



Immunotoxicology Technical Committee (ITC)

HESI Assembly of Members
January 19, 2009



Committee Leadership

Dr. Ellen Evans (Schering-Plough Research Institute), Chair
Dr. Tom Kawabata (Pfizer Inc.), Vice Chair

**Dr. Kimber White, Medical College of Virginia, Scientific
Advisor**

Dr. Hans Merk, University of Aachen, Scientific Advisor

**Dr. Jacques Descotes, Centre Antipoison-Centre de
Pharmacovigilance, Scientific Advisor**

Dr. Raegan O'Lone, Staff

Mr. Eric Moore, Staff



ITC Members

- Abbott
- Amgen, Inc.
- Astra-Zeneca
- Bayer AG
- Boehringer-Ingelheim
- Bristol-Myers Squibb
- Dow Chemical
- DuPont Haskell Labs
- Eli Lilly and Company
- GlaxoSmithKline
- Hoffmann-La Roche
- Johnson & Johnson
- Merck Research Labs
- Novartis Pharma AG
- Pfizer, Inc.
- sanofi aventis
- Schering-Plough Research Institute



ITC Public Sector & Other Participants

- U.S. Environmental Protection Agency (EPA)
- Center for Biologic Evaluation and Research, FDA
- Center for Drug Evaluation and Research, FDA
- European Medicines Agency (EMA)
- Johns Hopkins University
- Lyon Poison Center (France)
- Medical College of Virginia
- Michigan State University
- National Institute for Occupational Safety and Health, Centers for Disease Control
- National Institute of Allergy and Infectious Diseases
- National Institute of Environmental Health Sciences
- National Institute of General Medical Sciences
- Sunnybrook and Women's College Health Science Center (Canada)
- University of Aachen (Germany)
- University of Paris (France)
- University of Pennsylvania
- University of Toronto (Canada)
- Utrecht University (The Netherlands)



ITC Mission

- To identify and address scientific issues related to the development and application of immunotoxicology to public health and human health risk assessment
- To promote the understanding and appropriate use of immunotoxicologic data to protect human health
- To contribute substantively to the scientific decision-making processes relative to the development of guidelines and regulations for immunotoxicologic testing at the local, national, and international levels



ITC Projects: 2008-2009

Immunomodulators

Immunogenicity

Non-human Primates

- Control data evaluation (immunophenotyping and TDAR)
- Workshop – infections

Canine Immunotoxicity Testing

Immune Function Monitoring in Clinical Trials

Developmental Immunotoxicity



2008 ITC Activities at/near Completion

Project focus	Activities	2008 Committee Efforts	Outcome
Immunogenicity: <i>Risk assessment and application of the EMEA guideline on the immunogenicity of therapeutic proteins</i>	Roundtable session at Fall 2007 Summerschool in Immunotoxicology, Lyon, France	Manuscript in preparation	Submission to peer reviewed press anticipated in 2009
Immunomodulators	Workshop on Immunomodulators and Clinical Immunotoxicology Spring 2007, Washington DC	Manuscript preparation through mid 2008	Workshop proceedings accepted for publication November 2008 in the Journal of Immunotoxicology
Non-human Primates – Control data evaluation	Sponsored retrospective inter-laboratory analysis of immunophenotyping and T-dependent antibody responses (TDAR)	Ongoing statistical analysis	Completion of statistical analysis and manuscript preparation anticipated in 2009



H E S I[®]

NHP Infection Project

Issue: NHP harbor and are exposed to a variety of pathogenic and commensal organisms which may develop into clinical infection during the course of toxicology studies.

This frequently confounds data interpretation, but can also potentially be useful in identifying immunosuppression. There is misinformation and misunderstanding amongst the various scientists involved in NHP research.

Goal: Better understanding of NHP infection from the perspectives of key stakeholders (toxicologists, pathologists, lab animal veterinarians and regulatory scientists) of:

- infectious agents, screening and preventative approaches, and
- how infection may impact interpretation of toxicology studies or be useful in immunomodulation assessment.



NHP Infection Workshop

Approach:

ITC hosted a public workshop “Naturally Occurring Infections in Nonhuman Primates and Immunotoxicity Implications” in Silver Spring, MD in October 2008

- Nearly 60 attendees
- Speakers and discussion panelists from industry, FDA, and academia

Outcome:

A series of manuscripts describing the proceedings is in progress; anticipated submission to a peer reviewed journal in 2Q 2009



Canine Immunotoxicity Testing Project

- Issue:** Dogs are the most commonly used “large animal” species in toxicity testing of small molecules. There is a need to increase the knowledge of the canine immune system as well as availability of reliable reagents and testing methods for immunotoxicity testing in dogs.
- Goal:** Gather more information regarding the extent and nature of immunology and immunotoxicity assessments available in the dog



Canine Immunotoxicity Testing Project

Approach:

- Issued a survey broadly to scientists from the pharmaceutical industry, contract research organizations, academicians, and veterinary clinicians
- Results currently being compiled and under review by Work Group
- The results of this survey will be used to initiate a discussion between representatives of the pharmaceutical industry, academia, and hopefully representatives of the reagent industry aimed at addressing identified gaps



Immune Function Monitoring in Clinical Trials

Issue: Better approaches to assess immune function monitoring in clinical trials are needed (key clinical gaps identified in the 2007 Immunomodulatory Drugs Workshop).

Goals: Increase awareness of clinical immunologists in academia of the opportunities and challenges for the development of immune function monitoring methods for clinical trials.

Enhance collaboration between stakeholders to develop better methods to assess immune function in clinical trials and utilize methods which are already available. This will enhance our ability to more readily assess efficacy and safety in clinical trials.



Immune Function Monitoring in Clinical Trials

Approach (2009):

Co-organization and sponsorship with CIS (Clinical Immunology Society) of a satellite session on Immune Function Monitoring in Clinical Trials at the Annual FOCIS (Federation of Clinical Immunology Societies), San Francisco, CA, June 2009

Session focus:

- The drug development process (non-clinical and clinical) with particular emphasis on immunomodulatory drugs.
- The challenges that industry and investigators face in assessing immune function in clinical trials (intended or unintended). Types of assays needed for the future.
- Practical considerations with the implementation of immune function assays in clinical trials
- The potential use and challenges with vaccine immunization studies to assess immune function
- Challenges in the translation of immune function data in humans to assessing risk for infections



Developmental Immunotoxicology

Issue: Concern that the developing immune systems may be more susceptible than the adult immune system.

- Issue is re-emerging due to the recent need for Pediatric Investigative Plans for drugs being developed
- A position from the pharmaceutical industry on the state-of-the-science and research gaps has not been published.

Goal: Provide input from industry experts on non-clinical developmental immunotoxicity testing. This will be the cornerstone for future discussions with academia and industry regarding focused research in the key gaps.



Developmental Immunotoxicology

Approach:

Develop white paper discussing possible endpoints, study designs, and timing. Manuscript in progress

- A workshop is anticipated for 3Q 2009 to obtain feedback from academic, industry, and regulatory scientists on the draft white paper prior to finalization and submission to peer-reviewed press



Summary – 2009 Planned Activities

Project	Activities/Products Planned in 2009
Non-human Primates: Control data evaluation	Complete analysis; prepare and submit manuscript(s)
Non-human Primates: Workshop (infections)	Prepare and submit proceedings papers
Canine Immunotoxicity Testing	Complete compilation/analysis of data; determine next steps
Immune Function Monitoring in Clinical Trials	Sponsor session at 2009 FOCIS meeting
Developmental Immunotoxicity	Preparation white paper; hold public workshop



Thank you.



Back-up slides



Nonhuman Primate (NHP) Project

Issue: Increased need to understand immunology and immunotoxicology in NHP; responses in standard assays and appropriateness of human reagents not fully characterized

Goal: Understand/characterize immune responses in NHP's to aid in hazard identification/human risk assessment



Nonhuman Primate (NHP) Project

Approach:

- Identify assays used or proposed for use to characterize immune functions in NHP
- Sponsor retrospective inter-laboratory analysis of immunophenotyping and T-dependent antibody responses (TDAR) in nonhuman primates
- Subteam of ITC plus consultant statistician
- Provide perspective on the impact of study design on immunophenotyping results in non-human primates for potential immunotoxicological assessments of pharmaceuticals.
- Publication submission anticipated by year end 2009