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Application of pharmacogenomics to vaccines

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Abstract

The field of pharmacogenomics and pharmacogenetics provides a promising science base for vaccine research and development. A broad range of phenotype/genotype data combined with high-throughput genetic sequencing and bioinformatics are increasingly being integrated into this emerging field of vaccinomics. This paper discusses the hypothesis of the 'immune response gene network' and genetic (and bioinformatic) strategies to study associations between immune response gene polymorphisms and variations in humoral and cellular immune responses to prophylactic viral vaccines, such as measles–mumps–rubella, influenza, HIV, hepatitis B and smallpox. Immunogenetic studies reveal promising new vaccine targets by providing a better understanding of the mechanisms by which gene polymorphisms may influence innate and adaptive immune responses to vaccines, including vaccine failure and vaccine-associated adverse events. Additional benefits from vaccinomic studies include the development of personalized vaccines, the development of novel vaccines and the development of novel vaccine adjuvants.

Keywords

genetic association; genetic predisposition to disease; immunization; immunogenetics; vaccination; vaccine

What is vaccinomics?

The development of the field of pharmacogenomics (associations of whole genomes and drug or vaccine response) and pharmacogenetics (associations of individual genes and drug or vaccine response) has provided both the science base and clinical outcomes that together

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increasingly allow for the practice of individualized drug therapy. The application of this same science when applied to vaccines we have labeled 'vaccinomics' [1]. Thus, just as we now recognize that a variety of drugs, such as antidepressant and antihypertensive medications, may require different dosing based on individual genetic differences and result in different side-effect profiles, resulting in variations in therapeutic effect based on genetically-based individual variations; we have now begun to recognize similar attributes in terms of vaccine indications, dosing, side effects and outcomes. As one clinician noted, '…vaccines licensed in the USA are safe and effective. However, not every vaccine is equally safe or equally effective in every person' [2].

As discussed later in this paper, we have done extensive work identifying associations between immune response gene polymorphisms and variations in immune responses to several prophylactic live viral vaccines [3–13]. Such phenotype/genotype data, in combination with high throughput genetic sequencing and bioinformatics, we believe will accelerate the field of vaccinomics and personalized vaccinology. In turn, the growth of this area of inquiry will increasingly allow us to understand and predict immune responses to vaccines, adverse events to vaccines and accelerate new vaccine development. Such research is a logical extension of what physicians now do – tailor any intervention to the unique characteristics of the patient before them. For example, patients with renal failure or who are immunocompromised may get a hepatitis B antigen dose two- to four-times the usual dose in order to improve the chances of seroconversion and protection. Similarly, an HLA-extended haplotype that is associated with nonresponse to this vaccine has been defined [14]. Multiple repeat dosing may seroconvert such identified individuals [15]. Thus, such findings result in changes in clinical care, such as requiring higher doses, alternative vaccines, and accelerated or enhanced schedules. Vaccinomics will also chart new courses for novel vaccine development. It will drive novel scientific approaches and solutions to vaccine nonresponse, such as new vaccine adjuvants and peptide cocktail vaccines based on HLA supertype and other approaches.

How does vaccinomics inform vaccine development & vaccine science?

It is clear that the ability to respond to the threat of infectious disease depends on the ability of the host to mount an effective defense against an invading pathogen. However, for this to occur, a variety of biologic systems must be activated by the host, eventually resulting in the activation and secretion of cytokines, antibodies, chemokines and immune effector cells. In turn, for these events to take place, a variety of genes must be activated or suppressed and their products transcribed and their proteins translated, modified, expressed and secreted. In this regard, we have previously discussed the theory of the 'immune response gene network' whereby it is clear that the interactive and iterative activation and suppression of specific pathway genes must occur in a choreographed fashion in order for a coherent immune response to result after recognition of a pathogen [11]. Genes involved in virus binding and cell entry, antigen recognition, processing and presentation, immune effector cell function and immunoregulation are all necessary for a coordinated attack against an invading pathogen. Our work with the measles–mumps–rubella (MMR) vaccine, for example, has illustrated significant associations between class I and II *HLA*, cytokine, cytokine receptor, signaling lymphocyte activation molecule (*SLAM*) and *CD46*, and other immune response gene polymorphisms, humoral immune responses (IgG enzyme-linked immunosorbent assay [ELISA]and neutralizing antibody levels) and markers of cell-mediated immune responses (lymphoproliferative assays, cytokine secretion, enzyme-linked immunosorbent spot [ELISPOT] assays, and so on) [3,5,7–9,16–19]. In addition, we have advanced such work by expanding the scientific NIH data-sharing database to include microarray data, and more recently, transcriptomics data at increasingly remarkable levels of sensitivity [20].

The next evolution in understanding such data will be in analyzing and better understanding such issues as gene family pathways, epigenetic modifications and complementation. For example, we have developed protocols whereby *ex vivo* infection of human peripheral blood mononuclear cell (PBMC) cultures and the application of mass spectrometry tools have allowed us to identify naturally processed and presented pathogen-derived peptides – the very entity responsible for pathogen-induced adaptive immune responses [21]. Coupled with a growing body of data regarding pathogen-derived peptide promiscuity and HLA supertypes, such data will lead to identification of peptides capable of stimulating humoral and recall immunity [21–23]. A repertoire of such peptides (peptide cocktail) may permit the design and development of new vaccines for particular subpopulations [24]. For example, certain polymorphisms in the *SLAM* (CDw150) receptor for live measles vaccine virus are associated with poor humoral immune responses [7]. Since both vaccine and wild-type measles virus strains infect host cells via the interaction of the measles virus hemagglutinin protein with the V-domain of the SLAM receptor, SNPs in the *SLAM* gene are significantly associated with variations in immune responses to measles vaccine. Microarray experiments demonstrate gene-expression patterns (13 upregulated and 206 downregulated genes) in PBMCs from children with acute measles and children in the convalescent phase, which were consistent with the prolonged alteration of lymphocyte responses to measles [25]. It may well be possible to design new vaccines for use in individuals who suffer from variant cell-based receptors for viral recognition and do not respond well to current vaccines. Investigators may develop new vaccine models that do not depend upon such receptors or develop new vaccines that effectively allow vaccine virus to bind to a range of receptor polymorphic areas [26,27].

The goal of pharmacogenomics and vaccinomics is to identify genetic variants that predict adverse responses to vaccines, predict aberrant immune responses, contribute to personalized therapy and that predict susceptibility to diseases and response to vaccines [28]. Vaccinomics may also be useful in the development and use of existing and novel vaccine adjuvants and stimulants. For example, specific polymorphisms of the *TLR3* gene are associated with significantly diminished humoral and cell-mediated immune responses to the measles vaccine [8]. Understanding the mechanism by which such polymorphisms diminish innate and other immune responses may offer a critical insight into designing work around the limitations imposed by such polymorphisms – either by developing new adjuvants that utilize other receptors, or by the addition of stimulant molecules that can potentiate or augment the immune response.

Similarly, complement components are key factors of the innate and adaptive immune response against pathogens. Without a fully functioning complement system normal immune response, lymph node organization and B-cell maturation, differentiation, responsiveness and tolerance is adversely affected [29]. Products from the cleavage of complement or component proteins can bind to cell-surface receptors to influence inflammation [30], T-cell immunity [31] and B-cell response [32]. These receptors are known as regulators of complement activation (RCA) and are a family of common receptors present on most cells [33]. It has been demonstrated that any deficiencies in C4, C2 or C3 proteins can lead to a weakened antibody response to bacterial infections [34]. For example, targets for complement components C4b and C3b on both *Neisseria meningitidis* and *Neisseria gonorrhoeae* have been described [35]. Most genes of the complement system are polymorphic, with the C4 molecule having over 35 identified variants [36]. While it has been demonstrated that complement genes play a critical role in the immune response to influenza [37,38], rubella [39] and other viral infections, there have been no studies to date investigating how complement gene polymorphisms may affect immune response to viral infections and/or viral vaccines.

Another area of importance is genetically determined vaccine-associated adverse events, which we have called ‘adversomics’. Scarce data are available regarding the immunogenetics of

adverse vaccine responses. Black *et al.* recognized differing and more severe adverse events to receipt of the measles vaccine in Amazon Basin Indians compared with other groups – suggesting a possible genetic contribution [40]. More recently, Vestergaard *et al.* demonstrated an association between receipt of the MMR vaccine and subsequent febrile reactions and febrile seizures [41], providing a logical genetic basis for increased susceptibility to adverse events to live viral vaccines. Very recently, debate has arisen over the hypothesis that live viral vaccines could in some fashion exacerbate pre-existing genetically-coded problems such as mitochondrial or metabolic defects, for example, inborn errors of amino acid and organic acid metabolism, lipid metabolism, carbohydrate metabolism and of purine and pyrimidine metabolism [2,42]. Mitochondrial disorders in particular are estimated to occur at an incidence of 1 in 4000–5000 births [43]. If knowledge of such disorders were to be identified as important in predicting vaccine-induced immune responses or adverse events, screening for such genetic defects or polymorphisms might become more commonplace. In an analogous manner, the routine screening for such disorders among all live children born in the USA, represents personalized and predictive medicine, particularly to the extent that findings of concern would result in different specific vaccine recommendations.

Concerns over more severe vaccine-related side effects, such as neurotropic and viseotropic reactions to yellow fever vaccine, encephalitis-related reactions to smallpox vaccine, Guillain-Barré reactions temporally occurring with vaccination and others, warrant further investigation for the potential of identifying genetic predictors of risk [44–47]. With the availability of high-throughput sequencing and large patient databases that allow identification of serious adverse events related to immunization, such studies are increasingly feasible. Such studies would be further enhanced by reliable and stable funding mechanisms for broader population-based studies of adverse events for other commonly administered vaccines.

Specific examples of prophylactic vaccines

Twin studies

Twin studies provide opportunities to explore genetic contribution to vaccine response and to identify specific gene polymorphisms. This benefit occurs for two reasons. First, a number of nongenetic factors may influence antibody levels (and cellular immune responses) following vaccination, including the presence of maternal antibodies [48], race [49], differences in vaccine storage, handling and administration [50,51], and concurrent illness at the time of vaccine administration [52–54]. However, twins who are raised together are highly likely to share these and other factors (such as exposure to viral diseases) that may influence measures of vaccine immunity. In addition, twins are also highly likely to be vaccinated at the same time with the same lot of vaccine, which has been stored and administered under the same conditions. They are also matched on age, exposure to older and younger siblings, and on overall family environment. Therefore, twin studies provide an ideal way to control for shared environmental factors. Second, monozygotic (MZ) twins share all of their genes, while dizygotic (DZ) twins share half their parents' genes. Therefore, differences in immune responses within MZ twin pairs can be attributed to differential environmental exposures and chance variation, while differences in immune responses within DZ twins can be attributed to differential environmental exposures, chance variation and genetic differences.

Investigators have used twin studies to estimate the genetic and environmental contributions to a variety of different diseases, including determining the genetic contribution to variation in total immunoglobulin levels and specific IgG antibody levels to pneumococcal capsular polysaccharides [55,56]. Recent studies have observed a high heritability of 77% (95% CI: 63–85) for antibody response to hepatitis B vaccine in 207 Gambian twin pairs aged 5 months [57]. Heritabilities for antibody responses to oral polio, tetanus and diphtheria vaccines were 60% (95% CI: 43–73), 44% (95% CI: 16–70) and 49% (95% CI: 17–77), respectively [57]. In

addition, significant heritability was also observed for IFN-γ and IL-13 cytokine immune responses to tetanus, pertussis and several Bacillus Calmette–Guérin (BCG) vaccine antigens, ranging between 39 and 65% [57]. Another study among 147 DZ and 43 MZ Gambian twin pairs showed that the IgG antibody response to *Haemophilus influenzae* type b (Hib) vaccine is highly heritable among Gambian infants. Heritability of antibody responses to Hib conjugate vaccine was estimated to be 51% (95% CI: 32–66), indicating a significant genetic contribution to the variation of antibody response to the polysaccharide antigen of Hib [58].

Since twin studies provide an ideal method for quantifying the magnitude of genetic contributions to the variability in vaccine-induced immunity, determining the proportion of variation attributable to specific genes in healthy individuals following live attenuated MMR vaccination was investigated. The Mayo Vaccine Research Group (MN, USA) conducted a twin study to determine the magnitude of genetic influence on variability in circulating antibody levels to measles, mumps and rubella viruses [59,60]. A total of 100 twin pairs (45 MZ and 55 DZ) residing in Minnesota were recruited and information regarding demographic characteristics, vaccine history and exposure to or occurrence of any vaccine-preventable diseases collected. Blood samples were collected from each child and viral-specific IgG antibody levels were quantified by ELISA. The genetic variance and heritability of the IgG levels were examined using analysis of variance techniques. It was found that the heritability was 88.5% for measles (95% one-sided CI: 52.4), 38.8% for mumps (95% one-sided CI: 1.6) and 45.7% for rubella (95% one-sided CI: 4.9). These data demonstrate that genetic influences play a substantial role in antibody levels following measles vaccination, and a somewhat lesser role in the antibody levels following mumps and rubella vaccination. Others have commented that ‘Knowledge that a trait of interest has high heritability can support a study that proposes to investigate the genetic determinants of that trait’ [61]. It is important to note that the unique genetic and environmental characteristics of different individuals and vaccines demand a clear understanding of the role of critical aspects of vaccine pharmacogenomics [11,62].

The pathways by which protective humoral and cellular immune responses develop to live viral vaccines is a multistep process: the vaccine virus (such as measles) must first be recognized by its cellular receptors (SLAM and CD46) and also activate toll-like receptors (TLRs) or other innate sensors, triggering innate immune responses. After antigen presentation by HLA molecules, cytokine and cytokine receptor gene activation occurs, along with signaling molecules, resulting in secretion of cytokines as intercellular messengers to stimulate Th1 and Th2 immune responses [63–65]. Individual variations within any of these relevant genes could effect gene transcription, regulation or expression, and thereby influence immune responses or the propensity to an adverse reaction to the vaccine antigen. Below we will give specific examples of genetic associations with immune responses to live viral vaccines.

MMR vaccine

As discussed above, we have performed and reported a twins study of measles vaccine immunogenicity. This study demonstrated that antibody levels to measles vaccine have a very high heritability of 88.5% [59,60]. Informed by advances in basic immunology on the role of the HLA complex in immune recognition and response, a series of immunogenetic studies designed to answer questions on the role of HLA in vaccine immune responses was performed.

The HLA proteins play an essential role in generating an immune response against pathogens. Generally, the class I A, B and C alleles bind and present peptides to $CD8^+$ T lymphocytes, while the class II *DR*, *DQ* and *DP* alleles bind and present peptides to $CD4^+$ T cells. The peptide-binding clefts of the HLA molecules contain highly polymorphic clusters of amino acids that act to control or restrict the spectrum of peptides capable of being bound and presented by a given HLA molecule. A single HLA molecule is able to bind self- and pathogen-derived peptides that share common amino acid motifs [66,67]. Differences in HLA-binding

affinities may result in decreased binding of specific pathogen-derived peptides and inefficient peptide presentation to T lymphocytes [68–70]. Inefficient peptide presentation may, in turn, result in decreased T-cell activation and cytolytic function, decreased cytokine production and decreased B-cell production of pathogen-specific antibodies.

We have reported a number of findings in relation to measles, mumps and rubella vaccine antigens and HLA genetics [9,17,71–73]. Recent reviews of these population-based clinical studies have revealed a number of findings of interest. Specific class I and class II *HLA* alleles are associated with variations in antibody levels after a single dose of measles vaccine [3–5]. In particular, class II *DRB1*03*, *DQA1*0201* and the class I *B8*, *B13* and *B44* alleles are associated with lower levels of measles antibodies in healthy schoolchildren. In the case of *HLA* homozygosity it was also demonstrated that overall lack of variation in the *HLA* alleles is associated with decreased measles-specific antibody levels following a single dose of vaccine, with increasing risks of vaccine nonresponse with increasing homozygosity [16]. The role of HLA molecules in vaccine-induced immune responses after two doses of MMR vaccine was also examined [6,9,17]. Little verification was found that either homozygosity at specific *HLA* loci or overall homozygosity had any disadvantage in terms of measles-specific cytokine immune responses, such as IFN-γ, IL-2, IL-4, IL-10 and IL-12p40, following two doses of measles vaccine, suggesting that at some level genetic restriction could be overcome by higher or repeated doses of vaccine [73]. In addition, associations between *HLA* haplotypes and *HLA* supertypes and MMR vaccine-specific humoral and cellular immune responses following two doses of MMR vaccine were investigated [23,74]. The haplotypes with the strongest evidence for association with lower measles-induced antibodies were *DRB1*07–DQB1*02–DPB1*02* and *DRB1*07–DQB1*03–DPB1*04*. Haplotype *A*26–Cw*12-B*38* was significantly associated with higher antibody levels and higher lymphocyte proliferation and response to the mumps vaccine [74]. Among our study subjects, the supertypes *B44* and *B58* were strongly associated with lower measles vaccine-specific antibody levels. In contrast, the most common *B7* supertype was associated with higher measles vaccine antibody response. For the mumps vaccine, it was found that the *HLA-DQB1*0303* allele was associated with lower mumps-specific antibody titers and the *B62* supertype was suggestive of an association with mumps-specific higher lymphoproliferation after the MMR vaccine [9,23]. Further, alleles of the *DRB1*, *DQA1* and *DQB1* loci were associated with significant variations in lymphoproliferative immune responses to mumps vaccine [9]. It was also demonstrated that *HLA-A* (**2402* and **6801*) alleles were associated with lower vaccine-induced IFN-γ secretion levels in response to rubella virus antigens [19]. Associations were further observed between measles (IFN-γ and IL-4) and rubella (IFN-γ and IL-10) specific cytokine responses and class I and class II *HLA* gene polymorphisms [19,75–77]. Class I *HLA-A* (**0101*, **3101*), *HLA-C* (**0303*, **0501*), and class II *HLA-DRB1* (**0301*, **1501*) and *HLA-DQB1* (**0201*, **0303* and **0602*) alleles were significantly associated with variations in measles-virus-induced *in vitro* IFN-γ secretion [75,76]. These studies demonstrated that both humoral (antibody) and cellular (lymphoproliferation and secreted cytokines) immune responses to MMR vaccine are clearly influenced by polymorphisms of the *HLA* genes.

HLA gene polymorphisms may also be related to variations in cytokine production following measles immunization through variations in T-cell activation; however, variation in the cytokine genes themselves may also directly affect cytokine secretion after antigen stimulation [10]. It is also possible that other immune response genes or other currently unknown genes may also influence vaccine immunity more strongly than the *HLA* genes. In this regard, polymorphisms in cytokine and cytokine receptor genes may also contribute to variations in vaccine immune response [78]. SNPs that are associated with differences in cytokine secretion levels could also influence vaccine-induced immune responses [18]. For example, the presence of minor allele T for intronic SNP rs2201584 within the *IL12RB2* gene and the presence of minor allele A of the rs373889 within the *IL12RB1* gene were strongly associated with an allele

dose-related decrease in antibody titer and lymphoproliferation, respectively, after two doses of mumps viral vaccine [9]. More recent preliminary data demonstrate that specific SNPs in the *IL10* and *IL12RB2* genes are associated with low antibody and low cell-mediated immune responses to the measles vaccine, while SNPs in the *IL2* gene are associated with high antibody and cellular immune responses to measles [18]. The same *IL2* promoter SNP (rs2069762) identified in our study was also found to be associated with the responder phenotype following hepatitis B virus (HBV) vaccination [79]. Significant associations were also found between *IL4R* gene polymorphisms and levels of measles-specific secreted IL-4 (major alleles for four SNPs were associated with lower levels of IL-4) [18], indicating that cytokine and cytokine receptor gene polymorphisms may be significant factors in the development of vaccine immunity.

We also examined gene polymorphisms in the two known genes that code for the measles virus receptors – SLAM and membrane cofactor protein – CD46. Both SLAM and CD46 are known to play a role in measles virus binding and entry into the host cell, as well as in cell tropism and pathogenesis. Our study demonstrates that increased representation of minor alleles for rs3796504 and rs164288 in the *SLAM* gene were associated with a significant allele dose-related decrease in measles-specific antibodies [7]. The SNP rs3796504 leads to an amino acid change of threonine to proline at position 333 of the *SLAM* gene, and may change the conformation of the SLAM receptor, making it unsuitable for binding to the measles virus hemagglutinin protein. Within the *CD46* gene, the minor allele C for intronic SNP (rs11118580) was associated with an allele-dose related decrease in measles-specific antibodies [7]. Although the mechanism is unclear, intronic SNP rs11118580 may also play a critical role in the regulation of gene transcription. Thus, variations in measles vaccine-induced antibody levels may be influenced by polymorphisms in the genes for the *SLAM* and *CD46* measles virus receptors.

Discovery of genetic variation (e.g., immunogenetic profiling) in a population is important for understanding its role in vaccine-induced immunity [26]. In this regard, polymorphisms of the *TLR* genes involved in innate immune responses have also been demonstrated to influence the susceptibility to infection and immune responses to pathogens. For example, Heer *et al.* have shown that TLR signaling is not required for anti-influenza effector T-cell responses, but through both direct and indirect ways it orchestrates anti-influenza B-cell responses [80]. It has been reported that laboratory adapted and vaccine strains of measles virus, including the Edmonston vaccine strain, induce TLR3 in human dendritic cells, which may be associated with protective immunity against measles via enhanced IFN-β secretion [81]. This suggests that measles virus-induced expression of TLR3 may be a sign of augmented IFN production that plays an important role in host defense to viral infection. Specific SNPs in the coding and regulatory regions of the TLR3 (and associated intracellular signaling molecule MyD88) were also associated with variations in antibody and cellular immune responses to measles vaccine, suggesting that TLR signaling may be required for antimeasles T- and B-cell immune responses [8,10]. However, more work in this area is required in order to understand how immune responses to vaccines can be impaired by SNPs within the genes encoding TLRs.

Influenza vaccine

Influenza is a single-stranded RNA virus that causes substantial morbidity and mortality. Influenza vaccines prevent disease in 80% of healthy subjects [82] Therefore, it is important to investigate the effect of immune response gene polymorphisms on humoral (and cellular) immune responses following influenza immunization [83]. While a variety of genes and gene pathways are involved in whole influenza virus immunity, it is essential to understand gene polymophisms that may be involved with generating an immune response to the influenza hemagglutinin (H) and neuraminidase (N) transmembrane glycoproteins, as these proteins

form the sole influenza virus-derived components of inactivated influenza vaccine. Serum antibody titers, measured by a hemagglutination inhibition assay, are believed to be a reliable correlate of immunity to influenza viruses [84]. Associations between *HLA* gene polymorphisms and influenza A virus H1- and H3-specific hemagglutination inhibition antibody titers in healthy subjects who received trivalent influenza vaccine, containing A/H1N1 New Caledonia/20/99, A/H3N2 California/7/2004 and B/Shanghai/361/2002 influenza virus antigens were examined. *HLAA* 1101* ($p = 0.0001$) and *A*6801* ($p = 0.09$) alleles (global p-value for *HLA-A* locus 0.007) were associated with higher median levels of influenza H1 vaccine-induced antibodies [12]. Gelder *et al.* demonstrated an increased frequency of *HLA-DRB1*0701* and a decreased frequency of *HLA-DQB1*0603–9/14* in individuals who were nonresponders to the influenza subunit vaccine [85]. Significant associations between both H1- and H3-specific antibody immune responses and polymorphisms of cytokine and cytokine receptor genes (such as *IL1R1*, *IL2RA*, *IL6*, *IL10RA*, *IL12B* and other genes) were also identified, suggesting that SNPs present in *HLA*, cytokine and cytokine receptor genes may influence humoral response(s) following seasonal influenza vaccination [12]. Further examination of the role of immune response gene polymorphisms and variations in influenza vaccineinduced immunity is warranted, particularly given the public health impact of both seasonal and pandemic influenza.

HIV vaccine

Variations within the host's genome may contribute substantially to the individual immune response to vaccination and susceptibility to infectious diseases. For example, evidence demonstrates that class I *HLA-B*35* and *B*08* alleles are associated with faster HIV type 1 (HIV-1) disease progression, and homozygosity at class I loci confers a significant risk of accelerated infection [86,87]. A study of canarypox vector-based HIV (vCP1433) vaccine (ALVAC)-HIV-1 recombinant canarypox vaccines showed that the *HLA-B*27* and *B*57* (the two alleles best known for an association with slower disease progression) were associated with earlier and positive $CD8^+$ cytotoxic T lymphocyte responses to Gag and Env viral proteins [88]. However, homozygosity at class I loci, although conferring an unfavorable prognosis following natural HIV-1 infection, showed no such disadvantage for ALVAC-HIV-1 vaccine response [88]. For class II, associations with the *DRB1*1300–DQB1*0603* haplotype and transporter gene products (*TAP2* Ala665) and progression of HIV-1 infection have been also reported [89]. There appears to be a strong association between polymorphisms in the *CCR5* chemokine receptor gene, located on the short arm of chromosome 3 and HIV-1 infection [90]. Caucasian individuals homozygous for a deletion of CCR5 (*CCR5-Δ32*), which encodes the cell entry co-receptor for HIV, appear to be at lower risk of acquiring HIV/AIDS [91]. Likewise, genetic studies of HIV demonstrate that the presence of the most frequent *TLR8* polymorphism, *TLR8 A1G* (rs3764880), confers a significantly protective effect against disease progression [92]. Recently, de la Torre *et al.* demonstrated the contribution of five polymorphisms in the vitamin D receptor (*VDR*) gene to HIV-1 susceptibility among Spanish HIV-infected patients [93]. Specifically, haplotypes for *VDR* (SNPs rs11568820, rs4516035, rs10735810, rs1544410 and rs17878969) polymorphisms revealed important associations with protection against HIV-1 infection (OR: 0.4; 95% CI: 0.22–0.72; $p = 0.0025$).

HBV vaccine

Hepatitis B vaccination of twin pairs is a valuable model with which to study the importance of host-genetic factors for the immune response to HBV antigens. The vaccine licensed throughout much of the world consists of recombinant hepatitis B surface antigen (HBsAg) and alum and induces protective antibodies (>10 IU/ml) in 95% of vaccinees following three doses. Hohler *et al.* studied 96 DZ and 95 MZ twin pairs and demonstrated that genetic factors have a significant effect on the immune response to the HBsAg vaccination [94]. In this study more than 60% of the observed variability in anti-HBsAg immune responses was attributed to

genetic factors. The heritability of the HBsAg vaccine response accounted for by the *HLA-DRB1* locus (such as *DRB1*01*, *DRB1*11* and *DRB1*15*) was estimated to be 0.25, leaving the remaining heritability of 0.36 to other gene loci, suggesting that approximately 40% of the genetic contribution to HBsAg response is affected by *HLA* genes and approximately 60% by non-*HLA* genes [94]. This study suggests that while genes encoded within the HLA complex are important for the immune response to HBsAg, more than half the heritability is determined outside of this complex, with strong evidence that other immune response genes (complement factor *C4A*, *IL2*, *IL4* and *IL12B*) are also important determinants of nonresponsiveness to HBV vaccination [95,79]. In addition, increased antibody levels and lymphoproliferative immune responses to HBV vaccination were found to be influenced by polymorphisms within the *IL1β* gene [96].

Several HLA association studies have demonstrated that the *DRB1*03* and/or *DRB1*07* alleles confer a higher possibility of HBV vaccine failure [97,98]. Further, analyses of genotyping data from 164 North American adolescents vaccinated with recombinant HBV vaccine demonstrated that the *HLA-DRB1*07* allele (relative odds [RO]: 5.18; $p < 0.0001$) was associated with nonresponse to full-dose vaccination [79]. However, when HBsAg-specific T-cell responses following HBsAg vaccination were compared *ex vivo* in 24 MZ and three DZ twin pairs, it appeared that the *DRB1* alleles associated with vaccine failure (such as *DRB1*0301* and **0701*), were able to competently present HBsAg-derived peptides [99]. This argues that *HLA-DRB1* allelic associations with HBV-specific immune response are not caused by differences in peptide binding or by a change in the ELISPOT Th1 (IFN-γ)/Th2 (IL-10) profile. The authors suggested that the defect in nonresponse to the HBV vaccine may be on the side of the T-helper cells and not on the side of the antigen-presenting cells [99].

Smallpox vaccine

Immunity to smallpox is an important issue for public health and vaccine development. In this regard, genetics play a critical role in the host immune response variation to smallpox vaccination within a population. The variability of humoral and cellular immune responses modulated by *HLA* and other genes is a significant factor in the development of a protective effect of smallpox vaccine (or live vaccinia virus). We tested whether associations exist between individual *HLA* alleles and vaccinia virus-specific humoral (neutralizing antibody) and cellular (IFN-γ-ELISPOT) responses in a group of healthy individuals (n = 1076; age: 18–40 years) who received one dose of smallpox vaccine (Dryvax™). Significant associations were found between class II *HLA-DQB1* 0302* ($p = 0.003$) and *DQB1*0604* ($p = 0.03$) alleles and higher vaccinia-induced neutralizing antibody levels (global p-value 0.01). A striking finding was an association of several class I *HLA* alleles with vaccinia-specific cellular responses. The global tests revealed associations between vaccinia-induced IFN-γ responses and *HLA-B* and *-C* loci ($p < 0.001$ and 0.03, respectively). Specifically, *HLA-B*1501* ($p = 0.006$), *B*3508* ($p = 0.02$), *B*4901* ($p = 0.04$), *B*5701* ($p = 0.04$), *B*5802* ($p = 0.05$), *C*0303* ($p = 0.01$) and *C*0704* ($p = 0.02$) alleles were significantly associated with higher cellular responses to vaccinia virus. In contrast, *HLA-B*3701* ($p = 0.03$), *B*4001* ($p = 0.03$), *B*5301* ($p = 0.04$), *B*5601* ($p = 0.03$), *C*0102* ($p = 0.03$), *C*0702* ($p = 0.04$) and *C*0801* ($p = 0.01$) alleles were significantly associated with lower IFN-γ responses to the smallpox vaccine [100]. These preliminary data suggest that both humoral and cellular immune responses to smallpox vaccine are, in part, genetically restricted by *HLA* genes.

Associations between smallpox vaccine-induced immunity and SNPs in cytokine and cytokine receptor genes were also studied. A variety of statistically significant associations between SNPs in the cytokine and cytokine receptor genes, in some cases associated with an allele–dose relationship, were found. For example, the minor variant for rs1035130 in the *IL18R1* gene was associated with higher ($p = 0.0002$) vaccinia-specific antibody titers, while the

heterozygous variant for rs2230052 in the *IL12A* gene was associated with lower levels of neutralizing antibodies ($p = 0.03$). The minor allele of rs2229113 in the *IL10RA* gene was found to be associated with a dose-related increase in IFN-γ responses ($p = 0.03$). Furthermore, two SNPs (rs1495963 and rs3024679) in the *IL4R* gene were associated with a dose-related decrease in IFN-γ production ($p \leq 0.05$) [101]. These preliminary data suggest that SNPs in cytokine/cytokine receptor genes may influence immune response following smallpox vaccine. Other genes in the region may also contribute to the genetic control of this immune response. Our group is currently conducting extensive genome-wide association studies of immune responses to the smallpox vaccine.

Severe complications due to the smallpox (live vaccinia virus) vaccine have been reported [102]. The licensed vaccinia vaccine against small-pox (Dryvax) is associated with rare severe side effects, including encephalitis and myopericarditis [47,103]. Common adverse events, such as fever after vaccination, have been observed in 13–15% of newly vaccinated individuals [104,105]. Stanley *et al.* examined associations between the development of fever (≥37.7°C) and SNPs in 19 candidate genes among 346 individuals assessed for clinical responses to smallpox vaccine [105]. Fever following smallpox vaccination was found to be associated with specific haplotypes in the *IL1* gene complex on chromosome 2 and with haplotypes within the *IL18* gene on chromosome 11. A specific haplotype in the *IL4* gene was significant for reduced risk for the development of fever after smallpox vaccination among vaccinia-naive subjects [105].

Recent papers have confirmed the association between receipt of the Dryvax vaccine and the development of myopericarditis [47,103,106]. It would be clinically important to determine if the individuals who developed myopericarditis after smallpox vaccination carry the *IL1*, *IL18* or other haplotypes. It is conceivable that *IL1*, *IL4* or *IL18* gene polymorphisms may also be influencing the development of more common adverse events, such as fever and febrile seizures, after MMR immunization in children [41,107]. Further exploration of the role of specific gene polymorphisms in adverse reactions to vaccines is crucial to our understanding of immune responses to vaccines and to preventing serious adverse events. We are confident that similar immunogenetic work on other vaccines (such as anthrax, yellow fever, avian influenza and so on) will be pursued in the near future.

The above data illustrate the clinical utility in regards to vaccinomics information. If we understood that a polymorphism in the *TLR* 'x' gene led to poor or absent immune response, and we knew the prevalence of that polymorphism, perhaps we could design a specific adjuvant that could overcome the genetic defect coded for by that particular polymorphism and direct the immune response in a favorable manner. For example, CpG oligonucleotide, which stimulates TLR9, was used as an adjuvant with the HBV vaccine to activate innate immune responses to the standard alum formulation of HBV vaccine in healthy adults [108]. Vandenbroeck *et al.* state that 'alterations in the expression levels of cytokines typically accompany aberrant immune activation … and demonstrate that cytokine gene association studies (of polymorphisms) are instrumental in identifying these disease states … such findings will ultimately lead to novel therapeutic strategies' [109]. Large-scale population-based immunogenetic studies will further inform us regarding molecular mechanisms of protective vaccine immunity and provide important clues in the development of novel vaccines. The data discussed above from numerous human studies demonstrate the genetic basis for interindividual variation in immune responses to viral vaccines in genetically heterozygous populations.

What's next? The developing field of personalized vaccinology

In many ways the era of personalized vaccines has already begun [110]. For example, the rationale behind and utilization of personalized vaccinology in cancer vaccines is increasingly clear and a benchmark in this regard [111,112]. In particular, in the field of cancer vaccines, much thought and progress has been demonstrated with the concept of personalized peptide vaccines [112].

Of particular interest to the personalized peptide vaccines concept is the peptide-based vaccine approach of identification of specific naturally processed pathogen-derived antigenic peptides. Targeting pathogenic T lymphocytes via vaccines consisting of synthetic peptides representing T- and B-cell epitopes is an interesting tactic since peptide-based approaches offer multiple advantages over whole-protein immunization strategies, including ease of manufacture, lower cost and the lack of a requirement for maintaining a cold chain [113–115]. Furthermore, identifying immunogenic peptides that would be restricted by numerous *HLA* alleles (promiscuous peptides) is one of the critical aspects to designing successful peptide-based vaccines that are useful among populations.

An increasing number of articles, editorials and scientific efforts are being directed toward personalized medicine [116–118]. These efforts will affect everything in medicine, and vaccines are no exception [110,111]. At a minimum, we predict that the role of genomics in the field of vaccinology will serve to elucidate new mechanisms and biologic pathways in understanding vaccine-induced immune responses and adverse responses, as well as provide new insights into vaccine development [119]. With high-throughput, low-cost genetic sequencing, large-scale phenotype/genotype databases, and bioinformatics; personalized vaccinology at the subpopulation and the individual level will occur. Of most value early in the development of this field will be associations with major or even dominant impacts (e.g., the SNP or allele that imparts a clinically impactful high relative risk ratio for poor response or adverse effect, or conversely protection from adverse events [120,121]. Such work will provide studies useful in clinical decision-making at the individual level. As sophistication increases, the ability to detect meaningful associations through the contributions of multiple genes will be discernible and potentially clinically useful. Finally, the ability to understand and predict the effect of the presence/absence and interactions of the entire genome or heritable non-DNA encoded differences (epigenetics, complementation and so on) may prove the most useful in understanding an individual patient's benefit or risk in receiving a specific vaccine [122,123]. In such a scenario, the finding of a particular SNP that confers a very high risk of a major adverse event to a vaccine, may be outweighed or mitigated by the simultaneous finding of other specific SNPs that confer protection against such a side effect. In this manner, the totality of the genetic risk or protective effects could be assessed and integrated with other aspects of a patient's personalized profile in regards to receiving a vaccine. Of course, to be useful we again caution that determining such a genetic profile will need to be inexpensive, easy to interpret and easy for physicians to understand and synthesize as clinical data. Thus, we see the following broad steps as necessary for the development of personalized vaccinology. If carried out such steps are likely to rapidly accelerate advances in the science and improve our ability to advise our patients on an individual (as opposed to a population level) level [124]. Without a coordinated approach, advances in the science are likely to be slow, uneven, disjointed, and less predictable and useful.

- Better designed gene-association studies are critical to advancing the science. Much has been written regarding this, but briefly such studies should be powered to detect scientifically and clinically meaningful associations [125–131];
- Studies should examine clinically meaningful end points. Studies designed to detect risks of vaccinia-associated encephalopathy are more important than studies defining

the risk of transient, low grade and spontaneously resolving local or systemic side effects such as fever;

- Studies should be designed to maximize the amount of genetic information derived. Initial studies of a small number of gene candidates are likely to be less promising than either genome-wide association studies or large candidate gene set studies for example, but may be appropriate as initial exploratory studies;
- Once initial genotype:phenotype association studies are completed and candidate SNPs or alleles identified, follow-up validation studies are critical to confirming true associations and to determining if such associations are also found in other ethnic/racial groups;
- The costs for such studies are currently high. Because of this, we applaud the NIH's efforts at directing funding toward such studies and in developing public databases that will allow other investigators access to study results and protocols so that results can be duplicated in other settings. It would be helpful, if possible, to develop biobanks of DNA material under study protocols so that studies could later be performed of vaccine immune response genotype:phenotype associations in as expeditious and inexpensive a manner as possible. By analogy, we need a 'Framingham study' [132] approach in order to develop clinically meaningful information;
- We must develop genetic tests that are reliable and reproducible, of low cost, for use in clinical settings, rapid, and are accompanied by sophisticated analytic tools in bioinformatics, informed by increasingly sophisticated understanding of genetics, immunology and immunogenetics.

Conclusion

The field of vaccinomics, adversomics and personalized vaccinology represents the evolution of new fields of study with new scientific possibilities informed by new paradigms and discoveries in immunology, genetics and bioinformatics. Growth in this field will be driven not only by scientific reasons, but also by consumer demands for increasingly safe and risk-free medical treatment, prevention and the desire to understand and prevent serious and severe vaccine adverse events. In turn, we believe that vaccinomics and an increasingly personalized vaccine approach will lead to new and better directed vaccine development – including the development of niche vaccines for those persons who are susceptible to serious or chronic outcomes from a given infectious disease and who are unlikely to, or have not, responded with protective immune responses to standard vaccines.

The finding that approximately 90% of the variation in measles vaccine immune response is explainable genetically provides but one insight into the importance of the field of vaccinomics. Understanding and defining associations between important immune response gene polymorphisms and subsequent immune response can aid in not only designing new vaccines, but also in developing new concepts that lead to a better understanding of viral vaccine-induced immune response variability in all human vaccines. In addition, such understandings may well allow us to predict who will not respond to a vaccine (and hence shouldn't receive the vaccine) or who is likely to suffer a serious adverse effect from a given vaccine. Thus, the broader development of vaccinomics data can be used to make individualized decisions regarding vaccine practice.

Nonetheless, as we have previously pointed out, difficulties remain in the study and application of the immunogenetics and immunogenomics of vaccine-induced immune responses [11]. First and foremost, the science base needed is still developing. We have yet to identify genotype:phenotype associations that would reliably call for variations in vaccinations (e.g.,

one more or one less dose, higher or lower concentration, or other changes in schedule). In addition, for the most part we do not yet have alternative vaccines to use to address poor immunogenetic responses (e.g., peptide cocktails and cytokine adjuvanted vaccines). The complexity and extensive polymorphic nature of immune response genes will require improved and increasingly powerful bio-informatic approaches in order to inexpensively acquire, display and understand complex genetic information. Further complexity results from issues of multigenic and gene–gene interactions and response effects such as complementation and heritable epigenetic modifications. Once initial data are available, validation studies in broader and more diverse subpopulations will need to be done in order to better understand the significance of gene-specific polymorphisms and to sort true-positive from spurious false-positive associations [133]. A recent editorial succinctly states that ‘use of genetic risk information to guide intervention must be justified by data demonstrating improved outcomes, reduced costs, or both’ [117]. We would endorse such a statement.

Second, to proceed with a program of personalized vaccines, the economics of the genotype:phenotype associations and the alternative interventions would need to lend themselves favorably to adjust vaccination. Vaccination succeeds currently as a population-level public health measure because it is cost-effective and that cost–effectiveness is driven by the universal application of a one-dose-fits-all model. We would need a situation with personalized vaccines that similarly saved costs. To illustrate, imagine a vaccine usually given in three doses at a cost of US$100 a dose. Let us assume a genetic association with complete penetrance that would permit us to give only two doses to a subgroup of individuals to get the same level of protection. With two doses, we would save US$100 for each of those individuals. Assume the genetic association occurs in the population at a rate of 10%. Identification of such individuals requires testing all in the population. As long as the test costs less than US$10 an individual, the new program would break even. For the program to save money, the test would need to be cheaper. To save an average of US$5, the test would need to cost only US$5. Third, such testing in practice would need a high diagnostic accuracy in order to base clinical decisions on the result.

In general, while substantial difficulties need to be solved, we nonetheless believe that the vaccinomics era of personalized predictive vaccinology [11,110] is coming and that this will eventually allow clinicians to predict the likelihood of a significant adverse event to a specific vaccine [105], develop novel vaccines in a directed, nonempiric manner, predict the necessity for a given vaccine as well as the dose and number of doses of a given vaccine needed to produce the desired immunologic outcome, and identify approaches to vaccination for individuals and groups (based on age, gender, race and other) based on genetic predilections to vaccine response and reactivity. As stated by one investigator ‘just as pharmacogenetics has suggested ways of designing drugs to minimize population variability, understanding mechanisms of immunogenetic variation may lead to new vaccines designed specifically to minimize immunogenetically based vaccine failure’ [134].

At the current time, a major barrier to vaccinomics and personalized vaccinology remains the cost. For the widespread application of personalized vaccinology, much data remains to be developed, genetic sequencing costs must be inexpensive and rapidly obtained with high-throughput sequencers, and increasingly more sophisticated and less labor-intensive bioinformatic approaches will need to be developed and validated. All these issues continue to experience substantial scientific and public interest, with regular new discoveries. Hence we believe that the future of vaccinology is bright indeed, and the era of empiric vaccine development, and a strict one-size-fits-all public health approach to vaccine delivery will diminish, with adoption instead of a philosophy of the best vaccine solution for each individual or subgroup of individuals. How fast and whether public health paradigms of vaccination against infectious diseases will evolve is unknown, but critical to the public’s health,

particularly in an era of consumer concern over safety, is the growing realization in healthcare policy that prevention is cheaper than treatment, and ultimately this will successfully drive advances in vaccine sciences to the benefit of all. In this regard, comprehensive and stable funding for childhood and adult immunization programs is critical to protecting the citizenry and national security.

Future perspective

Associations between *HLA* and other immune response gene polymorphisms, as well as innate and adaptive immune responses to vaccines are presently the best illustration of vaccine pharmacogenomics and pharmacogenetics (collectively called vaccinomics). To date, a number of immune response gene polymorphisms have been described that are associated with variations in vaccine-induced immune responses in genetically heterogeneous populations. This information, in combination with individual high-throughput genetic sequencing and bioinformatics will accelerate the field of vaccinomics and individualized vaccinology. Genetic sequencing approaches are critical for recognizing regulatory components of genes that are important in understanding immune responses following vaccination. Analysis of potential transcriptomic biomarkers for vaccine immune responses is another important technique informing the development of the next generation of prophylactic vaccines. Epigenetic aspects of heritable changes in gene-expression patterns in the absence of DNA sequence modifications of vaccine-related immune response genes will also be defined. Over the next decade, the role of immunogenetics relevant to personalized vaccines will also be further developed. We believe that the future of personalized medicine is such that with the appropriate enabling technology, one will be able to predict the likelihood of vaccine response, of numbers of doses need to achieve protection and the likelihood of serious adverse events due to vaccination. At the same time, additional immune response genes that influence variations in vaccine response will also be discovered, providing strategies for new immunotherapy approaches, novel vaccines and vaccine adjuvants. Prospective vaccine population-based studies should center on comprehensive genetic sequencing and epigenetic (DNA methylation, histone modifications) studies and on the mechanisms by which genetic polymorphisms and/or epigenetic modifications regulate gene expression and influence immune responses to vaccine antigens.

Executive summary

- The application of the science of pharmacogenomics and pharmacogenetics to vaccines has led to a new science of vaccinomics.
- Twin studies offer an ideal system for understanding the genetic contribution to variation in the immune response to vaccines, and for identification of SNPs.
- The activation and/or suppression of specific immune response pathway genes associated with response to vaccines provide a basis for the theory of the immune response gene network.
- *HLA* gene polymorphisms are important contributors to human immune responses to prophylactic vaccines.
- Genetic variants in immune response genes have important associations with immune responses to measles–mumps–rubella, influenza, HIV, hepatitis B vaccine and smallpox vaccines.
- A number of polymorphisms in *SLAM*, *CD46*, cytokine, cytokine receptor and *TLR* genes have been discovered that are associated with variations in both humoral and cellular immune responses to the measles–mumps–rubella vaccine.

- It may be feasible to design new personalized vaccines based on complex interactions of host genetic, environmental and other factors that control immune responses to vaccines.
- An emerging field associated with vaccinomics is the area of genetically determined vaccine-associated adverse events and atypical immune responses – collectively called adversomics.
- At the current time, cost is a major obstacle to vaccinomics and personalized vaccinology approach.

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