Systems Vaccinomics: The Road Ahead for Vaccinology

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Introduction

IN 1985, an Institute of Medicine report (Division of Health Promotion and Disease Prevention and Institute of Medicine, 1985) stated: "Vaccines are an elegant solution to one of the perennial problems of the human race—infectious disease. The body's own protective mechanisms are primed by specific interventions to thwart the invasion of or multiplication of pathogenesis." Vaccines are indeed one of the great triumphs of modern medicine and public health: they prevent disease, they are relatively inexpensive, easy to deliver and their effects long lasting, and their mechanism of action relies entirely on activation of our body's own protective immunological mechanisms.

Yet, despite the historic successes of vaccines, or perhaps because of these successes, vaccinology has evolved to rely almost entirely on an empirical, trial-and-error process, in which the pathways to protective immunity—the early events that lead to the development of long-lived protection against infection by a given pathogen—remain largely unknown, and for those successful vaccines, largely unnecessary to know (D'Argenio and Wilson, 2010). Despite this, vaccinology is undoubtedly the most powerful public health intervention available, saving millions of lives and preventing disease in hundreds of millions of people worldwide. However, a better understanding of the immune response, coupled with an improved ability to elicit these responses by immunization, appears to be key to future success in vaccine development against pathogens such as HIV, tuberculosis (TB), and malaria, that have, to date, been resistant to traditional trial-and-error approaches.

These three pathogens—the big three—account for a significant proportion of premature deaths and morbidity worldwide. In addition, the burden of treating these diseases has siphoned significant financial and health care resources away from other urgent global health needs. Over 11 million people live with TB, almost 250 million cases of malaria, including approximately 1 million deaths in children, were reported in 2008, whereas over 33 million people worldwide are living with HIV/AIDS, including 2.5 million people who became newly infected with HIV in 2009.

Recent advances in our understanding of the human immune system and the intertwined functions of the innate and

adaptive immune response, as well as new insights into host-pathogen interactions, and the development of powerful new postgenomic technologies, are now available to be focused on developing, testing, and improving vaccine candidates.

One indirect and largely unanticipated side effect of the Human Genome Project has been a transformation in the power of modern biology, driven by the development of powerful new "omic" technologies (genomics, proteomics, etc.), and associated computational and high-throughput technologies. Together, these advances are fueling the development of a new science of systems biology that has opened up the ability to understand the overall architecture of complex biological systems.

These advances have led to the development of new clinical investigative tools, which has made the human a robust experimental organism for discovery research (Brenner, 2003). It is timely, therefore, to undertake the development of a new science of vaccinomics that is grounded in leading edge science, including systems biology, and a culture of science-driven clinical trials and clinical research.

The goals of this new science of vaccinomics or systems vaccinology (Pulendran et al., 2010) are to develop new vaccines through understanding the global architecture of the human immune response and the changes that occur following vaccination, and to define the correlates of protection, or more appropriately, the signatures of protection that are required to elicit a protective immune response. Vaccine development has largely been focused on trying to identify a specific immune response that might be exploited to develop a vaccine capable of eliciting long-lived protection against a pathogen (Plotkin, 2008). However, the power of a systems approach in unraveling potentially novel mechanisms of vaccine action, and in enabling the prediction of the immunogenicity and efficacy of vaccines, has been highlighted by recent studies (Gaucher et al., 2008; Querec et al., 2009; Young et al., 2008). With the development of high-throughput approaches that allow exploration of the interconnected networks that control and drive the immune response, vaccine development is on the verge of a fundamental shift from the search for a single correlate (or multiple, independent correlates), to the identification of multifactorial signatures associated with immunological protection.

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This new science of vaccinomics also promises to close the current gap between clinical trials and discovery science, a gap that has compromised vaccine development. As highlighted in the 2010 Scientific Strategic Plan of the Global HIV Vaccine Enterprise (The Council of the Global HIV Vaccine Enterprise, 2010), human clinical trials no longer need be considered as separate from fundamental research but rather can be viewed and conducted as an integral part of the research continuum between discovery and clinical testing. This transformation in thinking has been made possible by the development of robust systems biology approaches to aid both in the design and testing of novel vaccine concepts and the analysis of the complexity of the immune response in humans. With powerful new laboratory and computational techniques, the design and testing of novel vaccine candidates in humans has become feasible. Capturing the full advantage of these advances, however, will require real-time laboratory analysis in order to extract the full depth of immunological, epidemiological, and clinical information that a well-conceived and conducted trial can yield. This objective will only be realized through close partnership between basic and translational scientists, computational biologists, clinicians, statisticians, industry, regulatory authorities, and funders.

Positioning Vaccinomics within Translational Research

Closing the gap between discovery and clinical research is not unique to vaccine development. There is considerable interest in both accelerating and improving drug design by taking advantage of the growing understanding of the molecular mechanisms responsible for human disease (Crowley

and Gusella, 2009; Hörig et al., 2005; Skarke and FitzGerald, 2010). For example, recent successes in the development of new anticancer drugs have been built on the discovery of “driver” mutations responsible for the aberrant growth characteristics of cancer cells (de Bono and Ashworth, 2010; Varmus, 2006). These fundamental biological insights, when combined with combinatorial chemistry, high-throughput screening technologies, and biomarker development, have transformed cancer clinical trials and the drug discovery process (de Bono and Ashworth, 2010).

Translational medicine is characterized by strong linkages between the lab and the clinic, and recognition that the success of translational medicine rests on iterative cycles of research between the laboratory and the clinic. Advances in basic science drive trial hypotheses, whereas trial results provide feedback and drive further refinements and hypothesis testing. Clinical trials should be designed from the beginning with such iterations fully built into their planning to ensure, for example, that the frequency and nature of biological sample acquisitions is adequate to allow for hypotheses to be tested and further trial iterations performed. In cancer trials, the development of intermediate biomarkers are key to accelerate trials and to assess interpatient response heterogeneity (de Bono and Ashworth, 2010).

We suggest that it is timely to develop a new science of vaccinology that is driven by similar considerations. As schematically shown in Figure 1, vaccine design and testing is undertaken by multidisciplinary teams of laboratory, computational, and clinical scientists. The goals of these teams are to apply the latest laboratory technologies and computer algorithms to develop and test novel vaccine concepts in humans through clinical trials, whereas trial results, especially

FIG. 1. Flow of activities in vaccinomics. Studies of the immune response in humans, analyzed by system biology approaches generate new biomarkers, new signatures of protection, and new questions that can be addressed by *in vitro*, *in silico*, and animal studies. The combined knowledge deriving from the study of human immunology and fundamental research generates new concepts and technologies that will instruct future vaccine development.

the immunological signatures associated with a particular vaccine, provide feedback and drive further refinements and hypothesis testing. This multidisciplinary, iterative approach to vaccine development requires new structures and innovative funding and training programs to catalyze these interactions and to ensure that the gap between the lab and the clinic is narrowed and ideally closed (Aderem, 2005; Skarke and FitzGerald, 2010; The Council of the Global HIV Vaccine Enterprise, 2010).

Outlook for the New Vaccinomics

Historically, the origins and early history of vaccinology is rooted in astute clinical observation and sound epidemiology. Building on these historic origins, vaccinology is now transitioning into a new era that is built on the powerful new tools of 21st century biology. The success of this new vaccinomics requires a deep systems understanding of the biology of the immune response and the creative application of this new knowledge to the clinical trials process. As discussed above and as others have emphasized in the context of translational approaches applied to drug development, this new era of vaccinomics calls for strong collaborative partnerships between laboratory, computational, and clinical scientists; new training programs for students in both the basic and clinical sciences that provide an opportunity to appreciate the multidisciplinary nature of modern vaccinology; iterative cycles between the clinic and the lab; appropriate grant mechanisms and criteria for advancement and career development pathways in academia that support and reward the teamwork required of systems vaccinomics; and policies that ensure rapid access to the large sets of molecular, clinical, and epidemiological data generated from laboratory experiments and clinical trials, so that the potential benefits can be fully realized and shared with the research, clinical and volunteer communities.

Author Disclosure Statement

The authors declare that no conflicting financial interests exist.

References

Aderem, A. (2005). Systems biology: its practice and challenges. *Cell* 121, 511–513.

- Brenner, S. (2003). Humanity as the model system. *Science* 302, 533.
- Crowley, W.F., and Gusella, J.F. (2009). Changing models of biomedical research. *Sci Transl Med* 1, 1–6.
- D'Argenio, D.A., and Wilson, C.B. (2010). A decade of vaccines: integrating immunology and vaccinology for rational vaccine design. *Immunity* 33, 437–440.
- De Bono, J. S., and Ashworth, A. (2010). Translating cancer research into targeted therapeutics. *Nature* 467, 543–549.
- Division of Health Promotion and Disease Prevention and Institute of Medicine. (1985). *Vaccine Supply and Innovation*. Washington, DC: National Academies Press.
- Gaucher, D., Therrien, R., Kettaf, N., Angermann, B.R., Boucher, G., Filali-Mouhim, A., et al. (2008). Yellow fever vaccine induces integrated multilineage and polyfunctional immune responses. *J Exp Med* 205, 3119–3131.
- Hörig, H., Marincola, E., and Marincola, F.M. (2005). Obstacles and opportunities in translational research. *Nat Med* 11, 705–708.
- Plotkin, S.A. (2008). Correlates of vaccine-induced immunity. *Vaccines* 47, 401–409.
- Pulendran, B., Li, S., and Nakaya, H.I. (2010). Systems vaccinology. *Immunity* 33, 516–529.
- Querec, T.D., Akondy, R.S., Lee, E.K., Cao, W., Nakaya, H.I., Teuwen, D., et al. (2009). Systems biology approach predicts immunogenicity of the yellow fever vaccine in humans. *Nat Immunol* 10, 116–125.
- Skarke, C., and FitzGerald, G.A. (2010). Training translators for smart drug discovery. *Sci Transl Med* 2, 1–4.
- The Council of the Global HIV Vaccine Enterprise. (2010). The 2010 scientific strategic plan of the Global HIV Vaccine Enterprise. *Nat Med* 16, 981–989.
- Varmus, H. (2006). The new era in cancer research. *Science* 312, 1162–1165.
- Young, D., Stark, J., and Kirschner, D. (2008). Systems biology of persistent infection: tuberculosis as a case study. *Nat Rev Microbiol* 6, 520–528.

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