Purpose: While immunogenicity of biologics is widely acknowledged as a clinical necessity, varying from subject to subject and identifying those at risk of developing anti-drug antibodies (ADA) has been lacking. Several studies have identified HLA as one potential biomarker of immunogenicity, leading to the concept that immunity can be screened using computational and experimental methods that define HLA-binding peptides at pre-clinical and clinical stages of development. Here we report the use of our Individualized T Cell Epitope Measure (iTEM) tool for analyzing the HLA-dependent immunogenicity of 23 monoclonal antibodies in clinical use and its validation using clinical observations from antibody-treated patients.

Methods: The iTEM tool, a component of Epivax’s EPI platform and used for screening biological sequences, examines protein sequence for potential immunogenicity based on an individual subject’s HLA phenotype. Each of the input protein’s 11-mer frames is analyzed for potential binding to the individual’s HLA using the Epivax platform, resulting in a patient-specific iTEM score. A positive (or negative) iTEM score correlates with an increased (or decreased) T cell epitope content, compared to a random protein of similar length. Pairs of high-, moderate-, and low-risk HLA haplotypes can be defined based on the risk of each of the monoclonal antibodies. The same approach was applied to data available from cohorts of patients suffering from various immune disorders: Psoriatic Arthritis (PsA), Ankylosing Spondylitis (AS), and Rheumatoid Arthritis (RA). These patients were exposed to adalimumab and both HLA phenotypes and anti-adalimumab antibody titers detected at various time points were available.

Results: Heat maps were developed for 23 licensed monoclonal antibodies, revealing pairs of HLA high-risk alleles that may be linked to higher ADA titers in selected patients. For example, in adalimumab, HLA-DR01 and HLA-DR07 are associated with higher patient T cell epitope content compared to other HLA-DR alleles, which may contribute to higher levels of ADA in subjects expressing these alleles. Conversely, in infliximab, pairs of HLAs comprising HLA-DR01 are associated with lower patient T cell epitope content, suggesting that HLA-DR01 may decrease the risk of ADA formation in patients expressing this allele. A retrospective set of study patients’ potential risk for ADA to adalimumab was determined using the iTEM tool on each cohort separately. ADA responses were higher in PsA and AS patients whose iTEM score was elevated compared to low-risk patients. No associations between ADA response and iTEM scores could be made with the RA cohort. We hypothesize that ADA responses in these patients highly depend on the functionality of their regulatory T cells.

Conclusions: We have analyzed the immunogenicity of monoclonal antibodies and identified at-risk combinations of HLA haplotypes. We also found that our HLA-specific immunogenicity predictions using the iTEM tool correlated with observed immunogenicity, representing an important step forward in personalized medicine.

**ABSTRACT**

**INDIVIDUALIZED T CELL EPITOPE MEASURE (ITEM): PERSONALIZED IMMUNOGENICITY ASSESSMENT**

**Purpose:** While immunogenicity of biologics is widely acknowledged as a clinical necessity, varying from subject to subject and identifying those at risk of developing anti-drug antibodies (ADA) has been lacking. Several studies have identified HLA as one potential biomarker of immunogenicity, leading to the concept that immunity can be screened using computational and experimental methods that define HLA-binding peptides at pre-clinical and clinical stages of development. Here we report the use of our Individualized T Cell Epitope Measure (iTEM) tool for analyzing the HLA-dependent immunogenicity of 23 monoclonal antibodies in clinical use and its validation using clinical observations from antibody-treated patients.

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**ITEM ANALYSIS OF RHEUMATOID ARTHRITIS PATIENTS: ADJUSTING FOR TREG FUNCTIONALITY?**

**Case Study:** Item analysis of patients exposed to adalimumab

**Purpose:** To retrospectively analyze three cohorts of patients exposed to adalimumab and for which both ADA responses and HLA types were known.

**Methods:** We retrospectively analyzed three cohorts of patients exposed to adalimumab and for which both ADA responses and HLA types were known.

**Results:**

**Cohort 1:** 40 Psoriatic Arthritis (PsA) patients.
- High-risk patients developed higher antibody titers.
- Measured antibody titers in PsA patients.

**Cohort 2:** 28 Ankylosing Spondylitis (AS) patients.
- High-risk patient developed higher antibody titers.
- Measured antibody titers in AS patients.

**Cohort 3:** 207 Rheumatoid Arthritis (RA) patients.
- Insufficient results.
- Many studies have shown that RA patients do not have fully functional Tregs.

**Conclusions:**

- The individualized T cell epitope (iTEM) tool allows immunogenicity predictions to a patient-specific HLA phenotype.
- The iTEM tool allows the identification of HLA haplotypes that are associated with a greater risk of developing anti-drug antibody (ADA) responses.

**For questions regarding immunogenicity prediction services and desensitization options, please contact:** Steven Vessella at 401-272-2123, ext. 107, or at info@epivax.com www.epivax.com

**M1012**

Predicting Immunogenicity in the Era of Personalized Medicine: A Need for Individual Risk Assessment

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