

**CONTROL ID:** 170007

**PRESENTATION TYPE:** Workshop

**Secondary Pres Type - Proposal:**

**IAT/ITS Designation:**

**TITLE:**

Immunotoxicity Evaluation by Immune Function Tests

**ABSTRACT BODY:**

Increased expectations from a number of regulatory agencies, e.g., EPA, FDA, EMEA, and MHLW, (as summarized in ICHS8), for evaluation of potential adverse effects on the immune system, have led to the wide spread use of the T-cell dependent antibody response (TDAR) as a main functional test of immunotoxicity. While identifying immunotoxic potential is pertinent to both chemical and pharmaceutical industry, the use of the immunotoxicology data for risk assessment and/or hazard identification in each case is different, and there are multiple approaches to the testing. The assays that evaluate TDAR function include both well-established tests, e.g., anti-sheep red blood cell Plaque Forming Assay (PFA), and newer models, e.g., anti-keyhole limpet hemocyanin (KLH) antibody ELISA. These tests vary in the study design, antigen application and analytical methods. However, they all evaluate the same endpoint - a competent immune response to a neo-antigen.

The purpose of this workshop is to bring together experts to discuss the use of TDAR tests in evaluation of the immunotoxicity potential. Numerous issues have been identified, including high animal to animal variability; differences in antigen source and potency; a lack of established "normal range" of the immune response and uncertainty about degree of inhibition of TDAR to be considered toxicologically important. The workshop will seek to build a consensus on the implications of these factors on using TDAR results in risk assessment and/or hazard identification, and criteria to classify compounds as immunotoxicants. The discussion will also address the question, how the effects seen in non-clinical studies could impact safety assessment of compounds in humans?

**CATEGORY:** Immunotoxicology, Regulatory and Safety Evaluation

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**Member Type:** SOT Member

**Funding:** No SOT funding required

**Presentation Title:** Workshop Introduction

**Presentation Description:** A brief review of latest regulatory expectations and approaches to immunotoxicity testing will highlight the challenges and existing issues in the immunotoxicology testing of compounds. Current regulatory documents emphasize the need for assessment of unintended immunosuppression in development of pharmaceuticals and industrial chemicals and recommend an immune function study, such as the T-cell dependent antibody response (TDAR), be conducted for this purpose. Multiple test systems have been applied in TDAR evaluation, and there is uncertainty whether the various study designs and assays are validated and/or acceptable for use in the regulatory studies. A comparative review of existing data is needed to

improve communication between immunotoxicologists and to increase understanding of the impact of immunotoxicity evaluation on safety of novel compounds.

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**Presentation Title:** No  
**Presentation Description:** Discussion Moderation

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**Funding:** No SOT funding required  
**Presentation Title:** Primary Immune Response To Sheep Red Blood Cells (SRBC) As The Conventional TDAR Test  
**Presentation Description:** The widely used sheep red blood cell (SRBC) plaque forming cell (PFC) assay is considered the "gold standard" for TDAR based on extensive cross laboratory validation in mice. The data from application of SRBC tests using both PFC and ELISA for evaluation of potential immunotoxicity of chemicals in rodents will be discussed.

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**Funding:** SOT funding requested  
**Presentation Title:** Comparison Of Primary Immune Responses To SRBC And KLH In Rodents  
**Presentation Description:** TDAR tests evaluating immune responses to SRBC or KLH have similarities and differences between measured endpoints. Recent data indicate that the sensitizing dose of KLH used in rodents to elicit anti-KLH antibodies differentially affects the responses. Furthermore, within the same species, different strains of mice and rats produce different magnitudes of responses to the same sensitizing dose. This discussion will focus on the sensitivity of plaque assay and the KLH and SRBC ELISA based assays, when compared using several known immunosuppressive agents, including cyclophosphamide, dexamethasone and

azathioprine. The effects on the primary immune response in the B6C3F1 mice and the F344 rat, the primary immunotoxicological rodents used by National Toxicology Program as well as the Sprague Dawley rat and the CD1 mice primary test models used by industry will be addressed.

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**Member Type:** SOT Member

**Funding:** No SOT funding required

**Presentation Title:** Immunotoxicity Testing In Non-Rodent Species

**Presentation Description:** Evaluation of the immunotoxicity potential of some pharmaceuticals, including immunomodulatory chemicals and biologics, cannot be limited to testing in rodents. Thus, immune function tests have also been applied in studies with non-human primates and more recently dogs that assess various components of the immune system. These assays include TDAR responses with various immunogens, natural-killer cell activity, delayed-type hypersensitivity, and macrophage function assays. Approaches for incorporating immune function testing in non-rodent species, results from these tests, and their interpretation with respect to drug safety assessment will be discussed.

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**Member Type:** Non-member

**Funding:** No SOT funding required

**Presentation Title:** TDAR Tests: Meta-Analysis Of Results Generated Across Multiple Laboratories

**Presentation Description:** While a wealth of data have been generated for anti-KLH antibody responses, protocols have not been harmonized among laboratories using the tests. Aiming for a reduction in animal use and expedient application of recent advances in statistical science, the immunotoxicology community, under the leadership of HESI/ILSI Immunotoxicology Technical Committee, has explored non-experimental approaches to the comparative analysis of TDAR data. The outcome of meta-analysis of results from multiple laboratories using either SRBC or KLH as the T-cell dependent antigens will be presented.