Non-clinical Immunogenicity Risk Assessment (NCIRA)

Sophie Tourdot

on behalf of the NCIRA working goup members

EIP Open Symposium

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NCIRA and IRA, related but not the same

- Our working group focuses on discussing the use of the many non-clinical in silico, ex vivo and in vitro evaluation tools to support assessment of product-related risk factors and mitigation by design

- Share knowledge and increase understanding of the product-related risk drivers of immunogenicity, including innate responses, antigen processing & presentation, T & B cell epitopes and immune regulation

- NCIRA to avoid the term “prediction”

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Working group activities

1. Advance Standardization and Harmonization of in silico and in vitro tools

1. Advance tools to take advantage of the large body of existing immunogenicity pre-clinical and clinical data to further improve risk assessment and mitigation

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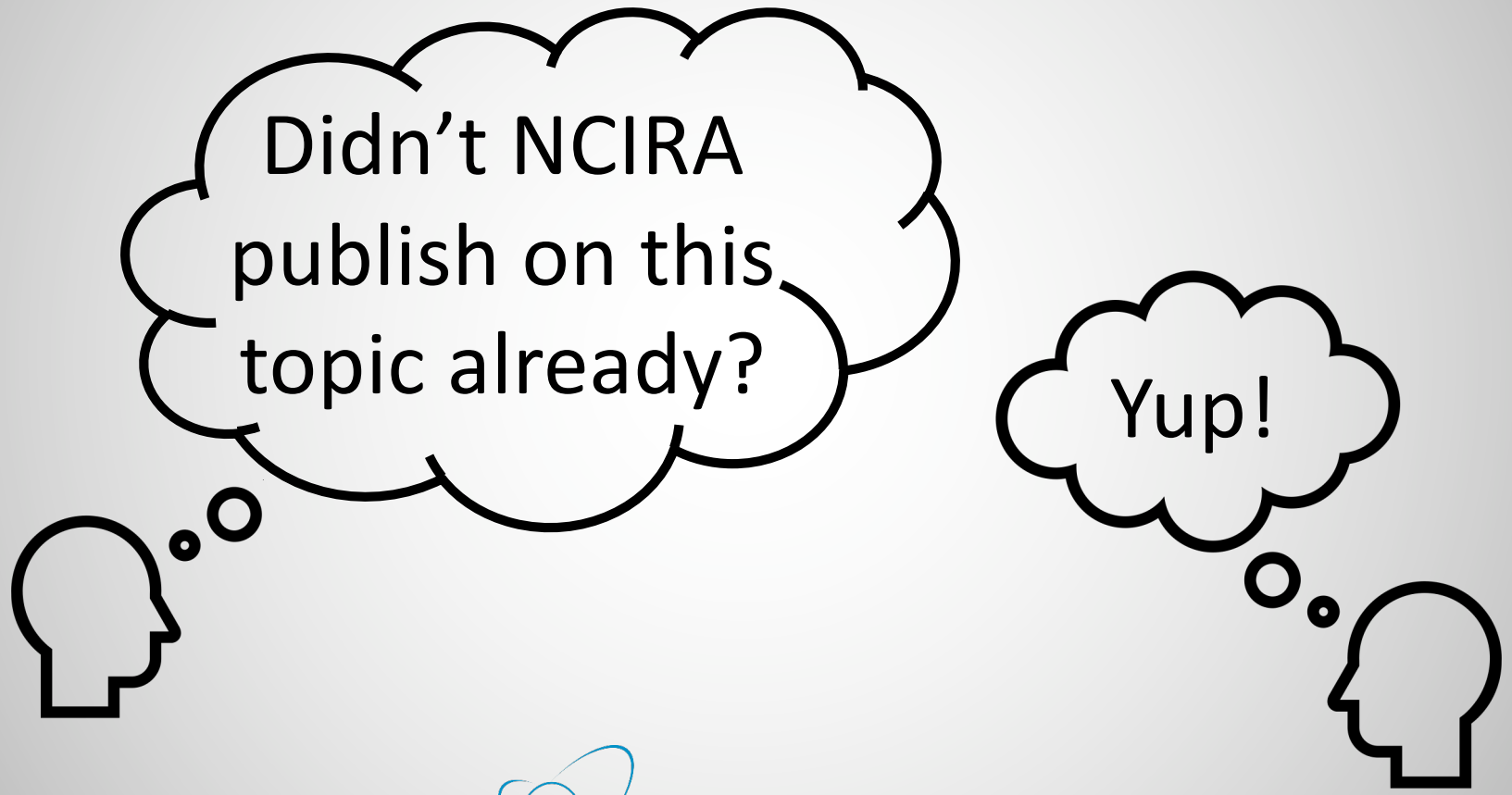
Standardization and Harmonization



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REVIEWS

OPEN ACCESS Check for updates

Assay format diversity in pre-clinical immunogenicity risk assessment: Toward a possible harmonization of antigenicity assays

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ABSTRACT

A major impediment to successful use of therapeutic protein drugs is their ability to induce anti-drug antibodies (ADA) that can alter treatment efficacy and safety in a significant number of patients. To this aim, *in silico*, in vitro, and in vivo tools have been developed to assess sequence and other liabilities contributing to ADA development at different stages of the immune response. However, variability exists between similar assays developed by different investigators due to the complexity of assays, a degree of uncertainty about the underlying science, and their intended use. The impact of protocol variations on the outcome of the assays, i.e., on the immunogenicity risk assigned to a given drug candidate, cannot always be precisely assessed. Here, the Non-Clinical Immunogenicity Risk Assessment working group of the European Immunogenicity Platform (EIP) reviews currently used assays and protocols and discusses feasibility and next steps toward harmonization and standardization.

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Standardization and Harmonization

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Objectif: Make Best Practices recommendations

1. Overview of existing tools / assays
2. Address regulatory requests & expectations
3. Outline potential future applications

4. Recommendations on:
    1. Appropriate and inappropriate use: which assay for what question
    2. Parameters to control
    3. Fit-for-purpose qualification

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Outline of the manuscript

- Terms and definitions
- Best Practices common to all in vitro assays
- Critical parameters specific to each assay and in silico tool

Under discussion: provide generic assay protocols as a starting point to establish a new assay in one's lab.

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Subgroups ☺

- In silico T cell epitope binding/presentation prediction algorithms
- MAPPs assay
- Innate immune response assays
- T cell assays
- B cell assays

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Overview of the T cell assay subgroup discussions

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Quality Control – donors and cells

Donors

- State exclusion criteria (age, medication etc.) if applied
- Representativity of HLA diversity of the population of reference
- Minimum number of donors statistically determined

Cell populations and viability

- Starting population, minimum 80% viability
- Cell population content (PBMC)
- Cell line purity (moDC)
- Activation state

Cell functionality

- Response to an **assay control** such as KLH, SEB, CEFT, LPS for APC, which ensures that cells can respond to a stimulus
- This is different from a **sensitivity control**, which assesses the ability of the assay to detect biological relevant responses; same nature of the test articles (e.g., peptide, antibody)

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Quality Control - material

Peptides

- Justify choice of length
- Purity level acceptable threshold might depend on the nature of contaminants

Full-length proteins

- Endotoxin level
- Add buffer/formulation control if could be a confounding factor

Critical reagents

- Lot testing, in particular system controls (e.g., CEFT)

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Quality control - assay characteristics

Signal-to-noise

- **Sensitivity controls (expected low and high responses)** must assess naïve responses
- Threshold determined by statistical analysis
- Particular attention to T cell precursor numbers in T cell assays (Cf Part 1)

Alignment

- Low and High frequency controls
- Ideally **AAPS HESI** standards; or well described ones chosen based on experience
- Monitor drifts

Ranking

- Able to detect statistical differences between test article responses

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The Immunogenicity Database Collaborative (IDC)

Volunteer members

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a Q² Solutions Company

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BIOTECH SQUARE

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IDC: Driving comprehensive access to publicly available immunogenicity data

What is the IDC?

The IDC is a global, cross-industry (pharma, biotech, and academia) consortium established with the purpose of creating an open-access, uniform and curated database encompassing clinical and pre-clinical immunogenicity information for protein-based therapeutics. It is a grass-roots initiative led by volunteer members and contributors and holds no formal association to any single organization or industry working group.

Mission

Establish a shared and easily accessible database cataloging descriptors and relevant data associated with the immunogenicity of biotherapeutics.

Vision

Make clinical and pre-clinical immunogenicity data easily accessible to support the development of safe and effective biotherapeutics.

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Clinical trial **databases**

FDA labels & BLA approval **documents**

Journal **publications**

Press and SEC **disclosures**

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

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