PERSPECTIVE

Pharmacogenomics and Vaccine Development

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Although pharmacogenetics and pharmacogenomics entered mainstream clinical medicine on the drug side, diffusion into the biologics side of clinical medicine has been slow—most notably regarding human vaccines. The consequence is an inadequate science base upon which to leverage new ways of understanding, designing, and evaluating vaccines—particularly for hypervariable viruses and complex pathogens.

VACCINOMICS, ADVERSOMICS, AND VACCINE DEVELOPMENT

The emergence of the field of vaccinomics, adversomics, and systems biology has generated enormous potential in transforming the science of vaccination and vaccine development. In 2007, our group published some of the first work in this area of science.[1] At that time, we outlined the immune response network theory, followed by a fuller integration and development of a new field called vaccinomics, which is the integration of a systems biology approach with the immune response network theory, immunogenomics, immune profiling, and functional studies in order to understand and predict vaccine-induced immune responses at the systems level, and use this information to engineer vaccine candidates and drive individualized vaccinology and personalized vaccinology.[1,2] Later, we developed the concept of adversomics, which is the application of immunogenetics, immunogenomics, and systems biology approaches to identify genetic and molecular signatures for vaccine-induced adverse events (AEs) at the individual and population levels.[3]

Significant evidence indicates that gene polymorphisms and other genetic and nongenetic factors contribute to the interindividual variation observed in immunity in humans. Interindividual variability in response to vaccination is a major challenge in vaccine development for complex and emerging new pathogens. Studies of monozygotic and dizygotic twins have shown heritability of vaccine-induced antibody responses to measles-mumps-rubella (MMR), hepatitis B (HBV), diphtheria-tetanus-pertussis, Hemophilus influenza type b, oral polio, and other vaccines.[4] Evidence of heritability has also been found for some cellular traits.[5] Over the last few decades, candidate gene and genomewide association vaccine studies have demonstrated that interindividual variability in human immune responses to vaccination is genetically determined and may be reliably predicted on an individual basis.[1] These genetic-association studies have identified common and rare gene SNPs/HLA/haplotypes, including epigenetic and gene copy-number variations, as predictors of immune response to vaccination in certain populations. Studies demonstrate that genetic heritability of the non-HLA (cytokines, chemokines, TLRs, viral receptors, vitamins, and others) and HLA class I and II molecules are associated with susceptibility and resistance to multiple human infectious diseases (including severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2)) and vaccine-induced protective immunity.[6,7] We have previously summarized such studies involving measles, mumps, rubella, smallpox, and HBV vaccines.[8] Vaccinomic approaches thus have the potential to provide new biological insights to identified causal variants, and assist in developing novel vaccine candidates.

Genetic polymorphisms/genetic susceptibility may also be an important determinant of "aberrant" immune-mediated responses associated with vaccines (e.g., adversomics).[3] Serious AEs, some for which genetic associations have been suggested, have been reported after influenza (e.g., narcolepsy and Guillain-Barré syndrome), yellow fever (e.g., viremia and neurotropic disease), smallpox (e.g., fever, rash, and lymph node swelling), MMR (e.g., febrile seizures), SARS-CoV-2 (e.g., allergic and anaphylactic reactions, thrombosis with thrombocytopenia syndrome, and Bell's palsy) and other vaccines.[9,10] Despite the significant benefit to populations as a result of vaccination, these rare AEs inhibit vaccine acceptance and infectious disease prevention. Applying vaccinomics/adversomics approaches along with systems biology can play a key role in identifying biomarkers of genetic predisposition to vaccine AEs.

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SYSTEMS BIOLOGY AND VACCINE DEVELOPMENT

Pharmacogenomics and personalized medicine share the conceptual foundation that genomic differences between individuals influence their response to drugs and medical treatments. Further, these differences can be used to design interventions that are safer and more effective. Current approaches to vaccination are focused on a narrow set of immunologic outcomes (e.g., antibody titer) and are rooted in a one-size-fits-all approach.[11] If we wish to apply the principles behind pharmacogenomics and personalized medicine to vaccines,[8] we must evaluate the immune system as a complex system and examine the full range of immunologic activity, ascertain which features are clinically relevant, and assess host characteristics to understand how they affect the immune response and to what extent they alter protection against disease. Systems biology is an approach that comprehensively assesses complex biological systems to identify differences in functional activity and utilizes statistical analyses and computational modeling to understand which of those differences contribute to the initiation, development, kinetics, sustainment, and durability of immune responses to vaccines. It is an ideal approach to study immune responses to infection and vaccination and a complementary method to reductionist approaches.[12]

The comprehensive evaluation of immune responses to vaccines are made possible by so-called "omics" technologies that can be grouped into several large categories.

1. Genomics: extends beyond the genetic sequence to also include the transcriptome, miRNAome, epigenome, and microbiome, as well as T and B cell receptor diversity
2. Proteomics: includes both cataloging the proteins in a serum sample or cell and characterizing protein-protein interactions as well as structure-function studies
3. Systems serology: includes measurements of antibody titers, isotype and subtype classification, Fc interactions and differential antibody functionality, and glycosylation
4. Metabolomics: includes the ability to measure metabolites, lipids, and glycans
5. Cellular phenotyping: advances in mass cytometry, spectral flow cytometry, and methods such as CITE-Seq and REAP-Seq have drastically expanded the number of markers that can be included, allowing for more comprehensive characterization of cells and the identification of novel subsets.

Collectively, these techniques allow investigators to assess biological activity from DNA to RNA to proteins to the biochemically active molecules that act in a sequential and choreographed fashion to create a functional phenotype. Many of these technologies provide data at the level of single cells, providing an ability to discriminate between different signals and responses from different cells within a sample.

Systems biology approaches and omics technologies have led to a deeper understanding of the immune response to influenza, zoster, and hepatitis B vaccines,[13–15] and have already informed the selection of appropriate antigens and/or adjuvants for new vaccines.[16] Such approaches can provide predictive biomarkers of protective or adverse immune responses (AEs) to vaccines[17] and allow the identification of new and additional correlates of protection.

CONCLUSION

In this Perspective, we have briefly summarized the more recent origins and advances in the field of biologic pharmacogenetics under the academic discipline of vaccinomics. Although many advances have been made and are slowly being incorporated into how industry and biotechnology develops novel vaccine candidates, much more needs to be done. Interest in personalized applications of vaccines and drugs is evident; as one example, consider the tremendous rise in the demand for direct-to-consumer genetic testing. This interest will further accelerate as genetic-based testing becomes cheaper and offers more in-depth information. For example, our own work with the measles virus has uncovered SNPs in the *CD46* and *IFI44L* genes that are associated with a substantial reduction in neutralizing antibody response to measles vaccine.[18] Such findings allow the potential for reverse engineering a vaccine that can overcome such a barrier. Understanding why certain individuals are predisposed to specific AEs and which vaccines have a higher risk of eliciting those AEs will allow healthcare providers to match the right vaccine to the right recipient in order to minimize risks and maximize benefits.

An important issue that will need to be addressed is the development of feasible ways to increasingly implement these concepts into clinical practice. If borne out by the data, could we create specific vaccines for women that contain lower antigen doses—as we do for infants for example? As an example, currently clinicians have seven different influenza vaccine platforms available for specific patients (young, immunosenescent, etc.). Can we streamline regulatory approval for multiple vaccine products that differ by antigen dose or another characteristic once safety and a correlate of protection is known?

As larger phenotype-genotype databases become increasingly available, we will be able to intelligently personalize our selection of the right vaccine, at the right dose, for the right patient—and abandon a purely population-based approach where we assume that everyone is at the same risk for every disease and should be immunized with the same series of vaccines and at the same dose in order to induce protection. As examples to consider, it is notable that women generally demonstrate higher immune responses to vaccines than men; however, that they also have significantly higher rates of local and systemic side effects. Do women need the same dose as men? Some individuals rapidly develop protective immune responses after one to two doses of HBV vaccine, whereas others may need six or more doses of HBV, and yet others never respond at all. The development of a CpG-adjuvanted vaccine (Heplisav-b) that requires fewer doses and retains immunogenicity in population groups that fail to respond to previous HBV vaccines is an excellent example of how the concepts described in this article can be leveraged for improved vaccines. Although it has become apparent just how diverse the range of genetic influencers on vaccine response is, we can begin to group them into helpful categories that will allow us to predict the risk of a serious infection, the likelihood of a protective or aberrant immune response to a vaccine, the number of

doses needed of a specific vaccine type, and the durability of that protective immune response—all questions that are currently under discussion regarding coronavirus disease 2019 (COVID-19) vaccines, for example. The integration of the new biology, systems-level approaches rather than reductionistic approaches, genomics, and multiomic approaches create a bright future for the use of vaccinomics and adversomics in developing novel vaccine candidates and advancing our understanding of how vaccines can help or harm individuals.

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CONFLICT OF INTEREST

Dr. Poland is the chair of a Safety Evaluation Committee for novel investigational vaccine trials being conducted by Merck Research Laboratories. Dr. Poland offers consultative advice on vaccine development to Merck & Co., Medicago, GlaxoSmithKline, Sanofi Pasteur, Emergent Biosolutions, Johnson & Johnson/Janssen Global Services LLC, Dynavax, Genentech, Eli Lilly and Company, Kentucky Bioprocessing, Bavarian Nordic, AstraZeneca, Exelixis, Regeneron, Vyriad, Moderna, and Genevant Sciences, Inc. These activities have been reviewed by the Mayo Clinic Conflict of Interest Review Board and are conducted in compliance with Mayo Clinic Conflict of Interest policies.

Drs. Poland and Ovsyannikova hold patents related to vaccinia and measles peptide vaccines. Dr. Kennedy holds a patent related to vaccinia peptide vaccines. Drs. Poland, Ovsyannikova, and Kennedy have received grant funding from ICW Ventures for preclinical studies on a peptide-based COVID-19 vaccine. Dr. Kennedy has received funding from Merck Research Laboratories to study waning immunity to mumps vaccine. This research has been reviewed by the Mayo Clinic Conflict of Interest Review Board and was conducted in compliance with Mayo Clinic Conflict of Interest policies.

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