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

Andres H. Gutierrez[1], Frances E. Terry[1], William D. Martin[1], Anne S. De Groot[1,2]

[1]EpiVax, Inc., Providence, RI, United States; [2]Institute for Immunology and Informatics, University of Rhode Island, Providence, RI, United States

Abstract

Background

- The potential for immunogenicity and anti-drug antibody (ADA) generation is a hurdle all drug developers must face in the process of developing new biologic products.
- T cell epitopes are key drivers, or modulators, of immunogenicity.
- Our group has developed comprehensive methods for identifying T effector and regulatory T cell epitopes (Tregitopes) in monoclonal antibodies (mAbs), enabling a more accurate forecast of immunogenic potential.
- We previously described a regression model for forecasting immunogenicity that was based on the analysis of 22 antibodies. The resulting model is used by most major BioPharma companies to estimate immunogenic risk in new monoclonal antibodies (De Groot and Martin, 2009).
- Here, 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.

Methods

- The variable heavy and variable light chain sequences were screened for the presence of putative effector T cell epitopes using the EpiMatrix system.
- Potential Tregitopes were also identified in the mAb sequences.
- We tested a set of novel candidate Tregitopes.
- Based on the putative effector and regulatory T cell epitopes, we calculated:
  - EpiMatrix score (a summary of all T cell epitope content).
  - Tregitope content (a summary of all Tregitope content).
  - Tregitope-adjusted EpiMatrix score (EpiMatrix score excluding Tregitope content).
- We then evaluated several regression models using EpiMatrix score, Tregitope content and 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.

Results

- Tregitope-adjusted EpiMatrix score had the highest correlation with observed ADA (Pearson correlation coefficient=0.69, p-value<0.001) and had the lowest RMSE (6.94), suggesting that ADA predicted using Tregitope-adjusted EpiMatrix score in an exponential model, was the closest to observed ADA.

Conclusion

- We identified new candidate Tregitopes that are now slated for experimental validation in our laboratory.
- Consistent with the original model, the new model is capable of relating antibody epitope content to observed immunogenicity with a high degree of correlation.

Methods

Monoclonal antibody data set

- We analyzed 43 mAbs, which included 38 licensed products (Source: IMGT/mAb-DB).
- Immunogenicity data were derived from package insert and/or literature.
- Monoclonal antibodies with cancer indications were excluded from the analysis.

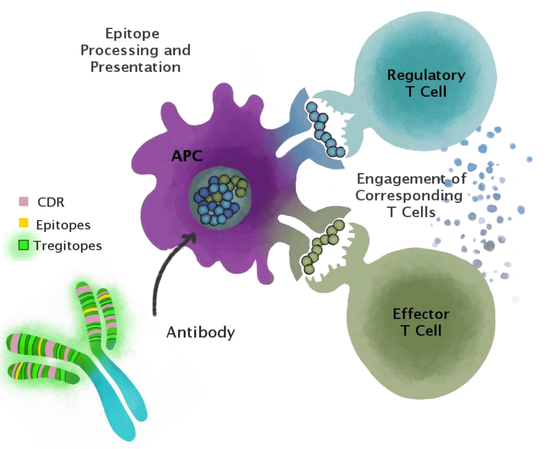
Assessment of T cell epitope Content and Tregitope Content

Variable heavy and variable light chain sequences of each mAb were screened for the presence of putative effector T cell epitopes using the EpiMatrix system [1]. Thus, we calculated:

(1) T cell epitope content predicted for 9 globally relevant supertype HLA-DR alleles.

(2) Regulatory T cell epitope (Tregitope) content
- Potential Tregitopes included highly conserved T cell epitopes derived from IgG that activate regulatory T cells and promote tolerance induction to associated antigens.
- We also tested models with a set of novel candidate Tregitopes.

(3) Tregitope-adjusted EpiMatrix score EpiMatrix score excluding Tregitope content



Adapted from De Groot AS et al.,2013 [2]

Development of the model for prediction of Immunogenic Potential

- EpiMatrix score, Tregitope content and Tregitope-adjusted EpiMatrix score were evaluated as individual predictors of antibody immunogenicity using univariate linear, polynomial, and exponential regression models.

Model evaluation

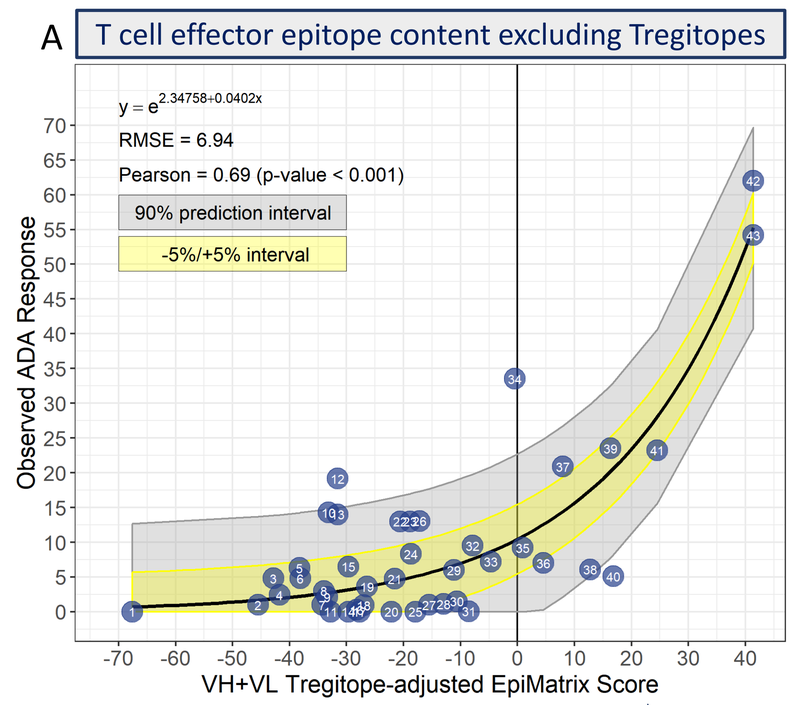
- The fit of each model was assessed using root mean square error (RMSE).
- Pearson correlation was applied to evaluate the relationship between Observed ADA Response and each immunogenic variable.
- Correlation was considered significant if p-value was below 0.05.

References

1) De Groot AS, Martin W. Reducing risk, improving outcomes: bioengineering less immunogenic protein therapeutics. Clin Immunol. 2009;131(2):189-201.
2) De Groot AS, Terry F, Cousens L, Martin W. Beyond Humanization and De-immunization: Tolerization as a Method for Reducing the Immunogenicity of Biologics. Exp Rev Clin Pharm. 2013;6(6):651-52.

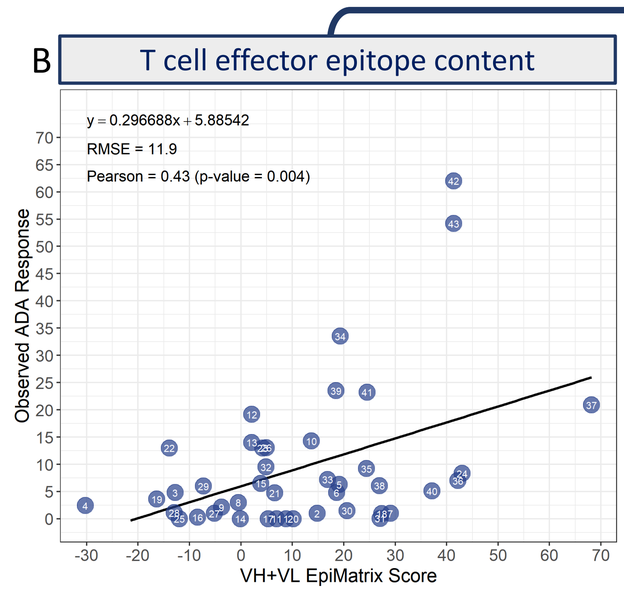
Results

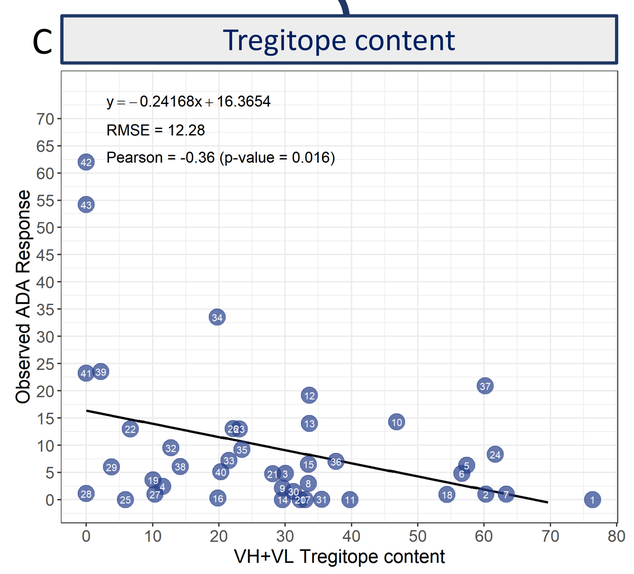
Tregitope-adjusted EpiMatrix Score is the best predictor of Antibody Immunogenicity



Antibody (Target)

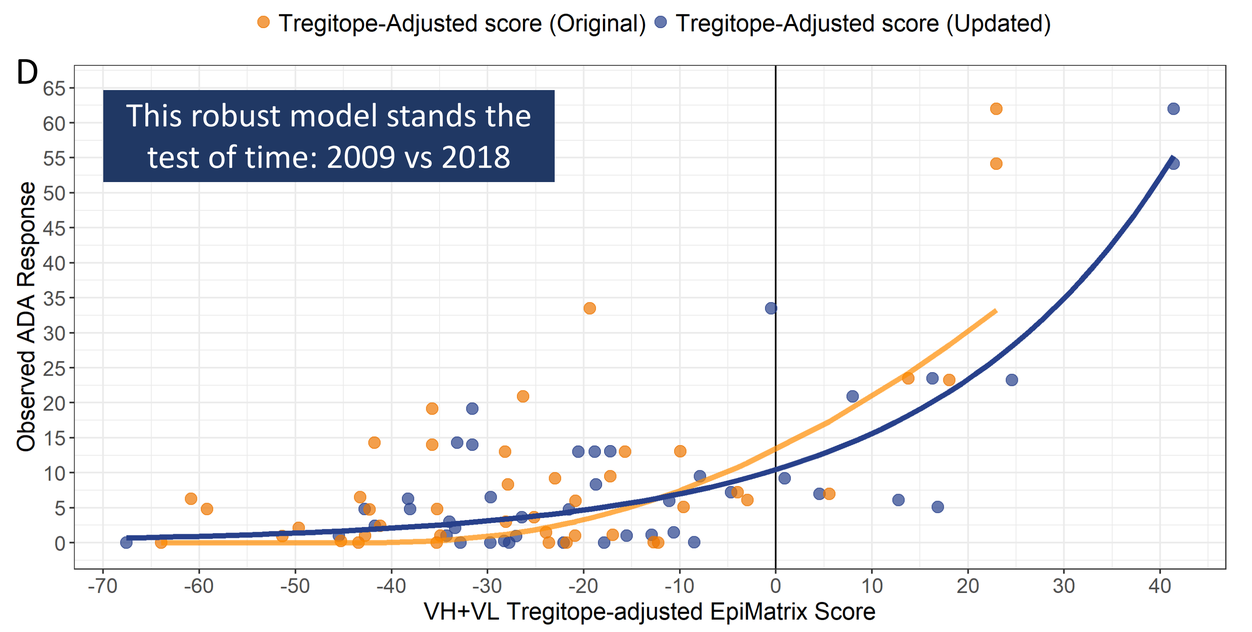
1 Prolia (RANKL)
2 Cosentyx (IL-17A)
3 Emgality (CGRP-L)
4 Benlysta (BLyS)
5 Raptiva (CD11a)
6 Praluent (PCSK9)
7 Ajovy (CGRP-L)
8 Siliq (IL-17RA)
9 Soliris (C5)
10 Simponi (TNF α)
11 Crysvita (FGF23)
12 Zinbryta (IL-2Rα)
13 Zenapax (IL-2Rα)
14 Zinplava (Cd toxin B)
15 Ilumya (IL-23 p19)
16 Repatha (PCSK9)
17 Visilizumab (CD3E)
18 Ocrevus (CD20)
19 Nucala (IL-5)
20 Leukarrest (CD11/18)
21 Aimovig (CGRP-R)
22 Entyvio (ITGα4β7)
23 Fasenra (IL-5Rα)
24 Takhzyro (KLKB1)
25 Trogarzo (CD4)
26 Taltz (IL-17A)
27 Synagis (RSV F)
28 Simulect (IL-2Rα)
29 Tremfya (IL-23 p19)
30 Ilaris (IL-1β)
31 Xolair (IGHE)
32 Tysabri (ITGα4)
33 Humicade (TNF α)
34 Bococizumab (PCSK9)
35 Kevzara (IL-6R)
36 Dupixent (IL-4Rα)
37 Humira (TNF α)
38 Stelara (IL-12/23 p40)
39 Remicade (TNF α)
40 Cinqair (IL-5)
41 Rituxan (CD20)
42 Lemtrada (CD52)
43 Campath (CD52)





- ADA predicted using Tregitope-adjusted EpiMatrix score in an exponential model (Figure A), was the closest to observed ADA (lowest RMSE and highest Pearson correlation coefficient), compared prediction with EpiMatrix score (Figure B) or Tregitope content (Figure C) alone.

Comparison between Original and Updated Models



- The new model includes an additional HLA-DR allele for prediction of T cell epitope content and uses an updated set of Tregitopes. The new model is consistent with the original model.

Conclusions

- Compared to T cell epitope content (EpiMatrix score, Figure B) and Tregitope content (Figure C), the model based Tregitope-adjusted EpiMatrix score is the best predictor of antibody immunogenicity (Figure A).
- The Tregitope-adjusted EpiMatrix score is significantly correlated with Observed ADA Responses (Figure A).
- The new model is based on almost double the number of mAbs compared to the original model. In addition, the new model uses 9 HLA-DR alleles for prediction of T cell epitopes, one allele more than the original model, added to increase population coverage in Asia. We also updated the set of Tregitopes, which we used to adjust the score and predict antibody immunogenicity.
- Despite these differences, the new model is consistent with the original model (Figure D).
- This analysis not only updates the immunogenicity predictions, but also supports them retrospectively.
- Once the novel candidate Tregitopes are validated experimentally in our laboratory, the new model for prediction of antibody immunogenicity will be incorporated into our interactive in silico screening and optimization platform (ISPRI) to facilitate development of monoclonal antibodies with reduced risk of immunogenicity.