# FDA/HESI-ITC Workshop on Preclinical and Translational Safety Assessment of CD3 Bispecifics

The mission of HESI, is to collaboratively identify and help to resolve global health and environmental challenges. The Immunotoxicology Technical Committee (ITC) is one of the HESI Scientific Technical Committees and is composed of Scientists from Industry, Academia and Government (http://hesiglobal.org/immunotoxicology/). The HESI-ITC identifies and addresses scientific issues related to the development and application of immunotoxicology to public health and human health risk assessment; promotes the understanding and appropriate use of immunotoxicologic data to protect human health; and contributes 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.

**Workshop Dates and Location: 1st - 2nd October, 2018 at US FDA Silver Spring, MD**

**Goal:** The goal of this workshop is to discuss the preclinical and translational safety assessment of CD3 bispecific therapies, focusing on 8 topics as described based on sessions below. The intent is to have multiple short talks (~10-20 min each) followed by longer in-depth discussion within each session.

**Keynote: A focus on Blincyto, the only FDA approved CD3 bispecific**

**Session 1. CD3 bispecifics and their effect on T cell biology**

A. Hallmarks of activity

**Session 2. Target (tumor antigen) expression and liability assessment**

A. Risk of off tumor/on target cytotoxicity
B. Methodologies to characterize target expression in human vs. nonclinical species
C. What level of expression should raise concern?
D. Path forward when human and nonclinical species pattern of expression are misaligned
E. Target expression with and without toxicological consequences? Why?
F. Can early in vivo nonclinical safety studies help?

**Session 3. Relevance of molecular design and bioactivity to toxicity assessment and potential**

A. Various platforms in use clinically and why from a T cell biology perspective (from Session 1)
B. Impact of platform on in vitro bioactivity, safety and efficacy
C. Impact of CD3 binding affinity on bioactivity, safety and efficacy
D. In vitro to in vivo (nonclinical species) translatability considerations

**Session 4. In vivo pharmacology and toxicology**

A. Role of mouse pharmacology studies in safety assessment
B. Species selection considerations for nonclinical safety studies
    a. Experience in cynomolgus monkey
        i. Need for adaptive study designs (e.g., staggered start, within study dose justification)
        ii. Pharmacodynamic markers and other typical parameters of assessment
        iii. Cytokine release as the driver of maximum tolerated dose
        iv. Strategies to overcome dose-limiting cytokine release
        v. Designs of exploratory vs. GLP toxicology studies and why?
    b. Experience in other species
B. Which parameters correlate best with tolerability
C. Decision-making based on toxicity data when “therapeutic index” is not fully understood
D. Pathologist perspective – Platform vs. tumor antigen-specific events
E. Path forward when there is no species?
    a. Tool molecules or surrogate molecules
    b. In vitro only assessments

**Session 5. In vitro assays to assess cytokine release**

A. What is the best assay format for CD3 bispecifics?
B. What assays provide value for safety evaluation?

**Session 6. FIH dose selection**

A. Approaches taken
B. Considerations for MABEL dose setting, assays and endpoints used (e.g., cytokines vs CTL activity)
C. Should in vitro cytokine release be considered for first-in-human (FIH) dose selection?
D. Assay design and optimization (e.g., E:T ratios, appropriate target cells, length of culture period)
E. Role of in vivo pharmacology data
F. PK/PD modeling approaches

**Session 7. Clinical experience**

A. Strategies for Phase 1 studies
    a. How to efficiently dose escalate while ensuring safety
B. Cytokine mitigation and treatment approaches
C. Non-cytokine safety concerns and management in the clinic
    a. Monitoring for target-related toxicities
    b. Neurotoxicity

**Session 8. Translation of nonclinical findings to the clinic**

A. Cyno vs. human biology (e.g., sensitivity to cytokine release, T cell activation, T cell numbers)
B. Do nonclinical safety findings translate (qualitative or quantitative) to the clinic?
    a. Clinical pathology
    b. Immunophenotyping
    c. Cytokine release
    d. Target organs?
C. Projected therapeutic index
    a. Challenges to accurate determination
    b. How is TI used for project-related decisions?