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COMMENTARY

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The Human Vaccines Project: Towards a comprehensive understanding of the human immune response to immunization

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ABSTRACT

Although the success of vaccination to date has been unprecedented, our inadequate understanding of the details of the human immune response to immunization has resulted in several recent vaccine failures and significant delays in the development of high-need vaccines for global infectious diseases and cancer. Because of the need to better understand the immense complexity of the human immune system, the Human Vaccines Project was launched in 2015 with the mission to decode the human immune response to accelerate development of vaccines and immunotherapies for major diseases. The Project currently has three programs: 1) The Human Immunome Program, with the goal of deciphering the complete repertoire of B and T cell receptors across the human population, termed the Human Immunome, 2) The Rules of Immunogenicity Program, with the goal of understanding the key principles of how a vaccine elicits a protective and durable response using a system immunology approach, and 3) The Universal Influenza Vaccine Initiative (UIVI), with the goal of conducting experimental clinical trials to understand the influence of influenza pre-exposures on subsequent influenza immunization and the mechanisms of protection. Given the dramatic advances in computational and systems biology, genomics, immune monitoring, bioinformatics and machine learning, there is now an unprecedented opportunity to unravel the intricacies of the human immune response to immunization, ushering in a new era in vaccine development.

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A break from the past is needed

From a historical perspective, the success of vaccination has been unprecedented, and by exploiting the two hallmarks of the mammalian immune system – specificity and memory, vaccines are considered one of the greatest public health advances ever implemented.[1] The approach to vaccine development to date has been largely empirical: identifying a pathogen, inactivating or attenuating it, injecting in animal models, testing for immunogenicity, identifying protective antigens, formulating a vaccine, injecting again, testing for safety in humans, and eventually widespread testing for efficacy. While this has worked for many infectious pathogens, it has failed for many as well. There has been a prevailing belief among some vaccinologists that an understanding of the underlying mechanism of how a vaccine elicits a protective and/or durable response is not as important as whether or not a vaccine actually works, and to date, the detailed mechanisms of how most vaccines elicit a protective immune response are not completely understood. The combination of the empirical approach to vaccine development and our inadequate understanding of the details of the immune response to immunization have resulted in countless recent vaccine failures that have cost billions of dollars and several decades of time lost in the development and testing of vaccines that are weakly immunogenic, not efficacious and sometimes capable of enhancing disease.

After several high-profile product development failures of vaccines for infectious and non-communicable diseases, there is a general consensus that animal models are imperfect in predicting human immune responses.[2,3] Moreover, we have begun to acknowledge that the human immune system is just that, a system, which is inextricably integrated with every organ system and cell type of the body as a means to surveil all sites for entry of foreign molecules and pathogens. Similarly, we are increasingly aware that accurate vaccine-specific responses must be tested and measured within the context of the overall biology of an individual, and biological variables, such as age and sex,[4-6] are factors that are integrated and inseparable from the immune system and its responses. Results from recent vaccine trials has also revealed that environmental factors, such as physical geography and prior exposures,[7,8] strongly influence the immune response to vaccination, and we are just beginning to acknowledge the impact of psychosocial and cultural factors (e.g., stress, sleep, diet, obesity, smoking, etc.) on vaccine responses as well.[9-11]

Because of these limitations in our understanding of the complexities of the immune response to immunization, in 2015, the Human Vaccine Project was launched with the mission to decode the human immune response to accelerate development of vaccines and immunotherapies for major diseases (www.humanvaccinesproject.org). Given the dramatic advances in computational and systems biology, genomics, immune monitoring, bioinformatics and machine learning, we believe we have the unprecedented opportunity to unravel the intricacies of the human immune system and the complexity of

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the human immune response to immunization, and usher in a new era in vaccine development.[12,13]

The Human Vaccines Project

The Human Vaccines Project is a human immunology-based clinical research consortium, established as a non-profit public-private partnership currently comprised of scientific hubs at: Vanderbilt University Medical Center (VUMC); The University of British Columbia (UBC), Canada; The Mesa Consortium, consisting of La Jolla Institute (LJI), The Scripps Research Institute (TSRI), The J. Craig Venter Institute (JCVI), and the San Diego Supercomputing Center (SDSC) at the University of California San Diego. Since its inception, the Project is also has engaged with the vaccine industry and has established partnerships with leading biopharmaceutical, biotechnology and product development groups that enable the translation of Project research findings into the design and testing of new and improved vaccines and biologics.

The Project currently has three programs: 1) The Human Immunome Program, with the goal of deciphering the complete repertoire of B and T cell receptors across the human population, which we term the *Human Immunome*, 2) The Rules of Immunogenicity Program, with the goal of understanding the key principles of how a vaccine elicits a protective and durable response using a system immunology approach, and 3) The Universal Influenza Vaccine Initiative (UIVI), with the goal of conducting experimental clinical trials to understand the influence of influenza pre-exposures on subsequent influenza immunization and the mechanisms of protection. The overall goal of the UIVI it to use the detailed data from our influenza clinical trials to inform the design of universal and 'universally responsive' influenza vaccines across all age groups, sexes, geographic locales and prior exposures.

The Human Immunome Program

Led by Dr. James Crowe at Vanderbilt University Medical Center, the Human Immunome Program involves an unprecedented level of sequencing and data analysis.[14] It is estimated that if the human genome contains approximately 25,000 genes, then the Human Immunome has the potential to contain 10^{11} to 10^{15} immune receptor genes. To date, the complete immunomes for 3 people have been sequenced and the data is now being analyzed to better understand the global repertoire of receptors within each person, the degree to which individual repertoires are unique, and the percentage of B and T cell clonotypes that are shared among individuals. With only 3 donors fully sequenced thus far, this program has already generated over 6 billion transcripts to process and analyze, which is being facilitated by the expertise and computing capacity of JCVI and the SDSC. An additional goal of the Human Immunome Program is to understand the differences in the immunomes of healthy vs diseased individuals, and we are currently sequencing the immunomes from individuals with multiple sclerosis for comparison to non-diseased individuals. We are also sequencing the immunomes from newborn cord blood to determine the repertoire of B and T cells receptors that humans are born already possessing. The overarching objective of the Human Immunome Program is to create a sequence database compiled from these various areas of inquiry that will allow us to more fully understand the adaptive immune system in health and in disease, in the young and in the old, and inform vaccine discovery and future vaccine development efforts.

The Rules of Immunogenicity Program

The second program of the Human Vaccines Project is the Rules of Immunogenicity Program, which is led by Dr. Tobias Kollmann at the University of British Columbia, Canada. The Rules Program involves conducting experimental clinical trials using licensed vaccines as probes to perform comprehensive omics and immunoassays to uncover the components the immune system that are responsible for generating a protective and durable response to a vaccine. Our first clinical trial began in 2017, and focused on the response to the hepatitis B vaccine, Engerix-B (GlaxoSmithKline) in two populations of older Canadian adults; a younger group (40–60 y.o.) and older group (61–80 y.o.). The reasons for choosing the hepatitis B vaccine were two-fold: First, the correlate of Engerix-B efficacy is well-established (i.e., titre $\geq$ 40 mIU/ml), and second, because seroconversion with this vaccine is dose-dependent, with approximately 30% of subjects reaching titers > 10 mIU/ml after 1 dose, 75% after two, and 90% after 3 doses), we could conduct a detailed comparison of the immune response between those who seroconverted after a single dose to those who did not. Participants received three doses of vaccine, on days 0, 28 and 180, and unlike most vaccine clinical trials, we specifically designed the trial to look at very early events immediately following immunization. This was to allow for the measurement of innate immune responses and the assessment of innate signatures and/or novel transcriptional activation patterns that could be directly correlated with subsequent adaptive responses and seroconversion. In addition to peripheral blood, we also performed fine needle aspiration (FNA) of axillary lymph nodes pre- and 2 weeks post-immunization to assay for antigen-specific germinal center B cells and T follicular helper (Tfh) cells in response to the vaccine.

We then conducted perhaps the most extensive series of assays on a total of 10 blood draws from each participant over the course of 208 days. These assays included: antibody responses (serology, sub-class, avidity), B cell analysis (B cell ELISpot, NextGen sequencing of IgG memory B cells), flow cytometry immunophenotyping (FlowBin analysis), cell-mediated immunity (IFN-g ELISpot), single-cell RNA-sequencing of 5 different innate cell populations, transcriptomics, proteomics, metabolomics, epigenetics, microbiome analysis (stool, nose, mouth, skin), lymph node analysis using FNA for B and Tfh, and Tru-Culture Immunomonitoring (Darragh Duffy, Institut Pasteur).

The results from our preliminary transcriptomic data analysis showed a very strong association between vaccine-specific responses and sex and age, which was also observed in the flow cytometry data and the complete blood counts with differential, similar to results previously reported by other groups.[15-17] For systems analysis across multiple data sets, the UBC team of researchers employed the NetAnalyst platform (open access), which takes into account known protein-protein interactions to develop a functional network of interactions between select data sets, revealing the emergence of numerous networks with unique hubs connecting novel transcriptional pathways. In contrast, a second analysis

was also conducted that was agnostic and not based on any prior assumptions about known interactions within the data set (DIABLO, open source). This data-driven approach simply considers all data points as "features" and compares them against each other, and then calculates all correlations within a multivariate space.

The power of both of these systems approaches lies in their capacity to identify novel immune correlates by integrating across multiple data sets to identify positive and negative associations that are uncovered only after data unification. The integration of flow cytometry data, DNA methylation, plasma proteomics, whole blood proteomics and transcriptomics showed several positive and negative immune correlates in both the younger and older adult participants and for men and women following hepatitis B immunization. When the data from both the gnostic (NetAnalyst) and agnostic (DIABLO) approaches were combined and their outputs compared for common transcriptional pathways, the same pathways were identified in both approaches. From these analyses of the transcriptomics, 6 novel pathways involved in the immune response to hepatitis B immunization were identified (unpublished data).

Although we are still in the early stages of data analysis, the information and insight that will be gained from this experimental clinical trial of hepatitis B immunization will likely yield the broadest and deepest assessment of a vaccine response ever conducted. The power to integrate data across multiple data sets and across the multi-omics platforms (e.g., identify novel and distinct transcriptional pathways, quantify specific cell types, assess changes in cellular activation states, determine characteristic effector cell ratios and monitor effector cell dynamics, measure the kinetics of soluble mediator secretion, assay for changes in DNA methylation patterns, detect alterations in microbial populations, measure tissue-specific immune responses, identify changes in blood and plasma protein composition and concentrations, and measure changes in metabolic intermediates), will set new standards for systems vaccinology research and will undoubtedly lead to groundbreaking discoveries about the human immune response to vaccination.

The Universal Influenza Vaccine Initiative (UIVI)

The third program of the Human Vaccines Project is the Universal Influenza Vaccine Initiative, with the purpose to understand the underlying immune mechanisms involved in the response to influenza in order to facilitate the research and development of universal influenza vaccines.

Because current seasonal influenza vaccines are consistently ineffective due to antigenic drift, and because the potential for pandemic influenza outbreaks remains a threat, the Human Vaccines Project has begun planning experimental clinical trials designed to increase our understanding of the mechanisms that underlie the immune response to initial influenza exposure (infant cohort) and more fully elucidate the mechanisms of how B and T cell memory responses (older adults) affect subsequent responses to influenza immunization.[18] The information gained by conducting these experimental influenza trials that will also involve in-patient challenge studies, are desperately needed if we are to make any significant gains in the development of a vaccine that will be broadly efficacious in all populations, regardless of previous influenza exposures.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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