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Systems Immunogenetics of Vaccines

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1. Introduction

Since the 1700s, vaccine development has utilized an empirical model (e.g., the “isolate – inactivate/attenuate – inject approach”) [1]. The development for vaccines against highly variable and incurable diseases, including acquired immunodeficiency syndrome, malaria, dengue fever and others has largely been unsuccessful which further emphasizes the need for a paradigm shift in vaccine strategies [2]. These diseases require a rational approach for directing vaccine responses toward different immune cell subsets that can vary based on the genetics and cellular tropism of these pathogens [3, 4]. An additional component is host variability that includes the multiplicity of immune response genes, as well as the diversity of human leukocyte antigen (HLA) haplotypes, allowing human populations an almost limitless immune response repertoire [5]. Vaccine efficacy can be impacted by a number of other host factors including age, gender, ethnicity, and other possible confounders [6, 7, 8, 9]. It is now clear that pathogen and host variability, as well as the interactions between them, must be considered in vaccine design.

2. Current Challenges in Vaccine Development

Oyston and Robinson [10] recently summarized some of the key issues and barriers currently faced in vaccine development that we have aggregated into several major challenge areas (Figure 1). The first major challenge is clinical characterization. This highlights the need for identification of signatures of immune correlates of protection, novel approaches to quantify patient exposure and immune responsiveness as well as pathogen genetic variation in the population. The lack of well-defined correlates of protection with most vaccines has been a major impediment to the successful development of new vaccines [11]. The second challenge area is the research and development, in which economic constraints can lead to an inflated false nondiscovery rate (e.g., promising candidates are incorrectly discarded early in the pipeline). There is tremendous potential for data mining and computational approaches to “rescue” candidates, emphasizing the need for public repositories and open data. A third challenge area is delivery and includes not only socio-

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economic concerns regarding vaccine availability and manufacturing but also mode of administration and appropriate dosing. It is here that the systems approaches from precision medicine and pharmacogenomics can lead to “individualized” vaccine delivery.

3. Rationale for Systems Thinking

In each of the challenge areas described above, there is opportunity for innovative, systems-level and computational approaches (Figure 1). The response to infection results from complex interactions between the host immune system and the pathogen. Our ability to predict this response and to develop effective vaccines or treatments is complicated by two key factors: 1) the enormous amount of genetic variability in the human population, and 2) the constant evolution of pathogens. These two factors produce a wide spectrum of possible host-pathogen interactions and necessitate the use of systems-level approaches for studying infectious disease [12, 13, 14, 15]. Rather than focusing on individual components within a larger process, systems-level approaches attempt to model the entire set of interactions among individual components in a system. These models are then used to predict the behavior (i.e., host response) that results from those interactions.

Systems-level research is dependent on having a complete inventory of the components of a system. The large amount of genomic and proteomic data resulting from advances in high-throughput technologies has greatly improved the ability of researchers to construct models of the host immune system and its interaction with pathogens. This allows us to better characterize the phenotypic variation that is a culmination of multiple interactions among numerous genetic and environmental factors. The field of *systems genetics* integrates the approaches and methods of systems biology with those of genetics to correlate genotype and phenotype in complex diseases [16]. Critical for vaccine development is the related field of *systems immunogenetics* in which the interplay of systems approaches and genetics is focused on the immunological domain.

Gene or protein interaction networks provide a framework for modeling the complex molecular interactions within cells. These networks are built on the idea that disease states are rarely the consequence of a single molecular abnormality (i.e. genetic variation), but are instead the result of the interaction of one or more abnormalities with numerous other cellular components. Network analyses done in a wide variety of diseases have been used successfully to identify sets of functionally related genes, sometimes called modules, associated with disease states. These modules provide insight into disease mechanisms and have also been used to predict outcomes [17].

Recent methodological advances in network analysis are ideally suited for the study of infectious disease. For instance, differential network analysis, which models the change in network structure across time or across multiple conditions, will be a key technique for studying the response to infection and the response to a vaccine [18]. Furthermore, cross-species interaction networks modeling the interactions between pathogen and host, will allow researchers to identify the key factors associated with host response and potential molecular targets for treatment or vaccine development [19].

4. The Power of Multi-omics Comparative Studies

Rapid ‘omics’ technological advances allow high-throughput, quantitative measurement of diverse biological data types including transcriptomics, (mRNA transcripts), proteomics (proteins/peptides), metabolomics (metabolites) and interactomics (molecular interactions). As these approaches are complementary and offer different insights, integration via a multi-‘omics’ approach, is key to realize a systems perspective. The scale of omic data from biomedical and clinical researchers has recently expanded to an unprecedented level - from

basic biology to translational medicine, multi-omic data can enable phenomenal discoveries. To handle these data, a wealth of complex statistical techniques and algorithms has been developed to process, transform, and integrate data.

In addition to the high throughput, high dimensional readouts for ‘omics’, there is also the development of high throughput, high dimensional immune phenotypes. While classical studies focused on antibody response to vaccination, it is now possible to characterize the complexity and heterogeneity of the immune response. Flow cytometry is a key approach for the characterization of immune phenotypes and function in diverse subsets of cells from complex mixtures [20]. Mass cytometry, or CyTOF (DVS Sciences) is a recent variation of flow cytometry, in which antibodies are labeled with heavy metal ion tags and readout is by time-of-flight mass spectrometry [21]. This allows for the combination of many more antibody specificities in a single sample, without significant spillover between channels.

A major objective in systems immunogenetics is the identification of molecular signatures associated with the immune response after vaccination. Recently, systems biology approaches have been used to study the response to the yellow fever vaccine YF-17D and two influenza vaccines (inactivated and live attenuated) [22, 23, 24]. In both studies, a range of molecular measurements and gene expression data were analyzed to identify signatures predictive of vaccine response. Beyond testing for simple correlations within the data, sophisticated machine learning algorithms for feature selection and prediction of the outcomes of interest were utilized. One such approach is ‘discriminant analysis via mixed integer programming’ (DAMIP) algorithm [22, 23, 25, 26] that provides an optimization-based predictive modeling framework. This approach combines a discrete support vector machine coupled with a robust feature selection module. This well-established approach has the ability to classify with high prediction accuracy even with small training sets [22, 23]. These studies were successful in showing that important markers of vaccine protection can be predicted soon after vaccination. This provides a hypothesis-testing framework that can guide future trials or follow-up studies in model systems [27, 2, 11]. These studies would follow a systems-level “life cycle” focused on the development, refinement, and validation of immune correlates of protection, which can be used to classify innate immune response and protective vaccines in human subjects (Figure 2).

An important consideration for the development of these signatures of immune response is validation. The development of nanoliter-volume multiplexed real-time PCR allows simultaneous, high resolution, temporal quantification of expression signatures. This is particularly useful for detailed analysis of a candidate signature over many conditions (e.g., multiple time points, stimuli, etc.) and at different levels of resolution (single cells, rare cell types and flow sorted/deconvoluted subsets). It is important to note that the validation plan and choice of platform should be determined during the initial experimental design planning to ensure feasibility and power for both the training/testing and validation phases.

5. Population Genetic Considerations for Targeting Vaccine Development

Genetic research on infectious disease requires studying genetic variation in both the host genome and the pathogen genome. Identifying genetic variants that impact susceptibility to, and progression of, infection may provide significant progress in the development of treatments and vaccines. A better understanding of pathogen evolution may also provide benefits for vaccine development.

Population genetic studies have provided a great deal of understanding about the genetic factors responsible for the variation in susceptibility to infection, and in turn have also provided a more complete understanding of the key interactions between host and pathogen that contribute to the host response. There are numerous examples of host genetic variation

having a significant impact on susceptibility to infection, from the beta-globin polymorphism that protects against malaria infection [28] to the deletion in the chemokine receptor 5 (CCR5) gene that provides resistance to HIV infection [29]. Yet, for the most part, susceptibility to infection is a complex trait influenced by multiple genes of small effect, the environment and, of course, the pathogen's own genome. In taking this complex-trait perspective of infectious disease, methods used to study the genetics of other common complex disorders have been adapted to the study of infectious disease [30].

Before genome-wide genotype measurements were possible, candidate gene studies provided the first evidence of the impact of host genetic variation on susceptibility to infection [31]. In HIV research, for example, the human leukocyte antigen (HLA) genes were studied and found to be important host factors associated with the progression of the disease.

The genome-wide association study (GWAS) provided a method to detect novel genetic factors associated with infection, without the need for any *a priori* knowledge about the genes being tested. HIV infection was the subject of the first GWAS in infectious disease [32]. The study confirmed findings from earlier candidate genes studies, but also identified a novel association between the ZNRD1 gene and CD4 T cell decline. Subsequent GWAS of HIV progression have identified multiple other significant novel associations [31]. GWAS of a small number of other infectious diseases have also been conducted (Table 1). However, the results from GWAS of infectious diseases have been plagued by the same problems seen in other complex diseases. For the most part, the associations discovered have small effect sizes, and not all associations have been replicated [30]. These studies represent a first step in identifying the genetic factors involved in susceptibility to infection and disease outcome.

Contextually, genes are interacting in networks in intricate ways. However, most GWAS have focused on main effects, primarily via additive models of common variants and more recently examining contributions of rare variants [33]. Here again, the network models and approaches mentioned above can offer a way to fully realize the potential of these public population data sets via secondary analysis and mining in order to identify epistatic interactions and aggregate-level characteristics (e.g., pathway, network).

To build on the knowledge gained from GWAS and to take the next step towards the ultimate goal of new treatments and vaccines, we must use the information about host genetic susceptibility factors to identify the precise host-pathogen interactions that are potential targets for intervention. An obvious example of the potential benefits of this line of inquiry was the development of a new anti-retroviral therapy prompted by the discovery of the protective CCR5 deletion [34]. An open area for future studies is the characterization of causal variations and host-pathogen interactions in the context of disease outcome [35].

5.2. Pathogen Evolution

Just as important as the study of host genetic variation is the study of pathogen genetic variation. In particular, the ability to predict pathogen evolution could significantly improve vaccine development as well as provide new treatment regimens that can anticipate and avoid drug resistance. Recent research on the genetic diversity of *Mycobacterium tuberculosis* complex (MTBC) suggests that different lineages of MTBC may have adapted to specific human populations in different geographical regions. These findings highlight the important effects of interactions between host and pathogen genomes in determining the outcome of tuberculosis (TB) infection.

A consequence of TB adaptation that has become a major public health threat is the emergence of drug resistance, with some strains recently identified that are resistant to all antituberculosis drugs. The drug resistance of bacteria depends primarily on the acquisition of specific resistance-conferring genetic mutations. However, it is becoming clear that the impact of drug resistance mutations depends also on the larger genetic context in which those mutations arise. For instance, it has been hypothesized that particular strains of TB (e.g. the "Beijing" family) may be more likely to develop drug resistant mutations. In addition, there is a mounting body of evidence that epistatic interactions—other mutations that modulate the effect of drug resistance mutations—are an important factor affecting the emergence of drug resistance. There is evidence that epistasis can both promote the evolution of drug resistance ("positive epistasis") by lowering the fitness cost of drug resistance conferring mutations, as well as inhibit it ("negative epistasis") by increasing the cost [36]. Not surprisingly, these same evolutionary processes can also affect the ability of pathogens to escape the human immune system. Knowing the specific effects of different genetic backgrounds (i.e. epistatic interactions) on the development of drug resistance and immune escape could have important implications for the treatment of infectious diseases.

Using influenza as a use case, Kryazhimskiy and colleagues have developed a statistical method to detect positive epistasis between pairs of variant positions in a protein sequence. The method is based on the idea that during the course of sequence evolution, an initial mutation will be rapidly followed by a second mutation if the two are involved in positive epistasis [37]. Techniques like this one, in combination with effective monitoring of pathogen strain evolution, could greatly enhance our ability to predict and overcome drug resistance and immune escape.

The long history of repeated pathogen adaptation followed by host adaptation, sometimes referred to as an arms race, has played a large role in the evolution of both genomes. Just as epistatic interactions in pathogen genomes allow pathogens to withstand assaults by drugs and the human immune system, epistasis also plays a role in the immune system's ability to adapt to ever changing pathogens (an example is the adaptation of the PKR antiviral protein in response to the poxviral K3L protein) [38].

Systems biology approaches will be crucial for developing a more comprehensive view of the effects of genome variation in infectious disease. Techniques will be needed to identify, model and predict the effects of genetic interactions within host and pathogen genomes, as well as interactions between the two genomes.

6. Towards Precise Vaccine Development and Delivery

Precision medicine is focused on providing clinically actionable information to ensure the timely delivery of the appropriate drug at the correct dose specific to a given patient [39]. The use of 'precision' rather than 'personalized' is deliberate as it emphasizes the concept that the molecular information improves the precision with which patients are categorized and treated [40]. While popularly associated with determination of therapeutic interventions for cancer, the field is actually much more broad and has clear implications for vaccine development and delivery.

Studies have begun to quantify the genetic variation related to vaccine-specific immune responses and investigate appropriate dosing in light of this information. A twin study for measles vaccination determined that the heritability of response to measles vaccine was 89% [41]. Follow-up studies identified HLA-restricted recognition of measles virus epitopes with quantifiable impacts on immunity that appeared to be overcome by additional dosing regimens [42]. This suggests that there is tremendous potential for systems immunogenetics guided stratification and individualized delivery.

7. Conclusion

System Immunogenetics provides a powerful and robust framework for vaccine discovery, development, and delivery. Mechanistic studies can reveal new vaccine targets or “rescue” candidates discarded previously by elucidating how genetic variation can influence innate and adaptive immune responses to vaccines. This can provide signatures to allow early identification and patient stratification related to vaccine failure and adverse events. Taking a cue from the clinical pathways for precision medicine in oncology and other disciplines will allow for more ‘precise’ vaccine development for subsets of patients relative to their immune phenotype and genomic architecture.

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Systems Immunogenetics of Vaccines Highlights

- Systems approaches offer new paths for vaccine discovery, development, and delivery
- More studies needed to elucidate both host and pathogen genetic variation
- Goal is to learn how genetics impacts development of protective immune responses
- Immune correlate of protection signatures can guide clinical patient stratification
- Potential to leverage precision medicine framework in vaccinology

Figure 1.

Current Challenge Areas in Vaccine Development offer opportunities for application of systems biology and computational approaches.

Figure 2. System "life cycle" focused on the development, refinement, and validation of immune correlates of protection signatures that can be used to classify innate immune response and protective vaccines in human subjects

Table 1

Key findings from Genome Wide Association Studies relevant to infectious disease and vaccine development.

Year	Phenotype	Most Significant Association / Mapped Gene (SNP-Risk Allele)	P-value	Replication	Ref.
2009	HIV-1 control	HCP5 (rs2395029-G)	5e-35	Y	43
2010	HIV-1 control	MCM8 (rs454422)	1e-6	N	44
2010	HIV-1 control	WASF5P - HLA-B, intergenic (rs9264942-C)	3e-35	N	45
2010	HIV-1 susceptibility	RPL4P5 - C9orf123, intergenic (rs842304)	4e-6	N	46
2011	HIV-1 susceptibility	GLTSCR1 (rs3745760)	8e-7	N	47
2009	AIDS progression	SEPT2P1 - PRMT6, intergenic (rs4118325-G)	6e-7	N	48
2009	AIDS progression	HCP5 (rs2395029-G)	3e-19	Y	49
2012	Immune response to smallpox vaccine	WDR92 (rs4078978-A)	2e-18	N	50
2012	Immune response to smallpox vaccine	MKX (rs10508727-?)	1e-10	N	51
2012	Influenza severity	CD55 (rs2564978)	0.011	Y	52
2009	Hepatitis B	HLA-DPB1 (rs9277535-G)	6e-39	Y	53
2011	Hepatitis B	HLA-DPA1 (rs3077-G)	2e-61	Y	54
2011	Hepatitis B	GRIN2A (rs11866328-G)	2e-8	N	55
2011	Response to Hepatitis B vaccine	BTNL2 - HLA-DRA, intergenic (rs3135363-?)	7e-22	Y	56
2010	Chronic Hepatitis C	IFNL3 - MSRBIP1, intergenic (rs8099917-G)	6e-9	N	57
2012	Response to anthrax vaccine	SRSF10P1 - MEX3C, intergenic (rs7230711-C)	1e-6	N	58
2009	Leprosy	LACC1 (rs3764147-G)	4e-54	Y	59
2011	Leprosy	ADGB (rs2275606-A)	4e-14	Y	60
2009	Malaria	OR51V1 - HBB, intergenic (rs11036238-?)	4e-11	Y	61
2012	Malaria	ABO (rs8176719-G)	4e-21	Y	62
2010	Meningococcal disease	CFHR3 (rs426736-?)	5e-13	Y	63
2010	Tuberculosis	RPS4XPI8 - UBE2CP2, intergenic (rs4331426-G)	7e-9	Y	64
2012	Tuberculosis	RCN1 - WTI, intergenic (rs2057178-?)	3e-11	Y	65

Source: <http://www.genome.gov/gwastudies/> (accessed May 9, 2013)