Non-clinical Immunogenicity Risk Assessment (NCIRA)

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on behalf of the NCIRA working group members

EIP Open Symposium

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European Immunogenicity Platform

NCIRA

Advancing science-based and harmonized approaches to non-clinical immunogenicity risk assessment

- **Expert platform**
  Bringing together experts from industry, academia, CROs, and regulatory environments.
- **Identify gaps**
  Evaluate current limitations and knowledge gaps in NCIRA tools and approaches.
- **Forum to discuss controversial topics**
  Open scientific discussion and alignment on challenging or controversial areas in the field.
- **Promote harmonization**
  Science-based consensus and harmonized approaches for NCIRA.
- **Provide guidance to the field**
  Share outcomes through position papers, publications and presentations.

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NCIRA Achievements

Three major publications in Frontiers in Immunology

EIP publications will be included in *Frontiers in Immunology* research topic "Advances in Immunogenicity Risk Assessment, Monitoring and Mitigation of Biologics" (Sophie Tourdot, Daniela Verthelyi, Marc Pallardy, and Tim Hickling)

Successful Cross-industry collaboration between pharma, CRO and academia

Contributed to **greater harmonization and scientific rigor** in non-clinical immunogenicity risk assessment

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DC maturation assay for non-clinical immunogenicity risk assessment: best practices recommended by the European Immunogenicity Platform

Chloé Ackaert, Bruno Gonzalez-Nolasco, Marc Rosenbaum, Mercedes Perez-Olivares, Michael Gutknecht, Axel Ducret, Anette C. Karle

Why this work matters

- DCs link innate and adaptive immunity, providing key signals that initiate T-cell responses and ADA development
- DC maturation assays assess innate immune activation and adjuvanticity caused by the drug or impurities

Key contributions of the NCIRA team

- Provided best practices for DC maturation assays, addressing variability between laboratories
- Defined recommendations for
  - PBMC sourcing and quality control
  - monocyte isolation and DC differentiation
  - appropriate controls and interpretation criteria

Impact on the field

- Enables more reliable assessment of innate immune activation during drug development
- Helps identify product-related risk factors such as aggregates, impurities, or formulation components
- Supports mechanistic understanding of immunogenicity drivers

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Front. Immunol. 16:1704045. doi: 10.3389/fimmu.2025.1704045

MAPPs assays for non-clinical immunogenicity risk assessment: best practices recommended by the European immunogenicity platform

Anette C. Karle, Katharina L. Kopp, Robert J. Seward, Sophie Tourdot, Chloé Ackaert, Michael Gutknecht, Edward Cloake, Noel Smith, Axel Ducret

Why this work matters

- The MAPPs assay identifies peptides presented on HLA class II molecules, revealing potential T-cell epitopes
- MAPPs plays a central role in candidate selection, de-immunization strategies, and mechanistic investigations

Key contributions of the NCIRA team

- Defined best practices to increase assay robustness, sensitivity, and reproducibility
- Addressed critical aspects including
  - donor selection and HLA diversity
  - cell culture and APC preparation
  - LC-MS/MS analysis and data interpretation

Impact on the field

- Supports identification of immunogenic hotspots in protein therapeutics
- Enables candidate ranking and molecular de-immunization strategies

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Front. Immunol. 16:1690101. doi: 10.3389/fimmu.2025.1690101

T cell assays for non-clinical immunogenicity risk assessment: best practices recommended by the European Immunogenicity Platform

Sophie Tourdot, Anette C. Karle, Marc Rosenbaum, Chloé Ackaert, Pauline Le Vu, Michael Gutknecht, Maryam Ahmadi, Annelies W. Turksma, Timothy P. Hickling

Why this work matters

- T-cell activation is central to clinically relevant ADA responses, driving class switching and affinity maturation.
- Multiple assay formats exist (PBMC, CD8-depleted PBMC, DC:T assays), but lack of harmonized approaches limits comparability across laboratories

Key contributions of the NCIRA team

- Defined best practices for in-vitro T-cell assays used in immunogenicity risk assessment.
- Established recommendations for
  - donor selection and HLA coverage
  - cell quality control and assay controls
  - data interpretation and assay readouts

Impact on the field

- Improves data robustness and reproducibility of T-cell assays across laboratories
- Enables better use of T-cell assays for candidate selection and immunogenicity risk evaluation

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Front. Immunol. 16:1723110. doi: 10.3389/fimmu.2025.1723110

Open for submissions

Frontiers in Immunology Research Topic

Advances in Immunogenicity Risk Assessment, Monitoring and Mitigation of Biologics Volume II

Topic Editors: Sophie Tourdot, Tim Hickling, and Lydia Michaut

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What next?

- In-silico manuscript progressing, expect publication this year
- Revive IIRMI (Innate Immune Response Modulating Impurities) subgroup
- External knowledge sharing
  - Short course on best practices at CHI Washington 2026
- New Subgroups:

Consequences on safety	Immunogenicity Risk Assessment Strategy	What are we missing?
Linking to toxicology and immunotoxicology, e.g. assays for hypersensitivity	Guidance on which assessment to perform in which situation	Are we missing something which renders current tools less predictive?

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Purpose / Mission

The **B Cell Immunogenicity Risk Assessment – BIRA-** working group is an exploratory and collaborative forum dedicated to **advancing the understanding the B cell component of unwanted immune responses to biologics**.

BIRA operates as a joint effort between the **European Immunogenicity Platform (EIP)** and the immunogenicity community of the **American Association of Pharmaceutical Scientists (AAPS)**, bringing together a global, cross-field community.

The group aims to foster open dialogue to help clarify concepts, share perspectives, and improve how unwanted immunogenicity is assessed, interpreted, and mitigated across the drug development lifecycle.

Topics to be Covered by BIRA

- Scientific discussion of B cell immunogenicity mechanisms, drivers, and outcomes relevant to biologics
- Conceptual and practical approaches to B cell immunogenicity risk assessment
- Interpretation of experimental, clinical, and translational data related to unwanted immunogenicity
- Identification of knowledge gaps, limitations, and areas of uncertainty
- Harmonization of terminology, conceptual frameworks, and best practices where possible

Contact:
- Daniel Leventhal
- Sophie Tourdot

Goals and Intended Outputs

- Developing shared understanding and language around B cell immunogenicity risk
- Hosting subject-matter experts and key opinion leaders for focused discussions
- Coordinating coverage of B cell immunogenicity topics at major immunogenicity-focused conferences
- Producing non-confidential, educational materials such as review articles, perspective pieces, or community summaries
- Exploring opportunities for voluntary, pre-competitive collaborations aligned with the group's mission

Out-of-scope
Product-specific comparisons or competitive positioning
Commercial deal-making or promotion of services or platforms

Ways of Working

- Participation is open to all interested individuals (industry, academia, regulatory agencies, non-profit organizations) at no cost.
- The working group is coordinated by two co-chairs, responsible for organizing meetings, facilitating discussions, maintaining meeting notes and shared materials
- Meetings are held periodically. Cadence is determined by activities timelines. Co-chairs will share updates at the NCIRA WG meetings.
- Material and working documents reside on the EIP SharePoint, within the EIP NCIRA folder (Access to other SharePoint folders is restricted to EIP members).

Participation does not imply endorsement of specific views, methods, or conclusions by any individual or affiliated organization. Information shared by participants will be considered non-confidential and will not be subject to any duty of confidentiality by other participants.

NCIRA – Advancing Immunogenicity Risk Assessment

Together, we are building a more robust scientific framework to understand and mitigate immunogenicity risk.

Thank you to all NCIRA contributors and collaborators

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Do you want to join the NCIRA working group or a subgroup?

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