Non-clinical Immunogenicity Risk Assessment (NCIRA)

Sebastian Spindeldreher
on behalf of the NCIRA working goup members

EIP Open Symposium

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Members

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- Anja ten Brinke (Sanquin)
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Problem statement

- Unwanted immune responses (cellular and humoral) to therapeutics can have major safety, efficacy and/or commercial implications.
- Various pre-clinical evaluation tools (in silico, ex vivo and in vivo) are commonly used to assess immunogenicity risk (e.g. ADA).
- Challenges: over prediction, pharmacology of drug leading to false positives or negatives, HLA diversity, specific $CD4^+$ T cell frequency, assay sensitivity etc.
- Robust, consistent and, where feasible, standardized approaches and methods are required to better inform and mitigate risk.

Key Deliverables

- An evaluated position on the limits of ex vivo and in vivo assays
- Best assay combinations to more robustly inform drug design, development, lead selection and risk assessment
- Increase understanding of the drivers of immunogenicity – innate response, antigen processing & presentation, T & B cell epitopes, immune regulation
- An evaluated position on the utility of pre-clinical/non-clinical assays to inform critical quality attributes such as aggregation, glycosylation, deamidation, etc.

Short term deliverable

Position paper covering current diversity in ex vivo / in vivo assay methods:

Define minimal common requirements for non-clinical immunogenicity assays in terms of endpoints and assay parameters (e.g. positive and negative controls) for current ex vivo and in vivo assays, to be able to compare data across assay methods and models.

Comparison of different T cell assay approaches

Assay parameter	Assay 1	Assay 2	Assay 3	Assay 4
Tested antigens	Infliximab, adalimumab, rituximab, natalizumab, Betaferon® and Rebif®			
No of donors	50	16	50	50
Cells	Ag-loaded DC (maturation stim not specified) + CFSE-labelled CD8-depelted PBMC	Ag-loaded DC (matured with LPS) + CD4 T cells	Ag-loaded DC (matured with TNFα + IL-1β) + CD4 T cells	Ag-loaded DC (matured TNFα) + CD4 T cells
Readout	CFSE FACS	IFN-γ ELISPOT	EdU FACS	Thymidine incorporation and IL-2 ELISPOT
Data evaluation	Positive if % stimulation ≥ 0.5% and 2 SEM above background	Positive when spot count ≥ 2x background and minimal difference of 25 spots	Positive if SI ≥ 2 and significant vs control ($p<0.05$)	Positive if SI ≥2 and significant vs control ($p<0.05$)
Ranking	Ranking based on donor frequency and magnitude	Ranking based on precursor & donor frequency	Ranking based on donor frequency and magnitude	Ranking based on donor frequency

Different T cell assay protocols lead to different ranking

	Infliximab	Rituximab	Adalimumab	Natalizumab	Betaferon®	Rebif®
Assay 1	1	3	2	4	2	1
Assay 2	3	2	1	4	1	1
Assay 3	3	1	1	4	1	2
Assay 4	1	2	3	4	1	1

Colour coding indicates ranking, from high to low

Ranking on this slide does not necessarily reflect statistically significant differences!

Manuscript on assay format diversity: towards a possible standardization?

- Scope
  - Overview on current methods, like DC maturation, MAPPs, T cell assays, pre-existing antibodies, B cell precursors assays, in vivo models - principles, highlights and examples of use
  - Description of drawbacks and difficulties in comparing various methods addressing the same elements of the immune response
  - Provide proposals for strategies that allow a cross-comparison between methods
- Topics
  - Antigen presentation
  - T cell recognition
  - B cell response
  - In vivo models
- Contributors

  Axel Ducret (Roche), Campbell Bunce (Abzena) , Chloé Ackaert (immuneXperts), **Grzegorz Terszowski (Novartis)**, Kasper Lamberth (NovoNordisk), Laetitia Sordé (Novimmune), Mark Kroenke (Amgen), Noel Smith (Lonza), Sofie Pattjin (immunXperts), Sophie Tourdot (Pfizer), Vibha Jawa (MSD)

Session 7: Prediction of Immunogenicity

11:00 **EIP NCIRA Working Group update**
Sebastian Spindeldreher, Novartis, Switzerland

11:15 **Construction of humanized mouse models for preclinical risk assessment**
Nicolas Legrand, GenOway, France

11:45 **The development of a quantitative systems pharmacology platform to predict and manage immunogenicity in clinical development**
Mario Giorgi, Certara, The Netherlands

12:15 **Innovative methods for predicting clinical immunogenicity with high-dimensional data**
Philippe Broët, Université Paris-Saclay, France

12:45 ***Lunch***