iVAX Web-based Vaccine Design

Frances Terry[1], Matthew Ardito[1], Denice Spero[2], William Martin[1], Anne S. De Groot[1,2]
[1] EpiVax, Inc., Providence, RI 02903, United States; [2]Institute for Immunology and Informatics, University of Rhode Island

Abstract
iVAX comprises a suite of in silico tools for the design of genome-derived, epitope-driven vaccines generated from protein sequences. Triage, immunoinformatic analysis and manipulation of these sequences can produce high quality peptide candidates for use as components of epitope driven vaccines.

Methods
The iVAX database allows for storage and organization of large sequence files. Users may upload genomes, proteins, peptides or archives of previous analyses, all of which are stored securely on an Oracle 11g database. The *in silico* vaccine design process begins by identifying T-cell epitopes conserved amongst input sequences, such as proteins from multiple strains of the same pathogen. The *Conservatrix* algorithm parses input sequences into 9-mer frames and identifies those conserved amongst multiple whole sequences for all potential vaccine targets. *EpiMatrix* takes these conserved 9-mer frames and scores them for potential binding affinity against a panel of Class I or II HLA alleles. Using EpiMatrix output, *ClustiMer* identifies clusters of 9-mers with a high density of putative T cell epitopes. *BlastiMer* automates the process of submitting the most immunogenic and therefore most relevant sequences to BLAST to identify homologous sequences within the human genome. Such sequences could potentially elicit an undesired autoimmune response. *JanusMatrix*, an improved homology analysis tool examining pathogen/host sequence similarity at the TCR interface of any given epitope, is in development. *EpiAssembler* knits together the conserved sequences to form highly immunogenic consensus sequences.

Figure 1. Genome to Vaccine

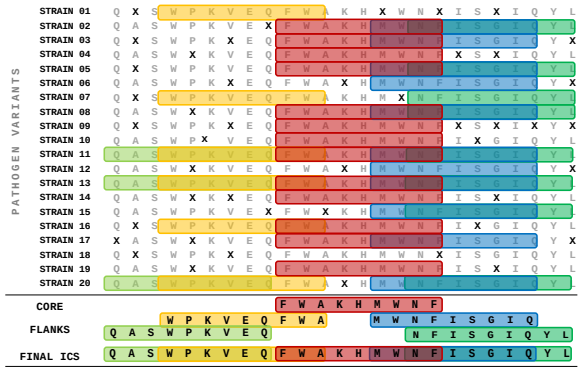

Figure 2. Construction of Immunogenic Consensus Sequences (ICS). *Class II T cell epitope clusters which represent multiple strains of a given pathogen and target multiple HLA alleles are designed using EpiAssembler.*

Aggregatrix determines the minimum set of epitopes necessary to cover the maximum number of HLA types, as well as the maximum number of strain variants of the target pathogen. *VaccineCAD* aggregates potential vaccine candidate epitopes into a string-of-beads design while minimizing deleterious junctional epitopes that may be created in the linking process.

Results
We have achieved proof of principle in animal models for three out of five vaccines for which we currently have prototypes. A therapeutically administered vaccine construct engineered against *H. pylori* using the iVAX system resulted in a significant reduction in gastric colonization compared to unvaccinated controls[1]. Similarly, VennVax, a DNA vaccine expressing conserved epitopes from seven Smallpox genomes, conferred 100% survival to HLA-Tg mice lethally challenged with *Vaccinia*[2]. TulyVax protected 57% of immunized mice against a lethal challenge with *F. tularensis*[3]. Two more vaccines are in the process of validation.

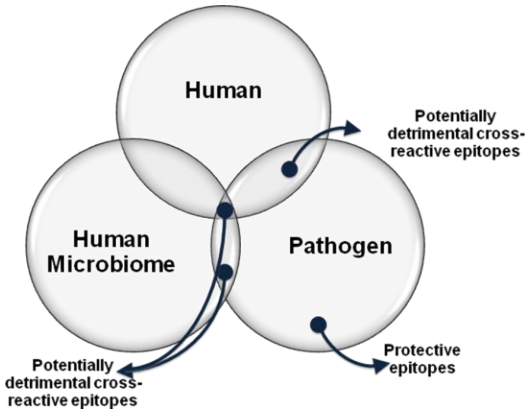

Figure 3. Removal of potentially detrimental epitopes from vaccines. *Using the BlastiMer and JanusMatrix tools, pathogen-derived epitopes with potential to cross react with human or commensal sequences may be identified and selectively excluded from vaccine consideration.*

We are applying the approach to influenza, tuberculosis and HIV, along with biodefense projects. Additional collaborations in the field of neglected tropical diseases are under development. The iVAX toolkit is available for use on neglected tropical diseases free of charge, offering customized vaccine design to investigators at research centers across the globe.

Conclusions
The effect of collecting these immunoinformatics tools, applying them to high-profile vaccine projects, and putting them in the hands of vaccine researchers will accelerate the development of safer, more targeted vaccines which will prove to be critically important for human health and biodefense.

To learn more about iVAX contact denice.spero@gmail.com

The research proposed and analyzed in this work was supported by NIH1U19AI082642

References
[1] Moss SF, Moise L, Lee DS, Kim W, Zhang S, Lee J, Rogers AB, Martin W, De Groot AS. HelicoVax: epitope-based therapetuic Helicobacter pylori vaccination in a mouse model. Vaccine. 2011 Mar 3; 29(11):2085-91.
[2] Moise L, Buller RM, Schriewer J, Lee J, Frey SE, Weiner DB, Martin W, De Groot AS. VennVax, a DNA-prime, peptide-boost multi-T-cell epitope poxvirus vaccine, induces protective immunity against vaccinia infection by T cell response alone. Vaccine. 2011 Jan 10; 29(3):501-11.
[3] Gregory SH, Mott S, Phung J, Lee J, Moise L, McMurry JA, Martin W, De Groot AS. Epitope-based vaccination against pneumonic tularemia. Vaccine. 2009 Aug 27; 27(39):5299-306.