Immunotoxicity Technical Committee (ITC)
Founded: 1992

HESI State-of-the-Science Session
January 23, 2007
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

Mr. J. David Sandler, Staff
Mr. Eric Moore, Staff
ITC Members

- 3M Pharmaceuticals*
- Abbott Laboratories
- 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.
- Procter & Gamble
- sanofi-aventis
- Schering-Plough Research Institute
- Syngenta CTL
- Wyeth Research International

*pharmaceutical business recently sold; uncertain if 3M will continue membership
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 (EMEA)
- 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 Committee 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.
Overview of ITC Impact

- Highly productive committee focusing on projects with high impact and relevance
- Publication of position papers as well as proceedings from roundtables and workshops in peer-reviewed journals
- Forum for dialogue between scientists from a variety of disciplines in industry, academia, and health authorities
- Identifying and understanding common scientific issues faced by industry and international government agencies alike
- Characterization of state of science and identification of research gaps, ways to address those gaps
- Financial and intellectual support for research
- Established credibility and relationships with regulatory scientists and academicians
- Robust membership which has expanded since committee was founded
|---------------------------------------------------------|-------------------------------------------------|----------|----------|
## ITC Project History and Accomplishments

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
<th>Leader/Contributor</th>
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<tbody>
<tr>
<td>Jun. 2001</td>
<td>DIT Workshop Leader: Mike Holsapple</td>
<td>Dvlpnt Immunotox &amp; Risk Assmt</td>
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<tr>
<td></td>
<td>(coplanners included EPA Reps); Pub. in Human and Experimental Toxicology (Vol. 21: 473-478, 2002)</td>
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<tr>
<td>Jun. 2001</td>
<td>Provided Comments for USA FDA, CDER’s</td>
<td>Draft Guidance for Industry: Immunotoxicology Evaluation of Investigational New Drugs Comments well received; many incorporated in final guidance document</td>
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## ITC Project History and Accomplishments, contin.

<table>
<thead>
<tr>
<th>Project Area</th>
<th>Year</th>
<th>Leader(s)</th>
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<tbody>
<tr>
<td>Respiratory Hypersensitivity</td>
<td>2003</td>
<td>Danuta Herzyk</td>
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<tr>
<td>T-cell Dependent Antibody Response</td>
<td>2003</td>
<td>Mike Holsapple</td>
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### 2003 TDAR; Leader: Danuta Herzyk

- Respiratory Hypersensitivity roundtable began dialogue on respiratory hypersensitivity of chemicals, proteins, and drugs.

### 2003 TDAR; Leader: Mike Holsapple

- Respiratory Hypersensitivity roundtable began dialogue on respiratory hypersensitivity of chemicals, proteins, and drugs.
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<tr>
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<tr>
<td>Nov. 2003</td>
<td>Workshop Leader: Tom Kawabata</td>
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<tr>
<td>2004</td>
<td>Initiated Nonhuman Primate Project: Jeanine Bussiere</td>
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<td></td>
<td>Goal is to understand immunotoxicology responses in NHP’s to aid in hazard identification/human risk assessment</td>
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<tr>
<td>Oct. 2004</td>
<td>Immunogenicity; Leader: Peter Bugelski</td>
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<td>Workshop Assessing the Potential to Induce Respiratory Hypersensitivity; in Toxicological Sciences (Vol. 91: 4-13, 2006)</td>
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<tr>
<td>Roundtable Discussion: Predictive Power of Preclinical Data for Human Immunogenicity of Large Molecules. Summary report prepared by ITC steering committee and FDA reps; pub. submission expected 3Q07</td>
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### ITC Project History and Accomplishments, contin.

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<td>American College of Veterinary Pathologists (ACVP) pre-meeting workshop: ILSI Seminars on Advanced Pathological Techniques: Immunopathological Techniques</td>
<td>Sub-committee provided input into ICH S8 guidance - many ITC suggestions incorporated into draft and final guidance; entire committee developed ITC responses during comment periods</td>
<td>Gordon Conference on Adverse Drug Reactions</td>
<td>for Dr. Raymond Pieters’ research project (Utrecht University in The Netherlands): Development of an Animal Model to predict Drug-induced Allergy and Autoimmunity by Using the Oral Route of Exposure</td>
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</table>
ITC Project History and Accomplishments, contin.

**Sept. 2005** Leader: Greg Ladics

ITC co-sponsored and co-organized (with EPA, NIOSH, NIEHS, and DuPont) immunotoxicogenomics workshop; pub.: Immunotoxicogenomics: the potential of genomics technology in the immunotoxicity risk assessment process. Toxicological Sciences 94(1): 22-27, 2006

**Feb. 2005** Clin Immunotoxicology; Leaders: Ian Gourley, Patrick Haley, Ellen Evans

Clinical Immunotoxicity testing Roundtable attended by ITC members + clinicians from member companies; intended as precursor to full workshop with regulatory authorities in attendance

**March 2006** Co-sponsored Immunotoxicology Workshop

at SOT Annual meeting Leaders: Danuta Herzyk and Michael Holsapple
Further Discussion of Selected Projects
Respiratory Hypersensitivity

• **Goals**
  - Determine state-of-the-science with respiratory hypersensitivity testing for proteins, chemicals and drugs
  - Identify research gaps

• **Approach**
  - Expert roundtable meeting (2003)
  - 2-day international workshop (2004)

• **Outcomes / Impact**
  - Being used as a starting point for scientific discussions between industry and regulatory agencies
Immune Mediated Drug Hypersensitivity

• **Goals**
  – Determine state-of-the-science of mechanisms and testing methods for IDHR
  – Identify research gaps
  – Strategies for overcoming barriers to IDHR research and addressing key research gaps

• **Approach**
  – Expert task force meetings and workshop

• **Outcomes / Impact**
  – Publications
    • Task Force Report *J. Allergy Clinical Immunol* 109: S461-78, 2002
    • Workshop summary *J. Immunotox* 1: 201-205, 2004
  – Discussions regarding funding initiated with NIH
  – Publications cited in IDHR publications and in research proposals by researchers in academia, government and industry
Popliteal Lymph Node Assay Research Project

• **Goal**
  - Modify PLNA to assess systemic IDHR liability of LMW compounds
    - oral dosing rather than sc footpad administration, which is more relevant for orally administered LMW compounds

• **Approach**
  - Funding of methods development projects in Dr. Raymond Pieters (Utrecht University) lab
    - First Project – 2001-2003, $40K (seed grant)
      - Determine model feasibility
      - Part of larger international project to evaluate LLNA
    - Second Project – 2006-2008, $40K
      - Continue development and validation with additional compounds

• **Outcomes / Impact**
  - First Project - Demonstrated positive responses with oral administration of known allergens (*Tox Sci* 83, 273-281, 2005)
  - Second Project - Ongoing
2004 Pathology Seminar Series

• Issue
  – FDA and ICH guidances place emphasis on standard toxicity study assessment to identify effects on immune system
  – Regulator concern that not all pathologists adequately trained

• Goals
  – Educate and engage pathology community

• Approach
  – ILSI Seminar Series on Advanced Pathologic Techniques: “Applications and Interpretation of Results,” Nov 2004; organized by ITC with participation by STP, ACVP
  – Part of 3-pronged seminar series; others were organized by STP/ACVP with ITC participation
    • STP meeting seminar: “Immunotoxicology for the Toxicologic Pathologist” June
    • ACVP Mini-symposium: “Predicting Drug-Mediated Immune Responses – A Need for Reciprocal Research” November

• Outcomes / Impact
  – Numerous follow-up seminars including ASVCP immunotox seminar, greater focus on immunotox by ACVP, STP; STP position paper
  – Greater understanding of regulatory concerns, responsibilities of pathologists
Nonhuman Primate (NHP) Project

• **Goal**
  - Understand/characterize immunotoxicology responses in NHP’s to aid in hazard identification/human risk assessment
    - Increased need to understand immunotoxicology in NHP; responses in standard assays and appropriateness of human reagents not fully characterized

• **Approach**
  - Collect baseline characteristics of immune status of NHP
  - Identify assays used or proposed for use to characterize immune functions in NHP
  - Characterize and qualify battery of known methods for other species for use with NHP

• **Progress to date**
  - Data gathered from companies conducting NHP flow cytometry and TDAR
  - Statistician identified, pilot project ongoing to test parameters

• **Next steps/timelines presented under ongoing projects**
Clinical Immunotoxicology Workshop

- **Goal:** stimulate discussion of issues related to clinical immunotoxicity assessment; ultimate goal of fostering dialogue with regulatory agencies.
- **Approach**
  - One-day workshop with presentations and cases to stimulate discussion of clinical assessments of immunotoxicity
  - ITC members and clinicians from member companies
  - Discussions focused on preclinical assessments and relevance to human risk as well as functional assays
- **Discussion**
  - Clinicians expressed concern animal data may not be relevant due to manipulated environments, species and strain differences
  - Interpretation of subtle effects in preclinical studies is problematic
    - Redundancy of immune system suggests subtle differences may be missed
    - However, subtle effects may not be relevant; searching for them may be futile
    - Inherent shortcomings of short term duration, small study size of preclinical immunotoxicity testing relative to dosing large numbers of patients over 15 years
Clinical Immunotoxicology Workshop

• Conclusions
  – Extrapolation between species and duration of dosing (preclinical to clinical) is difficult
  – There is a lack of good, validated methods for monitoring in the clinic
  – There is a lack of guidance from regulators
  – More communication with regulatory agencies is needed

• Next steps
  – Roundtable/workshop to include international regulatory authorities
  – Will be held in conjunction with immunomodulator project because of overlap between issues and stakeholders
Developmental Immunotoxicology

- Workshop held June 12-13, 2001 in Washington, DC
  - Attended by over 75 scientists
- **Primary Goal:** To examine scientific questions underlying developmental immunotoxicology (DIT) and interpretation of test results
- **Secondary Goal:** To provide a framework for a discussion about guidelines for DIT
- **Approach:** Series of plenary lectures and roundtable discussion of relevant questions
- **Outcome/Impact:**
  - Follow-up Roundtable to reach consensus regarding appropriate methods to assess DIT for hazard identification
Developmental Immunotoxicology

- Roundtable held May 2003 in Washington, DC
  - Attended by 30 immunotoxicology experts from US and EU representing government, industry, and academia
- **Goal**: To reach consensus regarding appropriate methods to assess developmental immunotoxicology for hazard ID and under what conditions testing might be required
- **Approach**: Panel discussion of 8 predetermined questions
- **Outcome/Impact**:
  - Publication: A proposed testing framework for developmental immunotoxicology (DIT). *Toxicological Sciences* 83: 18-24, 2005
  - Posters: ITC poster at ACVP November 2005, EPA science forum, May 2005
  - Scientific consensus reached regarding framework
  - Framework highlighted in chapter in Developmental Immunotoxicology (Steve Holladay, ed.) as appropriate testing schema from EPA viewpoint
  - Results of DIT roundtables, publications featured at SOT symposia
  - Papers from DIT roundtables have been cited in numerous publications
Ongoing projects: next steps

• **Raymond Pieters’ systemic hypersensitivity project**
  – project update fall 07
  – publication 4Q08

• **Clinical Immunotoxicology**
  – workshop in May 07 (will be combined with immunomodulator discussion)
  – publication to be submitted 4Q07

• **NHP project**
  – Review of pilot statistical analysis Feb 07; full statistical analysis May 07
  – Tabulation of results Sept 07; presentation to ITC Oct 07
  – Publication submission 2Q08
2007 Projects/Emerging Issues

- Cytokine release syndrome subcommittee
- Photoallergy
- Immunomodulator development
- Immunogenicity of biological therapeutics
Emerging Issues and ITC

Cytokine Release Syndrome

- **Issue:** TGN 1412 cytokine “storm”
- **Goals/approach**
  - Monitor scientific and regulatory climate
  - Determine research approaches to predict adverse reactions
  - Keep member companies abreast of new developments and scientific issues
- **Next steps**
  - Team will reconvene in March

Photoallergy

- Currently an issue in Europe, predominantly
- **ITC monitoring developments (DIA satellite symposium)**
- **Next steps**
  - ITC to determine if workshop or white paper most appropriate course May 2007 meeting
Immunomodulator Project

**Issue:** Gap between ability to identify and interfere with specific targets related to inflammation/immunity and ability to assess human risk potential in the face of increasing need and demand for understanding unexpected or adverse effects of drugs in this class. Current guidances do not adequately address immunomodulatory drug development.

**Goals**

- Identify and discuss development issues with special focus on clinical endpoints as well as need for and approaches for assessment of clinical immunotoxicity for drugs not intended to be immunomodulatory
- Identify research gaps and discuss strategies to address them
Immunomodulator Project, continued

• **Approach**: workshop conducted in conjunction with clinical immunotoxicology project
  - Health authorities, clinicians, industry scientists, academicians, ITC members (steering committee as well as participants)
  - Combined with clinical immunotoxicology project because similar issues, similar stakeholders are involved
    • More specific targets suggest need/greater relevance of assessment of target species

• **Milestones/timelines**
  - Survey distributed 12/06; responses due 1/07
  - Workshop May 07
  - Publication submitted by 1Q08
Immunogenicity Project

• **Issues:** Assessing immunogenicity of biologics; position paper released by EMEA; drafting a guidance; ICH determining need to revisit S6 guidance on biologics

• **Goals:** Explore state of science, risk assessment, regulatory approaches

• **Approach:** cooperative development of workshop/roundtable and response to EMEA draft guidance
  – ITC invited to participate in development of 2007 I’tox Summer School, theme is immune effects of biologics
  – Committee includes academics, ICH, ITC, and European regulatory scientists

• **Milestones/timelines**
  – Draft guidance anticipated 2Q07; ITC comments 3Q07
  – Summer School and roundtable discussion 9/07
  – Publication of Summer School/roundtable proceedings by 1Q08
Concluding Remarks:

Immunotoxicology continues to be a topic of interest among regulators, the general public, and the scientific community. HESI offers a unique forum for scientific dialogue, fostering research, and developing practical approaches to assessing immunotoxic effects of chemicals and pharmaceutical entities and understanding human risk potential.