State-of-the-art and new options to assess T cell activation by skin sensitizers

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Introduction

At present, three of the four key events of the Adverse Outcome Pathway (AOP) for skin sensitisation assessment are assessable by OECD-accepted in vitro methods. The fourth key event describes the immunological response in the draining lymph node where activated dendritic cells present major histocompatibility complex-bound, haptenised peptides to naive T cells, thereby priming the proliferation of antigen-specific T cells. Despite substantial efforts, the modelling and assessment of this adaptive immune response to sensitisers with in vitro T cell assays still represents a challenge.

Hence, Cosmetics Europe organised a workshop, bringing together experts from academia, industry and regulatory stakeholders to review the scientific status of T cell based assays, foster a mutual scientific understanding and conceive new options for immunogenicity and allergenicity assessment. Here we present the applicability and challenges regarding usability and reproducibility of existing T-cell based assays. In addition how a tiered testing approach using T cells may be applied to assess the immunogenicity of a substance. When combined with exposure information, genetic and environmental factors, this information could help to assess its allergenicity.

T cell-based assays/approaches

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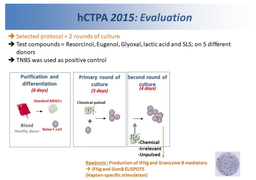
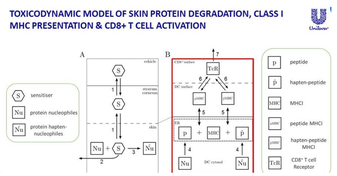
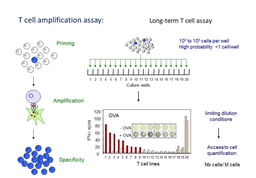


human T Cell Priming Assay (hTCPA) for T cell response assessment
Vocanson et al., 2014

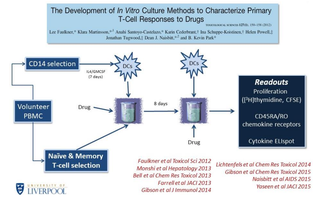


Toxicokinetic/Toxicodynamic Skin allergy assessment (SARA) model
Maxwell et al., 2014

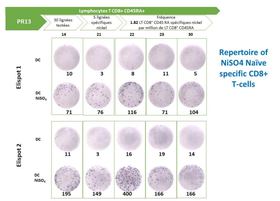
The Human Artificial Lymph Node Model (HuALN)
Giese and Marx, 2014



New in silico and in vitro options to assess T cell activation
Castelli et al., 2013

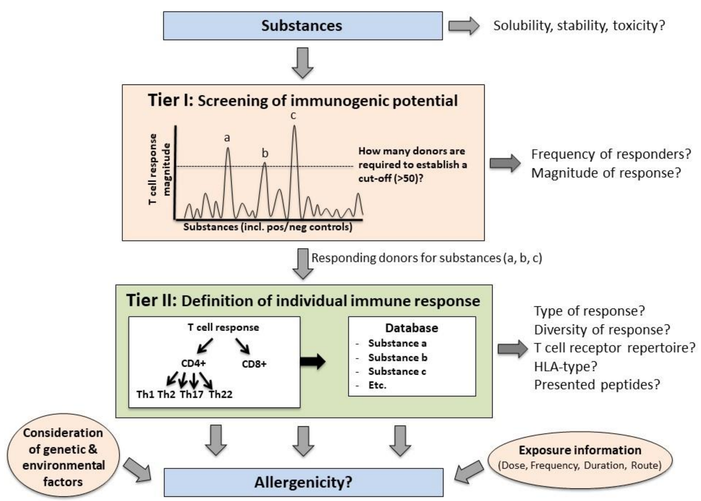


T cell assay to predict immunogenicity of drug and cosmetic compounds
Faulkner et al., 2012



In vitro functional T cell assays for T cell repertoire identification
Scornet et al., 2016

T cell assay-based tiered testing approach



T cell assay-based tiered testing approach for immunogenicity and allergenicity assessment:

•Tier I: screening of immunogenic potential using in vitro T cell responses in human blood donors may generate information on the frequency of responders towards a substance and the variability of T cell response magnitude.

•Tier II: more complex T cell assays could provide mechanistic information on the antigen-specific T cell response at multiple concentrations using responding donors (Tier 1). Assays could evaluate T cell receptor repertoire, HLA type, presented peptide by DCs and T cell subset activation.

By testing substances with different properties in multiple human donors, a database could be established. The immune response data in combination with exposure information and considerations of genetic and environmental factors could be used to assess the allergenicity.

Ref: van Vliet et al. State-of-the-art and new options to assess T cell activation by skin sensitizers: Cosmetics Europe Workshop; ALTEX. 2017 Oct 2. doi: 10.14573/altex.1709011.

Recommendations on T cell-based assays

- Improve the sensitivity of T cell assays
- Define the inter-donor variability and reproducibility
- Investigate the relation between skin sensitizer potency and T cell assay responses and repertoire
- Improve the understanding of the link between haptenization and immunogenicity
- Define the applicability domain of T cell-based assays
- Clarify the importance of human leukocyte antigen (HLA) system

Conclusions

- T cell-based assays show encouraging results in predicting the immunogenic potential of substances, but optimization and refinement are required to meet expectations regarding usability, predictivity and reproducibility for regulatory safety assessment
- It is important to address the donor-to-donor variability and identify the number of donors required to robustly detect T cell responses
- Advancement of T cell-based assays should also focus on standardization and transferability to allow ring-trial evaluation studies for predictivity and reproducibility assessment
- Skin sensitisation risk assessment case studies without the use of animal data are needed to further consider the benefit of assessing the fourth AOP key event

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