**New Regression Model Predicts Antibody Immunogenicity based on Effector and Regulatory T cell Epitope Content**

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Whether fully human or humanized, monoclonal antibodies (mAbs) can be immunogenic, derailing clinical success. Thus most major BioPharma companies use a model generated by De Groot and Martin (Clinical Immunology, 2009) to assess the immunogenicity risk of new monoclonal antibodies prior to moving these candidates to the clinic. The existing model scans antibody sequences for T cell epitopes, which are the key drivers, or modulators, of immunogenicity, and for regulatory T cell epitopes (Tregitopes) which down-regulate immune response, enabling a more accurate forecast of immunogenic potential. The existing regression model for forecasting immunogenicity was based on the analysis of 22 antibodies.

In the current study, we have updated our regression model based on clinically reported ADA data of 22 immunogenic (>5% ADA) and 21 non-immunogenic (<5% ADA) licensed monoclonal antibodies. The variable heavy and variable light chain sequences of these 43 mAbs were screened for the presence of putative effector T cell epitopes using the EpiMatrix system. We also screened the sequences for Tregitopes, which included highly conserved T cell epitopes derived from IgG that we and others have shown activate regulatory T cells and promote tolerance induction to associated antigens.

To develop the new regression model, we calculated the EpiMatrix score (a summary of all T cell epitope content), determined the Tregitope content, and developed a Tregitope-adjusted EpiMatrix score (EpiMatrix score excluding Tregitope content) of the combined light and heavy chains. We then evaluated several alternative models that used EpiMatrix score, Tregitope content and/or Tregitope-adjusted EpiMatrix score to predict ADA response. For each univariate model, Pearson correlation coefficients and root mean square error (RMSE) were calculated to assess and compare the linear relationship of the variables and the fit of each model. We compared the resulting scores to observed ADA responses that were available in package inserts and/or the literature.

Compared to EpiMatrix score and Tregitope content**,** the Tregitope-adjusted EpiMatrix score had the highest correlation with observed ADA for the new set, larger set of Monoclonal antibodies (Pearson correlation coefficient=0.85, p-value<0.001) and had the lowest RMSE (6.94), suggesting that predicting immunogenicity (as measured by ADA) using the Tregitope-adjusted EpiMatrix score, in an exponential model, was the closest to observed immunogenicity.

This new model for prediction of antibody immunogenicity, using an expanded set of mAbs for which clinical data is now available, is consistent with the original model in that Tregitope-adjusted EpiMatrix score is correlated highly correlated with observed immunogenicity. In addition, we identified new candidate Tregitopes that improved the accuracy of the scoring system, that are now slated for experimental validation in our laboratory. Further studies of this type will support deimmunization, humanization and other approaches to tolerizing monoclonal antibody therapeutics in our interactive in silico screening and optimization platform (ISPRI), enabling drug developers to move biologic candidates towards the clinic swiftly and with reduced risk.