)
- *Ex-vivo* Stimulation of Cytokines

Immunogenicity: The immunogenicity or the ability of a drug to elicit an immune response depends on a variety of factors, including the route of administration, the characteristics of the drug, its size and the protein or peptide structure. Both humoral and cellular immune responses can be evaluated. Drug immunogenicity is a concern for an IND for two reasons:

- The immune response can affect drug activity or metabolism
- The induction of clinically significant allergic responses

Hypersensitivity/Allergy: Hypersensitivity reactions involving IgE (Type I) are of concern because these reactions have the potential to be life-threatening. Antibody-mediated reactions with IgG or IgM (Type II and III) are also possible and the presence of drug-specific Igs are commonly assessed by custom ELISA (2). In some cases, the adverse reactions may be mediated by activated T-cells (Type IV). These T-cell hypersensitivities can be evaluated by *Ex-vivo* whole blood cytokine stimulation assays (3).

Autoimmunity: It is theoretically possible that drugs can alter the regulation of immune pathways and lead to a breakdown of self and non-self discrimination. Autoimmune responses are assessed by standard clinical immunology test methods.

Adverse Immunostimulation: The chronic non-specific stimulatory effect of a drug can be evaluated by measuring a variety of biomarkers of inflammation (e.g. cytokines, ECP, C3a, etc).

Tests and Technology Platforms Available:

- ABI Real-Time PCR (Gene Expression)
- Luminex (Cytokine Profiles)
- Immulite 2000 (Automated Immunoanalyzer)
- Pharmacia UniCAP1000 Allergy (IgE)
- Fluorescent Microscopy
- Radioimmunoassay
- Microplate Fluorescence Immunoassay
- Cell Culture & Proliferation
- ABI 310 (Gene Sequencing)
- ELISA (Histamine, Leukotriene, C3a)
- Luminometry (PHA Responses)
- Roche LightCycler (SNPs)
- Flow Cytometry (T and B Enumeration)
- Rate Nephelometry (IgG, IgA, IgM)
- ELISPOT
- Vaccine Antibody Responses
- Meso Scale Discovery

Quality systems and licensure: The lab is a fully-licensed clinical laboratory (CLIA). It has a strong commitment to meeting the quality standard (GCP, GLP) required for the conduct of laboratory investigations supporting pharmaceutical research and clinical trials.

References:

- (1) Guidance for Industry: Immunotoxicology Evaluation of Investigational New Drugs, Federal Register Vol. 67 No. 211, 66647 – 66648/2002.
- (2) Recommendations for the design and optimization of immunassays used in the detection of host antibodies against biotechnology products. Mire-Slius AR, et al.
- (3) Langezaal I et al. Whole blood cytokine response as a measure of immunocytotoxicity. *Toxicology in Vitro* 2001;15:313-318.

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