



Innovative Medicines Initiative

Immunogenicity: Assessing the Clinical Relevance and Risk Minimization of Antibodies to Biopharmaceuticals

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efpia

Open Information Day – 22 October 2010 - Brussels

Need for public-private collaboration 1



- All biopharmaceuticals are prone to induce immune responses (“immunogenicity”)
- The clinical relevance of anti-drug antibodies (ADAs) is generally poorly understood and highly variable
- At present it is hard to predict the immunogenicity of biopharmaceuticals due to:
 - complexity of the immunological mechanisms
 - wide diversity of biopharmaceuticals
 - complexity of the scientific approach concentrating on single products or dedicated predictive tools

Need for public-private collaboration 2



- A combination of the research capacities of pharmaceutical companies and academia/SMEs could allow to:
 - compare all relevant predictive tools
 - pool data in order to gain the statistical power to identify the factors relevant for immunogenicity
 - share scientific expertise on immunogenicity

Objectives of the full project



- Investigate the clinical relevance of biopharmaceutical-associated immunogenicity
- Evaluate the predictive value of existing tools and develop new ex-vivo methods
- Investigate the immunological mechanisms that drive the development of anti-drug antibodies
- Generate data useful to regulators and healthcare professionals

Expected impact on the R&D process



- Investigation of the clinical relevance of immunogenicity will increase patient safety, and optimize drug development
- The evaluation of the predictive value of existing tools and newly developed ex vivo methods will result in improvements of existing and development of innovative predictive tools. These tools might subsequently be used for candidate selection in early drug development
- The investigation of immunological mechanisms that drive the development of anti-drug antibodies may ultimately lead to the identification of patient stratification markers and reduce the risk of immunogenicity

Suggested architecture of the project



- The project will consist of 5 workpackages:
 - Package 1: Identification and description of immunogenicity relevant data
 - Package 2: Evaluation and development of predictive immunogenicity tools
 - Package 3: Establishment of a database for clinical, predictive immunogenicity and patient-related safety and efficacy data
 - Package 4: Data analyses and integration
 - Package 5: Project management and communication
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Expected contributions of the applicants



- Provide access to patient registries for a selected set of marketed drugs (e.g. TNF-alpha blockers, IFN-beta compounds and clotting factors). For these drugs a certain amount of immunogenicity data is already available and patient samples may be available/obtainable
- Provision of prediction tools and application of these tools to a selected set of marketed drugs
- Development of innovative methods and approaches leading to improved predictability of anti-drug antibody responses and/or characterization of ADA
- Establishment and maintenance of the database
- Identification of mechanisms of immunogenicity and its relationship to immune-mediated adverse events (AEs)
- Intellectual and practical scientific input to address bottlenecks in translation of pre-clinical to clinical data

Expected (in kind) contributions of EFPIA members



- Provision of prediction tools currently used by the EFPIA companies and application of these tools to a selected set of marketed drugs (e.g. TNF-alpha blockers, IFN-beta compounds and clotting factors)
- Scientific input for innovative approaches to further assay methodologies, ADA characterization and/or immunogenicity prediction technologies
- Know-how in immunogenicity assay development, validation and data interpretation
- Expertise in analysis of observational data and data management
- Clinical safety expertise

Key deliverables of full project



- Improved understanding of clinical relevance of ADAs
 - Evaluation of different technologies used to detect ADAs
 - Establishment of database to house patient and drug characteristics, exposures, safety and efficacy outcomes, ADA assay results, prediction tool results
 - Clearer understanding of the value of prediction tools, correlation to immunogenicity assay data and clinical outcome
 - Evaluation of relevance of factors currently used in risk based approach to immunogenicity assessment
 - Identification of early activation biomarkers as potential predictors of immunogenicity
 - Feedback to the health authorities regarding factors influencing the clinical relevance of immunogenicity
 - Educational materials for healthcare providers
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Thank you !!

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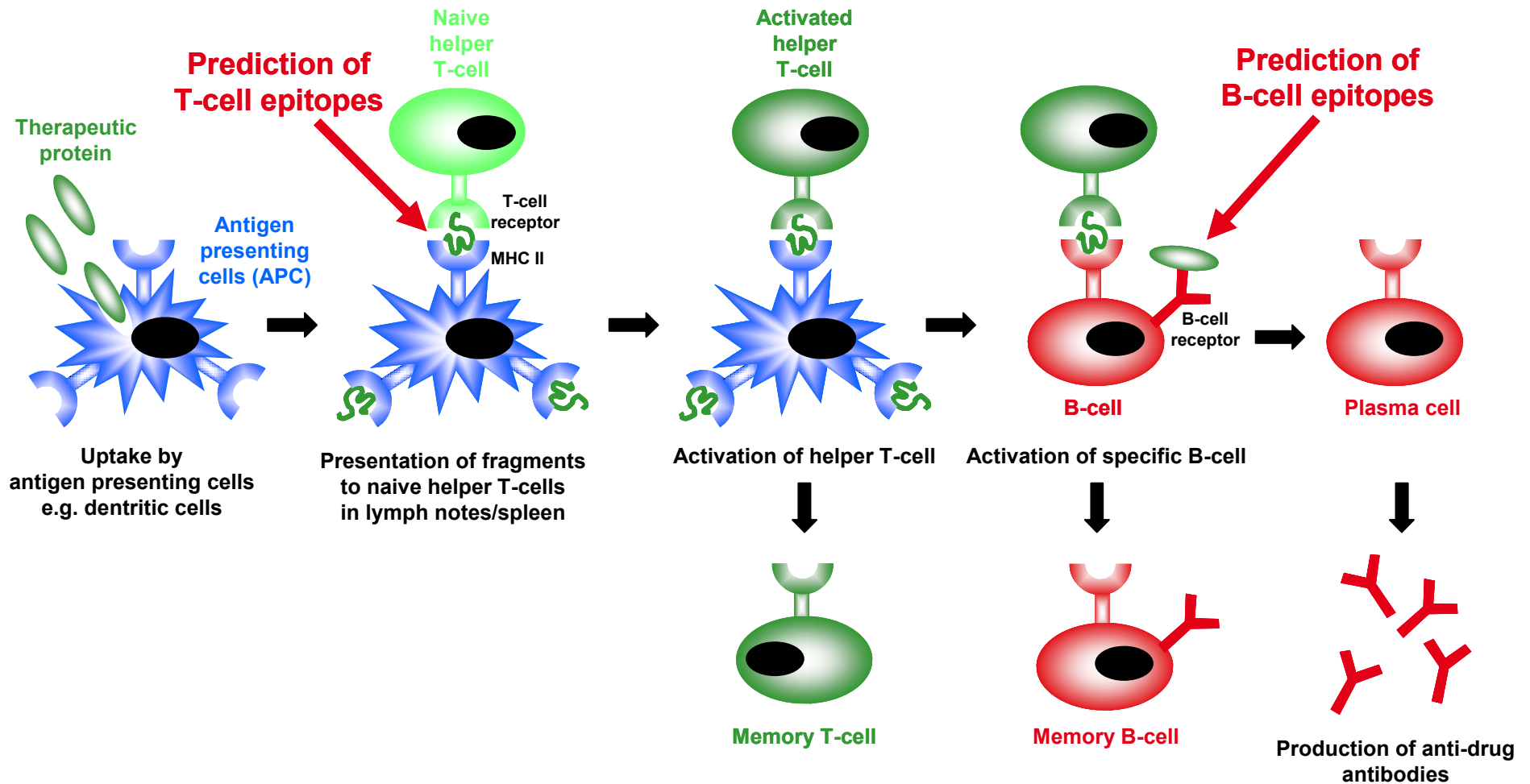
Webinar on 28 October at 13:00
(Bruxelles time)

www.imi.europa.eu



Back-up Slides

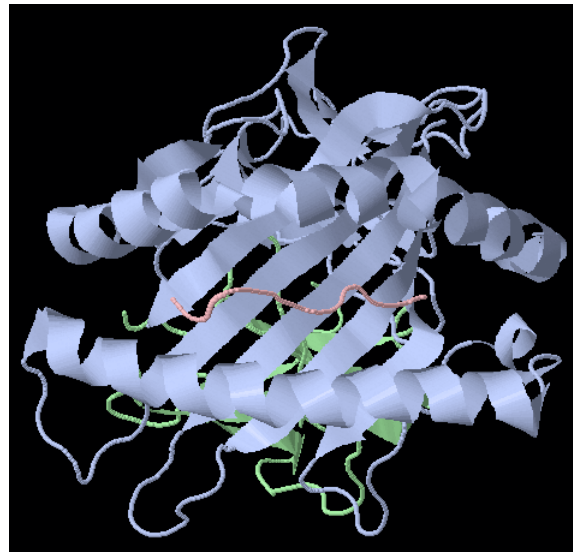
Prediction of Immunogenicity



In-Silico Prediction of T-cell Epitopes



- Based on the known crystal structures of HLA-DR1, DR2, DR3, DR4 and DR51 homology modelling has been applied to predict the structure of the peptide binding groove of all MHC class II alleles
- Based on this structural information, computer programs are used to predict the potential of peptide sequences to fit into the MHC binding groove
- Overlapping amino acid sequences are checked for their ability to bind to MHC class II and a „binding score“ for every amino acid of the therapeutic protein is determined



In-Vitro Prediction of T-cell Epitopes



- Monocytes are isolated from PBMCs and differentiated to immature dendritic cells (DCs) with IL-4 / GM-CSF
- After several days test antigens are loaded onto the dendritic cells, and incubated with IL-4 / GM-CSF to induce a mature phenotype
- Autologous T-cells are added to the mature DCs and incubated for several days
- Proliferation (e.g. ^3H Thymidine) and IL-2/IFN-gamma are measured (ELISpot)