Published in final edited form as:
Expert Opin Biol Ther. 2008 November ; 8(11): 1659–1667. doi:10.1517/14712598.8.11.1659.

Personalized vaccines: the emerging field of vaccinomics

Gregory A Poland, MD[†,1,3], **Inna G Ovsyannikova, PhD**[2,3], and **Robert M Jacobson, MD**[2,4]

[†]Mayo Clinic College of Medicine, Mayo Vaccine Research Group, Program in Translational Immunovirology and Biodefense, Mayo Clinic, Rochester, Minnesota, USA

[2]Mayo Clinic College of Medicine, Mayo Vaccine Research Group, Program in Translational Immunovirology and Biodefense, Mayo Clinic, Rochester, Minnesota, USA

[3]Mayo Clinic College of Medicine, Department of Medicine, Mayo Clinic, Rochester, Minnesota, USA

[4]Mayo Clinic College of Medicine, Department of Pediatric and Adolescent Medicine Mayo Clinic, Rochester, Minnesota, USA

Abstract

The next 'golden age' in vaccinology will be ushered in by the new science of vaccinomics. In turn, this will inform and allow the development of personalized vaccines, based on our increasing understanding of immune response phenotype: genotype information. Rapid advances in developing such data are already occurring for hepatitis B, influenza, measles, mumps, rubella, anthrax and smallpox vaccines. In addition, newly available data suggest that some vaccine-related adverse events may also be genetically determined and, therefore, predictable. This paper reviews the basis and logic of personalized vaccines, and describes recent advances in the field.

Keywords

gene association studies; gene polymorphism; HLA; immunogenetics; single nucleotide polymorphisms; vaccinomics

1. Introduction: the current paradigm in vaccinology

The current medical practice in vaccinology is to universally administer the same set of vaccines to everyone in the population, in the absence of a contraindication, with several assumptions underlying this approach. One of these assumptions is that essentially everyone will react in the same way immunologically by developing protective levels of antibody, or cell-mediated immunity, with near non-existent rates of relevant side effects. It also assumes that everyone is at approximately the same level of risk against the disease being prevented, and that the vaccine dose amount and number of doses needed to develop immunity are the same across the population. The major strength of this approach has been a population-level paradigm that has allowed the widespread, almost automatic delivery of vaccines, and as a

1Author for correspondence Director, Mayo Vaccine Research Group, Director, Program in Translational Immunovirology and Biodefense, Professor of Medicine and Infectious Diseases Mayo Clinic College of Medicine, Mayo Clinic 611C Guggenheim Building, 200 First Street, SW, Rochester, MN 55905, USA Tel: +1 507 284 4968; Fax: +1 507 266 4716; poland.gregory@mayo.edu.

Declaration of interest G Poland is the chair of a DMSB for novel vaccines being developed by Merck Research Laboratories. In addition, G Poland and R Jacobson are investigators for an influenza clinical trial funded by Protein Sciences, and a pneumococcal vaccine trial funded by Wyeth. G Poland has offered consulting advice on vaccines to GlaxoSmithKline, Novartis, Novavax, Dynavax, CSL Ltd and Biotherapies, PowderMed, Avianax, Emergent BioSolutions, Discovery Institute of Medicine and Merck Research Laboratories.

result, the control of many infectious diseases. The major weakness of this approach is that it ignores individual variability in disease risk immunologic response, and any genetic propensity for reactogenicity, as well as differences in dose amount needed to generate immunity. At the same time, advances in immunology, genetics, molecular biology and bioinformatics have demonstrated the value of a personalized approach to therapeutic drug selection and dosing. Thus, a new 'tension' is developing in the field of vaccinology between the traditional public health population-level paradigm and the newly evolving individual-level paradigm that recognizes genetically encoded unique individual variations in response to biologic agents.

2. Personalized vaccines and vaccinomics

Personalized as applied to vaccines refers to 'targeting' vaccine antigens towards an optimized outcome (maximizing immunogenicity and minimizing the risk of either vaccine failure or vaccine reactogenicity and side effects in a host at risk of serious disease or complications). It references an enhanced set of outcomes in terms of the goals of providing immunization. Personalized can refer to either the individual level (recognizing that the presence of polymorphism 'x' or haplotype 'y' will prevent the development of a protective immune response or predict a high risk of a serious adverse reaction), the gender level (so far whenever it has been studied females respond with higher antibody levels to vaccine antigens than do males), the racial/ethnic level (Native Alaskans and Native Americans carry a specific Km/Gm allotype that results in a poor immune response to polysaccharide vaccine antigens) or the subpopulation level (persons taking drug 'z', which suppresses transcription of an immune response gene, respond poorly to a vaccine antigen) [1,2] . In turn, recognizing these genetically encoded restrictions allow both informed clinical decision-making and opportunities to advance the science by utilizing this information to develop better vaccines and enhanced vaccine administration algorithms.

We previously defined the terms immunogenetics and immunogenomics as applied to vaccine immune responses as 'vaccinomics', which encompasses both immunogenetics and immunogenomics as applied to vaccine-induced immune responses [3]. The field of vaccinomics examines the influence of immune response gene polymorphisms on the heterogeneity of humoral, cell-mediated and innate immune responses to vaccines at both the individual and population levels. The development of vaccinomics and personalized vaccinology was enabled by the completion of the first phase of the Human Genome Project and the first phase of the international HapMap, and accelerated by new molecular assay tools that allow high-throughput detection of gene variations, particularly single nucleotide polymorphism (SNP) and linkage disequilibrium maps. More recently appreciated is the idea that polymorphisms in key immune response genes can lead to heterogeneity in immune responses to biologics such as vaccines [4-6] . Thus, we predict a time when both immune and adverse vaccine responses will be predictable, quantifiable, informative of clinical practice and lead to an acceleration of rational, directed vaccine development. For this to happen, newer sequencing tools that are low-cost, accurate and reproducible will be needed as well as a validated database populated with phenotype–genotype data, and the bioinformatics and statistical tools to analyze and interpret the resulting data. Importantly, the field of personalized vaccines, although dependent on laboratory tools, is inherently driven by the desire for enhanced patient-level outcomes (immuno-genicity, decreased risk of side effects, economic savings and so on) at both the patient and payer levels.

As we have previously pointed out [7] , vaccinomics has already advanced the science of vaccine immunogenetics by demonstrating the following:

- widespread polymorphism of immune response genes critical to the development of protective immune responses

- immunologically relevant outcomes related to these polymorphisms
- recognition of selective pressures to maintain and even enhance the type and number of immune response gene polymorphisms; for example, there may indeed seem to be a 'heterozygote advantage' at the population level to widespread diversity in immune response gene polymorphism to allow a broad range of immune responses to infectious disease threats
- vaccinomics initially focused on individual gene polymorphism associations, broadened to haplotypes and extended haplotypes, and is now evolving toward the ultimate: the real-time ability to understand, at the whole genome level, the effects of whole genome gene/polymorphic activation, suppression and modification *in toto* on the immune response to an antigen in a predictive manner
- recognition that although gene polymorphisms throughout the pathway from infection through the development of immune responses are important, so far there seem to be few specific polymorphisms that are dominant determinants of the immune response (i.e., few 'all or none' polymorphisms) and
- immune response gene polymorphisms can have positive, negative or neutral effects on adaptive immune responses, and these polymorphisms explain individual variations in immune responses.

3. Polymorphism of the HLA system

Theoretically personalized vaccines – the vaccine best suited for an individual person – are based on complex interactions of host genetic, environmental and other factors that influence immune responses to vaccines. Personalized vaccine development is inherently a multistep process, and we are at the beginning of the process. Therefore, it is important to identify associations between variations in vaccine immune responses and polymorphisms of immune response genes [7]. Knowledge of these associations could allow design of a vaccine or adjuvant that circumvents immunogenetic restrictions, and animal models provide proof of this principle [8,9].

The concept of personalized vaccines has emerged from a detailed understanding of how T cells recognize pathogenic antigens (peptides) within the human leukocyte antigen (HLA) system. The HLA complex includes the most polymorphic genes in the human genome with > 1000 HLA-A, -B and -C allelic variants already described [10-12] . It is believed that the HLA region contributes significantly to genetic susceptibility to infectious diseases and variations in immune responses to vaccines [12,13] . Because antibody production following vaccination is supported by HLA class II-restricted $CD4^+$ T-cell responses, HLA class II alleles influence the humoral response after vaccination. For example, the HLA-DRB1*03 allele was found to be associated with seronegativity or a low antibody response following hepatitis B and measles virus vaccines [14,15] . More candidate alleles that have been found in association with non-response to full-dose recombinant hepatitis B virus (HBV) vaccination include HLA-DRB1 * 07 and DQB1 * 03 alleles [16]. Although this finding needs to be replicated, it raises the possibility that persons who fail to respond to the HBV vaccine may be more susceptible to persistent HBV infection [17,18].

HLA studies of measles–mumps–rubella (MMR)-induced vaccine cellular and humoral immune responses revealed vaccine immune response associations with both HLA class I and II molecules [19-21]. Analysis of the HLA genes led to the identification of particular HLA haplotypes significantly associated with a decrease in IgG antibody levels (A*29-Cw*16-B*44 haplotype) and an increase in (A*26-Cw*12-B*38 haplotype) cellular immune responses to both measles and mumps viral antigens [22]. Several associations have been observed between HLA class I supertypes and MMR vaccine outcomes [23]. Perhaps the most interesting finding

has been with respect to the association of the HLA class I B44 and B58 supertypes and lower measles-specific antibodies following two doses of the MMR vaccine [23]. This knowledge begins to explain the genetic regulation of MMR vaccine immune responses, which could be leveraged in personalized vaccine design by designing promiscuous antigenic peptides that can bind across several HLA alleles or supertypes.

As an example, the current (non-personalized) MMR vaccine is limited by several factors such as interference from maternal antibody, cold chain requirements, vaccine failure and the inability to administer vaccine to immunocompromised persons. For this reason, significant research supporting new vaccine development is occurring. A protein or peptide-based (personalized) vaccine could overcome these limitations. In fact, we have identified 13 immunogenic measles peptides that could be used in developing a second generation vaccine, and these peptides were selected to circumvent HLA polymorphic restrictions we identified [24,25]. Others have also demonstrated immunogenicity of measles peptides *in vitro* in humans [26]. New methods for personalized vaccines are being developed based on HLA allele frequencies in human populations and the growing number of pathogen-derived peptides, which have been recently identified [27-30].

Normally vaccines provide immunity by simulating a natural infection; thus, polymorphisms in genes that play a role in the pathogenesis of the infection could also influence or regulate vaccine immune response. For example, the likelihood of developing cervical cancer has been shown to be increased in persons with certain HLA alleles. Genes involved in antigen processing for HLA class I presentation, such as transporter associated with antigen processing (TAP)1, TAP2, proteasome subunits LMP2, LMP7 and Tapasin, were suggested to contribute to susceptibility to human papillomavirus (HPV) type-16-associated cervical cancer [31]. We previously demonstrated a significant association between immune response genes (TAP1, TAP2 and HLA-DR2) and the risk of cervical cancer [32]. Recently, IL-10 gene polymorphisms have been associated with the clearance of infection with high-risk HPV types among immunosuppressed adolescent females with varying degrees of HIV-1-induced CD4 immunosuppression [33]. Such information creates a compelling argument for the importance of cytokine gene regions and/or a cluster of genes in the HLA region that regulates host immune responses to HPV infection in a manner that results in inherited susceptibility or resistance to the transforming properties of oncogenic papillomaviruses [32].

4. Immune response gene polymorphism

Evidence to support genetic determinants of variable immune response to vaccines for preventing infections is expanding. SNPs, variations at a single site within a host's DNA sequence, are the most frequent type of variation in the human genome, with ~ 90% of all genetic variation being attributed to SNPs [34]. The Human Genome Project has estimated that 1.42 million SNPs are distributed through the human genome with ~ 60,000 SNPs falling in coding regions [35]. SNPs in coding regions that cause amino acid changes, such as nonsynonymous SNPs (SNPs that change protein sequence), as well as SNPs in regulatory regions, are likely to have the greatest impact on phenotype as they may have a direct effect on protein structure and function [36]. 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" [37]. This concept encapsulates the thrust of vaccine response immunogenetics and its relationship to the field of vaccine development. Vandenbroeck and Goris recently published a paper pointing out that "cytokine gene polymorphisms may be gateways to novel targets for immunotherapy" [38]. Jin and Wang comment that "the lesson learned from HLA is that polymorphisms can occur preferentially in the functional domains of a given molecule with dramatic effects on epitope selection and

presentation" [12]. As an example of these concepts, HLA-DRB1*07 and cytokine SNPs at the IL-2 and IL-4 loci along with insertion/deletion variants at the IL-12B locus were found to be independently associated with hepatitis B vaccine non-response [16]. Development of a new HBV vaccine consisting of a peptide 'cocktail' (novel epitopes identified from chronic carriers) with cytokine adjuvants (for example, GM-CSF) could circumvent these immunogenetic restrictions. In fact, such vaccine development is continuing [39,40].

Genomic studies have also revealed mumps vaccine-induced immune response associations with SNPs in the IL-12RB1 and IL-12RB2 cytokine receptor genes. For example, the presence of minor allele T for intronic SNP rs2201584 within the IL-12RB2 gene was associated with an allele dose-related significant decrease in mumps antibody titers in healthy children (12 – 18 years of age) who previously received two doses of live mumps vaccine. Conversely, minor allele A of rs372889 within the IL-12RB1 gene was associated with significantly lower mumps vaccine-induced cellular lymphoproliferative responses [21]. Similarly, we have identified SNPs (rs3796504 and rs164288) in the signal lymphocyte activation molecule (SLAM, also known as CDw150) gene associated with an allele dose-related decrease (~ 70%) in measles vaccine-induced antibody levels [41]. We hypothesize that these SNPs negatively impact the ability of measles vaccine virus to bind to its receptor, and hence prevent induction of immunity. A candidate measles vaccine virus engineered with binding properties that allowed binding in both the presence and absence of such a receptor polymorphism could restore vaccine immunogenicity. This is similar to the identification of the CC chemokine receptor 5 (CCR5) deletion mutation in the coding region of CCR5 HIV receptor, which is now being exploited in the development of novel HIV therapeutic drugs and vaccines [42]. In addition, adjuvants such as six deoxynucleotide-long DNA sequences with a central CpG dinucleotide or monophosphoryl lipid-A could differentially activate toll-like receptors (TLR9 or TLR4, respectively) to circumvent restrictions in other receptors [43,44]. Genetic variations in the TLRs that play an important role in measles virus recognition could result in variable immune responses to measles vaccination. Our preliminary data suggest that heterozygous variants for SNPS rs3775291 and rs5743305 of the TLR3 gene are associated with low antibody and lymproliferative responses to measles vaccination [45]. As a final example, cytokine secretion is highly regulated by the transcriptional rates of their genes: SNPs in these genes can disrupt binding of transcription factors, or affect gene expression and function by altering the stability of RNA molecules [12]. Therefore, knowledge of such a polymorphism might facilitate development of vaccine candidates that incorporate cytokines to 'replace' those not made natively (i.e., a cytokine plasmid or cytokine adjuvants) and restore an optimal Th1/Th2 balance that would facilitate a protective immune response [46,47]. Thus, understanding and defining associations between key immune response gene polymorphisms and subsequent immune response can aid in designing new personalized vaccines.

5. Genetic predisposition for vaccine adverse events

Humans respond differently to vaccines and the host immune response significantly varies in a population [48,49]. There is no way to predict the reaction of a specific individual or a population to a particular vaccine. Identifying factors that influence the development of adverse reactions may allow personalized screening before vaccination [50,51]. For example, the smallpox vaccine (live vaccinia virus) has the highest complication and adverse reaction rate of any licensed vaccine at present. Severe complications owing to receiving live vaccinia virus vaccine have been reported [52]. Statistics collected during past smallpox vaccination campaigns reveal that death occurs in 1 to 2 in 1,000,000 primary vaccinees, although the risk of experiencing any one of the many serious adverse events (SAEs) complications is ~ 1 in 14,000 [53,54]. Reports identifying the risk of vaccinia-associated myopericarditis and the risks of SAEs in the context of the recent Department of Health and Human Services and Department of Defense large-scale vaccination programs have been published [55,56]. Studies

suggest that among US military personnel vaccinated against smallpox (New York City Board of Health vaccinia virus strain), myopericarditis occurred at a rate of 1/12,819 primary vaccinees [55]. Public health interests could be served by the development of an efficacious recombinant, peptide-based vaccine because of these risks. To further combat infectious diseases by vaccination, we must be able to develop safe and effective new vaccines at the individual and population levels [57].

Immunologic and host genetic factors are all likely to have an important role in the development of adverse events (AEs) following vaccination. For example, alterations in systemic Th1 and Th2 cytokine concentrations have been implicated in AEs in vaccinia virus-naive individuals after smallpox vaccination [50]. McKinney *et al*. [58] identified a group of cytokines, such as G-CSF, stem cell factor, monokine induced by IFN-γ (CXCL9), intercellular adhesion molecule-1, eotaxin and tissue inhibitor of metalloproteinases-2, that accurately discriminates between persons on the basis of AEs status. This cytokine pattern seems to be a characteristic of particular inflammatory response pathway and suggests that the secretion of cytokines by fibroblasts may play a central role in systemic AEs [58]. Immunogenetic approaches, such as comparing SNPs in candidate genes linked to the control of poxvirus infections in persons who developed adverse reactions (occurrence of fever) after smallpox vaccine with those in individuals who do not develop adverse reactions, offer enormous advantages [51,59]. For example, identification of such genetic markers may help to predict which individuals are at risk for vaccine-related AEs. Immunogenetic approaches will also supply physicians with information regarding the balance between the benefits and potential risks of vaccines such as smallpox vaccine if an individual has a specific genetic variation(s) that is associated with an increased risk of a serious adverse reaction. The presence of a nonsynonymous SNP in the methylenetetrahydrofolate reductase gene and two SNPs in the IFN regulatory factor-1 gene were found to be associated with the risk of systemic AEs (fever, lymphadenopathy or generalized acneiform rash) in two independent clinical trials of the smallpox vaccine [60]. Stanley *et al*. [59] demonstrated an association between fever after smallpox vaccination and specific haplotypes in the IL-1 gene complex and in IL-18 gene. In contrast, the SNP (rs2243250) in the IL-4 gene was highly significant for a reduced risk of fever following vaccination among vaccinia-naive individuals [59]. These studies offer preliminary information for understanding the variation in host response and could provide useful information that would predict or prevent SAEs after vaccination. Obviously, large-scale genetic studies are required to confirm these findings.

The development of AEs such as fever and febrile seizures has been observed after administration of live attenuated MMR vaccine. For example, in healthy children, ages 9 – 24 months, fever > 39.5°C was reported after 9.5 and 11.9% of the MMR (Priorix®, SmithKline Beecham Biologicals, London, UK) and Merck MMR (Merck & Co., Inc., Whitehouse Station, NJ, USA) vaccine doses, respectively [61]. Vestergaard *et al*. [62] studied incidence rate ratios and risk differences of febrile seizures following MMR vaccination in subgroups of children. This study found that at 15 – 17 months, the risk difference of febrile seizures in 2 weeks following MMR immunization was 1.56/1000 children overall (95% CI, 1.44 – 1.68), 3.97/1000 (95% CI, 2.90 – 5.40) for siblings of children with a history of febrile seizures and 19.47/1000 (95% CI, 16.05 – 23.55) for children with a personal history of febrile seizures [62]. MMR vaccination was associated with a transient increased rate of febrile seizures but the risk difference was small even in high-risk children. It was suggested that an increased risk for febrile seizures after MMR vaccination in children with a sibling with a history of febrile seizures may be owing to a possible genetic basis for increased susceptibility to this condition [59]. Furthermore, Stanley *et al*. [59] hypothesize that children with febrile reactions after MMR vaccination are more susceptible owing to certain haplotypes in IL-1, IL-4 or IL-18 genes. Thus, it is suspected that genetic factors, in part, may explain some of the differences in response to the current live attenuated MMR vaccine.

6. Sex-based differences in the immune response to vaccines

Generally, females demonstrate more vigorous humoral (and cellular) immune responses to antigenic stimulation, such as infection and vaccination, compared with males [63,64]. It has been previously shown that there is differential antibody recognition of measles and rubella virus proteins between females and males and that both hormonal (steroid hormones) and genetic (X-linked genes) differences may influence this humoral immune response [65,66]. Our recent studies also demonstrate sex-based differences in IgG antibody responses to two doses of rubella and mumps viral vaccines. We have demonstrated that female subjects demonstrated significantly higher antibody responses to rubella (median 42 versus 34 IU/ml; $p = 0.02$) and mumps (median 876 versus 677 IU/ml; $p = 0.003$) vaccine antigens than males [21,67]. However, these studies revealed that *in vitro* cellular immune response, such as lymphocyte proliferation, to both rubella and mumps vaccination was not sex-dependent. Similarly, gender disparities were observed in vaccinia-induced neutralizing antibody levels after a single dose of smallpox vaccine (Dryvax) in healthy adults with higher neutralization titers in females [68]. Thus, it is very important to address sex-based differences (that may predispose to differential immune responses) in the emerging field of personalized vaccines to provide optimal immunity regardless of gender.

7. Issues with the concept and execution of personalized vaccines

Personalized vaccines have potential conflicts with our current public health model of preventive vaccination. Our current model of preventive vaccination against infectious diseases depends on the universal acceptability and distribution of the vaccine. Standards first proposed in 1992 called for the identification and minimization of barriers to routine immunization [69]. Specific barriers mentioned in these standards included delays in scheduling appointments and requiring a well-child visit or physical examination. Attempts to individualize vaccination may move away from recommendations for the minimization of barriers and the facilitation of expedited vaccination. Furthermore, our public health success with vaccination depends in large part on creating herd immunity, an immunity across large segments of the population. To do this, some of our vaccines depend on 80 – 90% vaccine uptake [70,71].

At present we are achieving among the highest rates of vaccine uptake. We have accomplished this in part by minimizing the perceptions of contraindications and precautions for vaccines. Furthermore, with few exceptions, we do not adjust the dose for age or body mass nor do we vary the number of doses based on exposure to disease or timing of past vaccines. Our uptake-metrics that we now celebrate as the highest we have ever achieved in the history of public health depend on our one-size-fits-all approach to vaccination. Furthermore, it facilitates standing orders and mass vaccinations done to address large numbers of those who seek rapid and timely vaccination.

Practical matters may also stand in the way. Using different vaccines for different groups of persons based on personal characteristics or genetic makeup could require more effort and time in the vaccination process. Having to screen for individual factors to vaccinate differently could impose substantial costs to vaccination, although saving other costs. The concept of personalized vaccines depends on previous knowledge of genetic influence on immune response. At present we are not doing such testing. We do not even vary vaccination based on race and ethnicity and in the past have only done so transiently moving inevitably in each case toward universal vaccination (e.g., hepatitis B, hepatitis A, pneumococcal conjugate vaccine). We have certainly considered prevaccine screening for immune status but in many cases, with the exception of the unvaccinated adult with respect to varicella, vaccinating is cheaper than testing. In general, serologic testing in an adult with a negative history of chicken pox is cheaper

than two doses of vaccine. For example, the Advisory Committee on Immunization Practices comments: “In healthcare institutions, serologic screening before vaccination of personnel who have a negative or uncertain history of varicella and who are unvaccinated is likely to be cost effective” [72]. Nonetheless, such prevaccination testing is now routinely done among military recruits in the US. Again, our efforts in this regard diminish each year as we move toward universal vaccination of the next generation.

Furthermore, we must consider the practical issue of marginal benefit. Most of the vaccines that we routinely use have high immune response rates. Would we really impose across the population genetic screening to improve immune response for 5% of the population? We may, however, consider certain situations in which vaccines fail to achieve such high rates such as in overweight healthcare workers who have higher rates of non-responsiveness to the hepatitis B vaccine or American Native children and *Haemophilus influenzae* type b vaccine [73,74]. Still these groups are easily identified phenotypically and at this point no evidence suggests these groups should receive a different vaccination schedule. Screening for an increased propensity to certain AEs may also drive some forms of genetic screening.

We must also consider the practical difficulty of licensure of personalized vaccines. For patients with cancer, individualized cancer vaccines can be developed for individual patients without the problems that manufacturers of biologics face with licensure for mass production and distribution. With population vaccination, regulatory bodies will still require prelicensure testing in animals and humans for each species of vaccine and for each dose and schedule. One way to overcome this issue would be the development of one-size-fits-all adjuvanted peptide-vaccine cocktails that all receive with the expectation that different individuals respond to different agents, informed, for example, by population-level HLA supertype frequencies, contained in the cocktail.

8. Expert opinion

8.1 The future of vaccinomics

Assuming such barriers can be overcome or minimized, the new biology, in combination with increasing genotype, phenotype information and low cost, high output genetic screening will inevitably lead toward a more personalized approach to vaccines, just as it has with pharmaceuticals. In addition, a ‘zero defect’ societal perspective on risk may further drive individualized approaches to vaccines. Thus, although significant barriers remain, we predict an increasing vaccinomics’ approach to protection against vaccine-preventable diseases by vaccines, and an acceleration of the directed development of novel vaccine approaches. Such an approach will also provide models for deeper understanding of the mechanistic underpinnings of the antigen, immune response gene interface and drive new insights in genetic immunology. *In toto*, such an approach will result in a new golden age of vaccinology.

Despite much work yet to be accomplished and significant barriers that were discussed above, it is apparent that we are moving toward a new scientific frontier and a new era of personalized vaccinology. Vaccinomics will allow and accelerate directed vaccine development, and predictive vaccinology will eventually allow physicians to determine whether to give a vaccine (i.e., is this specific patient genetically susceptible to a disease and its adverse outcomes?), what dose to give, how many doses to give and whether a significant AE is likely to occur. This ‘second golden age of vaccinology’ is poised to begin, and along the way many insights into the immunogenetics of immune responses to antigens and accelerated and directed methods for vaccine development will become apparent [75].

8.2 Executive summary

- There is a strong genetic component to vaccine immune response variation.

- Personalized vaccines will be developed and informed by the particular genetics and biology of the individual.
- There will continue to be discovery of genetic markers that predict vaccine immune response and possible SAEs.

Acknowledgments

We thank CA Hart for her editorial assistance. In addition we acknowledge support from National Institutes of Health grants AI 33144, AI 48793 and AI 40065 for this work.

Bibliography

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Black FL, Schiffman G, Pandey JP. HLA, Gm, and Km polymorphisms and immunity to infectious diseases in South Amerinds. Exp Clin Immunogenet 1995;12:206–16. [PubMed: 8534507]
2. Granoff DM, Pandey JP, Boies E, et al. Response to immunization with Haemophilus influenzae type b polysaccharide-pertussis vaccine and risk of Haemophilus meningitis in children with the Km(1) immunoglobulin allotype. J Clin Invest 1984;74:1708–14. [PubMed: 6334101]
3. Poland GA, Ovsyannikova IG, Jacobson RM. Vaccine immunogenetics: bedside to bench to population. Vaccine. 2008 In press. • This paper provides a review of immunogenetic determinants of measles vaccine response.
4. Poland GA, Jacobson RM. The genetic basis for variation in antibody response to vaccines. Curr Opin Pediatr 1998;10:208–15. [PubMed: 9608902]
5. Poland GA. Variability in immune response to pathogens: using measles vaccine to probe immunogenetic determinants of response. Am J Hum Genet 1998;62(2):215–20. [PubMed: 9463343]
6. Poland, GA.; Ovsyannikova, IG.; Jacobson, RM. Genetics and immune response to vaccines. In: Kaslow, RA.; McNicholl, JM.; Hill, AVS., editors. Genetic susceptibility to infectious diseases. Oxford University Press; New York: 2008. p. 414-29.
7. Poland GA, Ovsyannikova IG, Jacobson RM, Smith DI. Heterogeneity in vaccine immune response: the role of immunogenetics and the emerging field of vaccinomics. Clin Pharmacol Ther 2007;82(6): 653–64. [PubMed: 17971814] •• A state-of-the-art overview of the field of vaccinomics and the role of immunogenetics and immunogenomics in understanding the mechanisms of heterogeneity in immune responses to vaccines.
8. Sinha P, Snyder JA, Kim EY, Moudgil KD. The major histocompatibility complex haplotypes dictate and the background genes fine-tune the dominant versus the cryptic response profile of a T-cell determinant within a native antigen: relevance to disease susceptibility and vaccination. Scand J Immunol 2007;65(2):158–65. [PubMed: 17257220]
9. Halassy B, Mateljak S, Bouche FB, et al. Immunogenicity of peptides of measles virus origin and influence of adjuvants. Vaccine 2006;24(2):185–94. [PubMed: 16122851]
10. Klein J, Sato A. The HLA system. First of two parts. N Engl J Med 2000;343:702–9. [PubMed: 10974135]
11. Klein J, Sato A. The HLA system. Second of two parts. N Engl J Med 2000;343:782–6. [PubMed: 10984567]
12. Jin P, Wang E. Polymorphism in clinical immunology – from HLA typing to immunogenetic profiling. J Transl Med 2003;1(1):8. [PubMed: 14624696]
13. Burgner D, Jamieson SE, Blackwell JM. Genetic susceptibility to infectious diseases: big is beautiful, but will bigger be even better? Lancet Infect Dis 2006;6(10):653–63. [PubMed: 17008174]
14. Desombere I, Willems A, Leroux-Roels G. Response to hepatitis B vaccine: multiple HLA genes are involved. Tissue Antigens 1998;51(6):593–604. [PubMed: 9694351]
15. Poland GA, Ovsyannikova IG, Jacobson RM, et al. Identification of an association between HLA class II alleles and low antibody levels after measles immunization. Vaccine 2001;20(34):430–8. [PubMed: 11672906]

16. Wang C, Tang J, Song W, et al. HLA and cytokine gene polymorphisms are independently associated with responses to hepatitis B vaccination. Hepatology 2004;39(4):978–88. [PubMed: 15057902]
17. Thio CL, Carrington M, Marti D, et al. Class II HLA alleles and Hepatitis B virus persistence in African Americans. J Infect Dis 1999;179:1004–6. [PubMed: 10068598]
18. Thursz M. Pros and cons of genetic association studies in hepatitis B. Hepatology 2004;40(2):284–6. [PubMed: 15368431]
19. Ovsyannikova IG, Jacobson RM, Vierkant RA, et al. Associations between human leukocyte antigen (HLA) alleles and very high levels of measles antibody following vaccination. Vaccine 2004;22:1914–20. [PubMed: 15121303]
20. Ovsyannikova IG, Jacobson RM, Vierkant RA, et al. Human leukocyte antigen class II alleles and rubella-specific humoral and cell-mediated immunity following measles-mumps-rubella-II vaccination. J Infect Dis 2005;191(4):515–9. [PubMed: 15655774]
21. Ovsyannikova IG, Jacobson RM, Dhiman N, et al. Human leukocyte antigen and cytokine receptor gene polymorphisms associated with heterogeneous immune responses to mumps viral vaccine. Pediatrics 2008;121:e1091–9. [PubMed: 18450852]
22. Ovsyannikova IG, Pankratz VS, Vierkant RA, et al. Human leukocyte antigen haplotypes in the genetic control of immune response to measles-mumps-rubella vaccine. J Infect Dis 2006;193(5):655–63. [PubMed: 16453260]
23. Ovsyannikova IG, Jacobson RM, Vierkant RA, et al. HLA supertypes and immune responses to measles-mumps-rubella viral vaccine: findings and implications for vaccine design. Vaccine 2007;25(16):3090–100. [PubMed: 17280755]
24. Johnson KL, Ovsyannikova IG, Poland G, Muddiman DC. Identification of class II HLA-DRB1*03-bound measles virus peptides by 2D-liquid chromatography tandem mass spectrometry. J Proteome Res 2005;4:2243–9. [PubMed: 16335972]
25. Ovsyannikova IG, Johnson KL, Muddiman DC, et al. Identification and characterization of novel, naturally processed measles virus class II HLA-DRB1 peptides. J Virol 2004;78(1):42–51. [PubMed: 14671086]
26. Ota MO, Ndhlovu Z, Oh S, et al. Hemagglutinin protein is a primary target of the measles virus-specific HLA-A2-restricted CD8+ T cell response during measles and after vaccination. J Infect Dis 2007;195(12):1799–807. [PubMed: 17492596]
27. Sette A, Fikes J. Epitope-based vaccines: an update on epitope identification, vaccine design and delivery. Curr Opin Immunol 2003;15(4):461–70. [PubMed: 12900280]
28. Ovsyannikova IG, Johnson KL, Bergen HR III, Poland GA. Mass spectrometry and peptide-based vaccine development. Clin Pharmacol Ther 2007;82(6):644–52. [PubMed: 17971823]
29. Doolan DL, Southwood S, Chesnut R, et al. HLA-DR promiscuous T cell epitopes from Plasmodium falciparum ore-erythrocytic-state antigens restricted by multiple HLA class II alleles. J Immunol 2000;165:1123–37. [PubMed: 10878392]
30. Bui HH, Peters B, Assarsson E, et al. Ab and T cell epitopes of influenza A virus, knowledge and opportunities. Proc Natl Acad Sci USA 2007;104(1):246–51. [PubMed: 17200302]
31. Deshpande A, Wheeler CM, Hunt WC, et al. Variation in HLA class I antigen-processing genes and susceptibility to human papillomavirus type 16-associated cervical cancer. J Infect Dis 2008;197(3):371–81. [PubMed: 18248301]
32. Gostout BS, Poland GA, Calhoun ES, et al. TAP1, TAP2, and HLA-DR2 alleles are predictors of cervical cancer risk. Gynecol Oncol 2003;88(3):326–32. [PubMed: 12648582]
33. Shrestha S, Wang C, Aissani B, et al. Interleukin-10 gene (IL10) polymorphisms and human papillomavirus clearance among immunosuppressed adolescents. Cancer Epidemiol Biomarkers Prev 2007;16(8):1626–32. [PubMed: 17684137]
34. Collins A, Lonjou C, Morton NE. Genetic epidemiology of single-nucleotide polymorphisms. Proc Natl Acad Sci USA 1999;96(26):15173–7. [PubMed: 10611357]
35. Sachidanandam R, Weissman D, Schmidt SC, et al. A map of human genome sequence variation containing 1.42 million single nucleotide polymorphisms. Nature 2001;409(6822):928–33. [PubMed: 11237013]
36. Collins FS, McKusick VA. Implications of the human genome project for medical science. JAMA 2001;285(5):540–4. [PubMed: 11176855]

37. Spielberg SP. Therapeutics and toxicology. Curr Opin Pediatr 1998;10:201–2. [PubMed: 9608900]
38. Vandenbroeck K, Goris A. Cytokine gene polymorphisms in multifactorial diseases: gateways to novel targets for immunotherapy? Trends Pharmacol Sci 2003;24(6):284–9. [PubMed: 12823954]
39. Kim M-J, Nafziger AN, Harro CD, et al. Revaccination of healthy nonresponders with hepatitis B vaccine and prediction of seroprotection response. Vaccine 2003;21(1112):1174–9. [PubMed: 12559795]
40. Lee HG, Lim J-S, Lee K-Y, et al. Peptide-specific CTL induction in HBV-seropositive PBMC by stimulation with peptides in vitro: novel epitopes identified from chronic carriers. Virus Res 1997;50:185–94. [PubMed: 9282783]
41. Dhiman N, Cunningham JM, Jacobson RM, et al. Variations in measles vaccine-specific humoral immunity by polymorphisms in SLAM and CD46 measles virus receptors. J Allergy Clin Immunol 2007;120(3):666–72. [PubMed: 17560639]
42. Dean M, Carrington M, O'Brien SJ. Balanced polymorphism selected by genetic versus infectious human disease. Ann Rev Genomics Hum Genet 2002;3:263–92. [PubMed: 12142357]
43. Fitzgerald KA, Golenbock DT. Immunology. The shape of things to come. Science 2007;316(5831): 1574–6. [PubMed: 17569850]
44. Mata-Haro V, Cekic C, Martin M, et al. The vaccine adjuvant monophosphoryl lipid A as a TRIF-biased agonist of TLR4. Science 2007;316(5831):1628–32. [PubMed: 17569868]
45. Dhiman N, Ovsyannikova IG, Vierkant RA, et al. Associations between SNPs in toll-like receptors and related intracellular signaling molecules and immune responses to measles vaccine: preliminary results. Vaccine 2008;26:1731–6. [PubMed: 18325643]
46. Perera LP, Waldmann TA, Mosca JD, et al. Development of smallpox vaccine candidates with integrated IL-15 that demonstrate superior immunogenicity, efficacy and safety in mice. J Virol. 2007 Online.
47. Keen LJ. The extent and analysis of cytokine and cytokine receptor gene polymorphism. Transpl Immunol 2002;10(23):143–6. [PubMed: 12216945]
48. Relman DA. Learning to appreciate our differences. J Infect Dis 2008;198(1):4–5. [PubMed: 18454681]
49. Plotkin SA. Vaccines: correlates of vaccine-induced immunity. Clin Infect Dis 2008;47(3):401–9. [PubMed: 18558875]
50. Rock MT, Yoder SM, Talbot TR, et al. Adverse events after smallpox immunizations are associated with alterations in systemic cytokine levels. J Infect Dis 2004;189(8):1401–10. [PubMed: 15073677]
51. Crowe JE Jr. Genetic predisposition for adverse events after vaccination. J Infect Dis 2007;196(2): 176–7. [PubMed: 17570102] • An editorial commentary on genetic factors that may influence an incidence of fever after smallpox vaccination.
52. Slifka MK. The Future of Smallpox Vaccination: is MVA the key? Med Immunol 2005;4(1):2. [PubMed: 15740619]
53. Poland GA, Grabenstein JD, Neff JM. The US smallpox vaccination program: a review of a large modern era smallpox vaccination implementation program. Vaccine 2005;23:2078–81. [PubMed: 15755574]
54. Henderson, DA.; Moss, B. Smallpox and vaccinia. In: Plotkin, SA.; Orenstein, WA., editors. Vaccines. 3rd edition. WB Saunders Company; Philadelphia, PA: 1999. p. 74-97.
55. Halsell JS, Riddle JR, Atwood JE, et al. Myopericarditis following smallpox vaccination among vaccinia-naive US military personnel. JAMA 2003;289:3283–9. [PubMed: 12824210]
56. Arness MK, Eckart RE, Love SS, et al. Myopericarditis following smallpox vaccination. Am J Epidemiol 2004;160(7):642–51. [PubMed: 15383408]
57. Wilson CB, Marcuse EK. Vaccine safety –- vaccine benefits: science and the public's perception. Nat Rev Immunol 2001;1(2):160–5. [PubMed: 11905824]
58. McKinney BA, Reif DM, Rock MT, et al. Cytokine expression patterns associated with systemic adverse events following smallpox immunization. J Infect Dis 2006;194(4):444–53. [PubMed: 16845627]
59. Stanley SL Jr, Frey SE, Taillon-Miller P, et al. The immunogenetics of smallpox vaccination. J Infect Dis 2007;196(2):212–9. [PubMed: 17570108]

60. Reif DM, McKinney BA, Motsinger AA, et al. Genetic basis for adverse events after smallpox vaccination. J Infect Dis 2008;198:1–7. [PubMed: 18544010] • This study demonstrates the relative importance of genetic contribution to the development of adverse events after smallpox vaccination.
61. Usonis V, Bakasenas V, Kaufhold A, et al. Reactogenicity and immunogenicity of a new live attenuated combined measles, mumps and rubella vaccine in healthy children. Pediatr Infect Dis J 1999;18(1):42–8. [PubMed: 9951979]
62. Vestergaard M, Hviid A, Madsen KM, et al. MMR vaccination and febrile seizures: evaluation of susceptible subgroups and long-term prognosis. JAMA 2004;292(3):351–7. [PubMed: 15265850]
63. Klein SL. The effects of hormones on sex differences in infection: from genes to behavior. Neurosci Biobehav Rev 2000;24(6):627–38. [PubMed: 10940438]
64. Fish EN. The X-files in immunity: sex-based differences predispose immune responses. Nat Rev Immunol 2008;8(9):737–44. [PubMed: 18728636]
65. Green MS, Shohat T, Lerman Y, et al. Sex differences in the humoral antibody response to live measles vaccine in young adults. Int J Epidemiol 1994;23:1078–81. [PubMed: 7860159]
66. Mitchell LA, Zhang T, Tingle AJ. Differential antibody responses to rubella virus infection in males and females. J Infect Dis 1992;166:1258–65. [PubMed: 1431244]
67. Ovsyannikova IG, Jacobson RM, Vierkant RA, et al. The contribution of HLA class I antigens in immune status following two doses of rubella vaccination. Hum Immunol 2004;65:1506–15. [PubMed: 15603879]
68. Ovsyannikova, IG.; Jacobson, RM.; Targonski, PV., et al. Racial and gender disparities in immune responses to smallpox vaccine in healthy adults [abstract]. 47th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy; Chicago, Ill. 2007 Sept 17 – 20;
69. Standards for child and adolescent immunization practices. National Vaccine Advisory Committee. Pediatrics 2003;112(4):958–63. [PubMed: 14523192]
70. Wallinga J, Heijne JC, Kretzschmar M. A measles epidemic threshold in a highly vaccinated population. PLoS Med 2005;2(11):e316. [PubMed: 16218769]
71. Huerta M, Davidovitch N, Aboudy Y, et al. Declining population immunity to mumps among Israeli military recruits. Vaccine 2006;24(3739):6300–3. [PubMed: 16844272]
72. Marin M, Guris D, Chaves SS, et al. Prevention of Varicella. Recommendations of the Advisory Committe on Immunization Practices. MMWR 2007;56(RR04):1–40. [PubMed: 17585291]
73. Siber GR, Santosham M, Reid GR, et al. Impaired antibody response to Haemophilus influenzae type b polysaccharide and low IgG2 and IgG4 concentrations in Apache children. N Engl J Med 1990;323:1387–92. [PubMed: 2233905]
74. Santosham M, Rivin B, Wolff M, et al. Prevention of Haemophilus influenzae type b infections in Apache and Navajo children. J Infect Dis 1992;165(Suppl 1):S144–51. [PubMed: 1588150]
75. Poland GA. Pharmacology, vaccinomics, and the 2nd golden age of vaccinology. Clin Pharmacol Ther 2007;82(6):623–6. [PubMed: 17998905] • **A detailed editorial of the field of vaccinology**.