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Vaccinomics and Bioinformatics: Accelerants for the Next Golden Age of Vaccinology

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Out of the germ theory of disease the field of vaccinology rapidly developed. It was further accelerated by rapid new scientific insights from public health, virology, bacteriology, and immunology. Despite this rapid scientific progress, a simple summary of the field of vaccinology from the first use of smallpox virus as a vaccine until the 1990's was of empirical vaccine development characterized by an "isolate-inactivate-inject" paradigm. The development of second generation hepatitis B vaccines began to move the field into an era of molecular medicine. Further developments have included immune-structure refinements with the utilization of protein conjugation (pneumococcal and meningococcal vaccines), and most recently, VLP vaccines (HPV vaccine). New insights from immunogenetics and an ever increasing array of high dimensional genetic and immunologic assays such as whole genome sequencing, mRNA transcriptomics, and novel bioinformatics approaches to understand the complexity of immune responses now provide accelerants that will allow vaccinology to explode into a new golden era – one which we have termed "vaccinomics". [1;2]

The basic idea behind vaccinomics is that critical components of vaccine development, immunogenicity, and clinical use will move from empiricism, to directed development and use of vaccines. This will be informed by phenotype:genotype data and comprehensive immune profiling that takes advantage of our growing abilities to decipher the effect of genetic polymorphisms and gene-gene interactions on immune response heterogeneity to vaccines. Of necessity this requires large phenotype (vaccine responder or non-responder for example) and genotype (gene sequencing, transcriptomics and others) data in order to provide sufficient data and power for analysis, discovery, replication, validation, and interpretation. New bioinformatic tools will allow such data to be used in developing sophisticated immune profiles that can, in turn, be used in a "reverse engineering approach" to understand how vaccines might be developed and used. In addition, the growing interest in individualized medicine is a concept that will permeate vaccinology just as it is currently revolutionizing drug therapeutics – what we have called "personalized and predictive vaccinology"[3].

In order to realize personalized and predictive vaccinology, statistical and bioinformatics analysis methods must undergo a paradigm shift as the days of per-gene analyses are fading.

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Modeling algorithms that incorporate *a priori* hypotheses and existing biological knowledge and at the same time integrate data sources from the DNA level to the protein level will be vital to improving our understanding, while not flooding the literature with false leads[4]. Study designs for vaccinomics must undergo a paradigm shift as well. Investigators have realized for quite some time now that clinical trials focusing on cancer therapies require larger sample sizes accrued from multiple institutions. This is realized through large cooperative groups such as the National Cancer Institute sponsored North Central Cancer Treatment Group (NCCTG). Similar strategies are being utilized in genome-wide association studies (GWAS) of cancer. For example, a recent report of SNPs associated with the risk of breast cancer utilized a total of 9,770 cases and 10,799 controls in a three-stage GWAS made possible by the Cancer Genetic Markers of Susceptibility (CGEMS) initiative. [5] Such approaches with prospective recruitment would allow unprecedented power and fundamental insights in vaccinomics studies, while protecting against false discoveries and maximizing the generalizability of conclusions.[6;7]

The implications of the above are enormous and, we fear, likely to have escaped the immediate notice of industry and academic scientists. As one example, increasing demands for higher and higher levels of vaccine safety will require the ability to understand the presumed genetic basis for rare but lethal or highly morbid serious adverse vaccine side effects – and then perform specific clinical testing to predict and avoid such consequences. This may well provide an answer and solace to those who question vaccine safety and who are amenable to data-driven decision-making about vaccines. Still, even such data will be insufficient for those innumerate who reject consideration of any vaccine.

We believe that vaccine development in the 21st century will be directed in nature and process and will be informed by population genetics. Clinical trials of candidate vaccines may well become faster and cheaper in terms of reaching early “go – no go” decisions by the development of population-level biomarkers resulting from comprehensive immune profiling models. For this and other reasons, the field of vaccinology must increasingly turn its collective attention to vaccinomics – particularly immunogenetics and immunogenomics. Such tools will allow us to answer such vexing questions as “why do some healthy individuals fail to develop protective immune responses to a given vaccine?” “Why do some people only need 1–2 doses of a vaccine, while others require 6 or more doses such as with hepatitis B vaccine?” In many ways we are just becoming truly aware of the immensely complex interplay of genetic and other factors that together determine immune responses to antigens and pathogens. Isn't it surprising that at an immuno-molecular-genetic level we cannot yet comprehensively explain how a vaccine results in immunity? Until we can, vaccine development and use can justifiably be labeled empiric.

We should not be satisfied with our current state of scientific knowledge in regards to vaccine development and function. Much, much, more work of a collaborative nature needs to be done between vaccinologists, bioinformaticians, geneticists, statisticians, and immunologists. The “fuel” for such efforts, is of course, research funding. A critical need is for NIH and other national research councils to funnel interest in these areas by creating and funding programs that are likely to draw interdisciplinary groups of scientists together to jointly collaborate on finding answers to these tough questions –much as is done with the large Cancer Cooperative Groups. And we need bright, motivated young scientists who question current dogma, and who bring innovation, new technology, new tools and questions, and content expertise into the field. If we do so, we will be able to address fundamental questions regarding pathogens that continually plague humans – and devise newer and safer vaccine solutions unimaginable a generation ago.

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