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## Personalized Vaccinology: A Review

GA Poland<sup>1</sup>, IG Ovsyannikova<sup>1</sup>, and RB Kennedy<sup>1</sup><sup>1</sup>Mayo Clinic Vaccine Research Group, Mayo Clinic, Rochester, MN 55905 USA

### Abstract

At the current time, the field of vaccinology remains empirical in many respects. Vaccine development, vaccine immunogenicity, and vaccine efficacy have, for the most part, historically been driven by an empiric “isolate-inactivate-inject” paradigm. In turn, a population-level public health paradigm of “the same dose for everyone for every disease” model has been the normative thinking in regard to prevention of vaccine-preventable infectious diseases. In addition, up until recently, no vaccines specifically had been designed to overcome the immunosenescence of aging, consistent with a post-WWII mentality of developing vaccines and vaccine programs for children. It is now recognized that the current lack of knowledge concerning how immune responses to vaccines are generated is a critical barrier to understanding poor vaccine responses in the elderly and in immunoimmaturity, discovery of new correlates of vaccine immunogenicity (vaccine response biomarkers), and a directed approach to new vaccine development.

The new fields of vaccinomics and adversomics provide models that permit global profiling of the innate, humoral, and cellular immune responses integrated at a systems biology level. This has advanced the science beyond that of reductionist scientific approaches by revealing novel interactions between and within the immune system and other biological systems (beyond transcriptional level), which are critical to developing “downstream” adaptive humoral and cellular responses to infectious pathogens and vaccines. Others have applied systems level approaches to the study of antibody responses (a.k.a. “systems serology”), [1] high dimensional cell subset immunophenotyping through CyTOF, [2, 3] and vaccine induced metabolic changes [4]. In turn, this knowledge is being utilized to better understand the following: identifying who is at risk for which infections; the level of risk that exists regarding poor immunogenicity and/or serious adverse events; and the type or dose of vaccine needed to fully protect an individual. *In toto*, such approaches allow for a personalized approach to the practice of vaccinology, analogous to the substantial inroads that individualized medicine is playing in other fields of human health and

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Address correspondence to: Gregory A. Poland, M.D., Director, Mayo Vaccine Research Group, Mayo Clinic, Guggenheim 611C, 200 First Street SW, Rochester, Minnesota 55905, Phone: (507) 284-4968; Fax: (507) 266-4716; [poland.gregory@mayo.edu](mailto:poland.gregory@mayo.edu).

#### Competing Interests:

Dr. Poland is the chair of a Safety Evaluation Committee for novel investigational vaccine trials being conducted by Merck Research Laboratories. Dr. Poland offers consultative advice on vaccine development to Merck & Co. Inc., Avianax, Dynavax, Novartis Vaccines and Therapeutics, Emergent Biosolutions, Adjuvance, Seqirus, and Protein Sciences. Drs. Poland and Ovsyannikova hold three patents related to vaccinia and measles peptide research. Dr. Kennedy has received funding from Merck Research Laboratories to study waning immunity to mumps vaccine. These activities have been reviewed by the Mayo Clinic Conflict of Interest Review Board and are conducted in compliance with Mayo Clinic Conflict of Interest policies.

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medicine. Herein we briefly review the field of vaccinomics, adversomics, and personalized vaccinology.

### Keywords

Vaccines; Immunization; Vaccination; Immunogenetics; Immunity; Cellular; Immunity; Humoral; Immunity; Innate; Immunity; Adaptive

## Introduction and Background

Vaccines have been one of the most effective public health strategies in preventing infectious diseases. A decade ago, we described the idea of vaccinomics and adversomics, based on the immune response network theory [5, 6], which utilizes immunogenetics/immunogenomics and systems biology approaches to understand the basis for inter-individual variations in vaccine-induced immune responses in human, as well as the basis for adverse side effects from vaccines [7]. Vaccinomics and adversomics explore the influence of genetic and non-genetic regulation on the heterogeneity of vaccine-induced immune responses at both the personal and population level [5]. In particular, vaccinomics and adversomics utilize high-throughput, high-dimensional systems biology approaches, which aim to predict variations in protective and maladaptive innate and adaptive immune responses to vaccines [6, 8]. In this regard, the basis of personalized (and predictive) vaccinology is the assessment of an individual's genetic background, sex, as well as other factors that may impact vaccine immunogenicity, efficacy, and safety [8–11]. We and others have widely published on the applicability of the tools and concepts of vaccinomics, including immunogenetics and immunogenomics, to the knowledge-based directed development of new and improved vaccine candidates [12–15]. The application of these concepts is likely to allow for explanation, quantification, and prediction of vaccine-induced protective immune responses—including the development of predictive immune signatures in response to vaccines. Indeed, we have previously published what we believe is the first draft of a mathematical model and predictive equation describing the *non-random* events that lead to a *pre-determined* immune response [6]:

$$y = \beta_0 + \sum_{i=1}^P \beta_i X_i + \epsilon$$

$y$  = measure of immune response

$\beta_0$  = intercept

$\beta_i$  = coefficient for the  $i$ th variable  $x_i$  and indicates the amount of change in  $y$  for a 1 unit change in  $x_i$

$E$  = random deviations from the model

We recognize that such an equation, given the current state of the science, is incomplete and cannot yet predict immune responses. But we present it as an early directional attempt to quantify such an equation. Such an approach begins to move us into a 21<sup>st</sup>-century model of directed vaccine development and an advanced understanding of how, and by what

mechanisms, vaccines and vaccine adjuvants trigger both useful and maladaptive innate and adaptive immune responses. We believe that vaccinomics and adversomics represent approaches counter to the standard methods of vaccine development until recently. Historically, vaccine development has been empirical, despite many emerging and re-emerging complex, hyper-variable pathogens—many with elaborate immune escape mechanisms. In addition, vaccine coverage rates continue to suffer as society is risk-averse toward vaccines and demands levels of safety that may not be achievable. Finally, the “one-size-fits-all” approach to the practice of vaccinology ignores the complexity and diversity of the human immune system and host genome. Thus, the promise of vaccinomics and related paradigms is to identify specific immune response profiles, immunosignatures, and biomarkers that predict vaccine safety and/or efficacy, and which may lead to new vaccine candidates.

## Rationale and Examples of Vaccinomics and Adversomics

Vaccinomics provides the opportunity to examine not only immune response genes likely to be involved in vaccine response, but also the possibility of identifying the influence of new (uncharacterized) genes on vaccine-induced immunity. In turn, the identification and directed study of such genetic variants allows recognition, often at the molecular level, of the effects of differential binding, processing, and expression/presentation of antigenic viral peptides used in vaccine development, identification of the differential range of presented peptides (genetic restriction), altered secretion patterns (cytokines) in response to vaccines or vaccine adjuvants, altered transcription of important genes (signaling molecules) and gene products, altered binding of virus/antigens by membrane-based receptors (TLR, other), differential receptor function, expression, and affinities, and the impact of epigenetics on vaccine-induced immune responses. We have utilized this knowledge in our own laboratory to create a research-oriented paradigm of “discover-validate-characterize-apply,” which may be used in new candidate vaccine development (Fig. 1) [6]. In this paradigm, we have been able to utilize vaccinomics approaches to discover genetic variants that are significantly associated with subsequent downstream immune responses, validate that such variants are indeed associated, then seek to characterize the mechanism whereby such effects occur and, finally, apply this knowledge, often in functional studies, that confirm the effect on immunity. Such knowledge can be exploited in developing immune strategies to enhance or circumvent genetic restrictions, for example, in triggering vaccine-associated immune responses, by “reverse engineering” around a given genetic or other obstacle to generating protective immune responses.

There are a growing number of studies reporting unbiased genome-wide assessments of genetic variation and its influence on adaptive (humoral and cellular) vaccine-induced immune responses across multiple viral and bacterial vaccines. For example, candidate and GWAS immunogenetic and pharmacogenetic studies have identified polymorphisms in HLA, KIR, MICA, and BTN genes associated with immune responses to pathogens causing disease in humans, such as hepatitis C [16], *Mycobacterium leprae* [17, 18], human immunodeficiency virus [19], and measles [20–22]. Similar studies have identified novel genes impacting immune responses to vaccines, including hepatitis B, rubella, influenza A, smallpox, anthrax, and mumps [23–33]. Our gene association studies of measles-mumps-

rubella (MMR) vaccines have demonstrated that inter-individual variations in measles vaccine virus-induced humoral and cellular responses are significantly associated with polymorphisms in immune response genes and, together with HLA alleles, explain ~30% of the inter-individual variability in humoral response [5, 34–36]. These findings, which illustrated the importance of key HLA alleles in the adaptive humoral immune response to measles vaccine, led to the identification of naturally processed and presented measles-derived peptides isolated from specific HLA polymorphisms associated with vaccine non- and hyper-response [37, 38]. These peptides containing specific components (adjuvants and biodegradable nanoparticles) are now being utilized in a reverse-engineering strategy to develop peptide-based candidate measles vaccines. Likewise, Homan *et al.* have attributed diminished protection to differential HLA presentation of T and B cell epitopes between vaccine and wild type strains of mumps virus [39]. This diminished efficacy could theoretically be overcome by incorporating defined critical immunogenic peptides into an improved vaccine.

TLR genes represent an important link between the innate and the adaptive immune system [40, 41]. As an example, we have demonstrated that measles vaccine-induced humoral responses are significantly associated with coding polymorphisms in the TLR2 (rs3804100) and TLR4 (rs5030710) genes [42]. For the rubella vaccine and TLR3 gene, a TLR3 gene SNP rs5743305 was associated with rubella-specific GM-CSF production [43]. Our recent mumps vaccine study has identified and replicated TLR4 SNPs associated with a ~45% decrease in antibody titer, and a TLR5 SNP associated with a 64% increase in T cell response (unpublished data). These data strongly suggest that robust TLR activation by measles, mumps, and rubella viruses is crucial for optimal vaccine response. Supporting these findings is a study demonstrating that an inactivated mumps vaccine containing a protollin-based TLR2/4 adjuvant is highly immunogenic in a mouse model; it led to superior total IgG levels, higher neutralizing antibody titers, greater mucosal IgA production, and enhanced Th1/Th2 cytokine secretion [44]. One potential application of this finding is to identify the specific and critical interactions between TLRs (and other genes) and virus, leading to advances in our knowledge of the precise mechanisms driving immunity to MMR vaccine.

## Sex-Based Differences in Immune Responses to Vaccines

Significant sex differences in humoral and cellular immune responses to vaccines are apparent [45, 46]. Additionally, local and systemic adverse rates are generally higher in females versus males. Protective antibody responses are significantly higher in females than males after vaccination against influenza, yellow fever, measles, mumps, rubella, hepatitis A and B, herpes simplex (HSV) 2, rabies, smallpox, and dengue viruses [47–55]. Sex-based differences in humoral immune responses are observed through various age groups [47–50, 52–57], suggesting that sex steroid hormones are not the singular mediators of sex differences in humoral immune responses to vaccines [45, 58]. This suggests that genetic, or other, factors may be an important driver of sex-related differences in humoral immune response [59]. Despite significant evidence of immune response differences between the sexes, for the most part, vaccine studies have not examined and analyzed immune response outcomes by sex [60, 61]. In fact, little information is known about potential mechanisms for

sex-based effects, which should be a priority for vaccine research studies. Discovery of specific factors involved in sex-based differences in immune response may allow the identification of new correlates of vaccine immunogenicity.

In a cohort of 556 older (ages 50–64) and 558 younger (ages 18–49) previously vaccinated individuals, the seasonal trivalent influenza vaccine induced >1.5-fold higher A/H3N2-specific HAI antibody titers in women than men across both age groups [47]. Similarly, a study of standard seasonal influenza vaccine and high-dose influenza vaccine responses in a sex-balanced cohort of 414 elderly subjects (ages 65–95) demonstrated significantly higher rates of seroconversion in females than in males [48]; however, no significant differences in antibody measures were found between males and females after seasonal influenza vaccination in another cohort of 158 older adults (ages 50–74) [62]. A study by Furman *et al.* examining gene expression, serum cytokines/chemokines, cell subsets, and phosphorylation events found several serum markers (LEPT, IL1RA, CRP, GMCSF, and IL5) to be more highly expressed in females than males after influenza vaccine [51]. This same report used a systems biology approach to identify a gene cluster involved in lipid biosynthesis that is regulated by testosterone and significantly correlated with poor humoral responses following influenza vaccination in men [51]. These data suggest that this gene cluster (e.g., genes involved in lipid metabolism) could be an important driver of sex-related differences in humoral immune response. This collective knowledge could substantially assist future personalized vaccine development efforts through the generation of new knowledge and the identification of targets and biomarkers that predict vaccine responses in specific populations (e.g., females vs. males; young vs. old; obese vs. lean). Further research is needed to clarify the effects of sex on immune response. Identification of molecular immune signatures of sex differences in innate and adaptive immune responses to vaccines may provide evidence necessary for additional efforts in designing personalized vaccination and vaccinomics approaches (i.e., in which males and females might be vaccinated differently using different doses or different vaccines) in an effort to provide equal protection while reducing side effects [46, 63, 64].

## Immune Responses to Vaccines in the Elderly

A significant global public health issue is the aging of the population. As individuals age, immunosenescence develops, leading to poorer immune responses to vaccines. Immunosenescence is an age-related dysregulation of the immune system due to age-associated changes in innate and adaptive immune system components, which leads to impaired immunity and protection following immunization or infection [65–67]. Published data reveal that innate and adaptive immunity is decreased with age, but the systems-level mechanisms for these findings are unclear [66, 68], particularly in regard to influenza and other viral vaccine responses where the morbidity, mortality, and associated healthcare costs are greater in older individuals [11]. Major signs of innate immune dysfunction commonly observed in the elderly include, but are not limited to, altered cytokine secretion; decreased NK cell activity; reduced TLR expression; and a chronic inflammatory state (elevated levels of IL-1 $\beta$ , MCP-1, TNF- $\alpha$ , and serum IL-6) known as “inflamm-aging” [8, 69–71]. Age-related humoral immune dysfunction, for example, might be overcome through optimal stimulation of innate and/or Th cell-specific genes, which may be different in males and

females. For example, adjuvanted zoster subunit vaccine (Hz/su) reduced the risks of herpes zoster, and postherpetic neuralgia in immunocompetent persons 70 years of age and older [72]. This Hz/su vaccine contains varicella zoster virus glycoprotein E and a novel AS01<sub>B</sub> adjuvant system aimed to improve and preserve with age zoster-specific CD4<sup>+</sup> T cell responses [73]. A TLR4 agonist GLA-SE (glucopyranosyl lipid adjuvant formulated in a stable emulsion) has been shown to enhance Th1 responses to influenza vaccine in older adults [74], suggesting a potential mechanism for targeting innate receptor agonists (e.g., TLRs) that enhance innate immune responses against influenza. Given the substantially diminished efficacy of influenza and other vaccines with age and the importance of developing improved vaccines [75], data from vaccinomics studies could be used to inform directed and rational development of next-generation influenza vaccines—potentially circumventing immunosenescence-related factors.

Systems biology approach provides a unique opportunity to identify biomarkers likely to be involved in immune responses to vaccination [8, 76, 77]. Fourati et al. applied a systems vaccinology approach to examine gene signatures and molecular pathways of age-related hyporesponse to hepatitis B vaccine (HBV) in naïve older adults [78]. They observed the B cell signaling pathway (and higher memory B cell frequencies) and inflammatory pathway (and increased frequencies of activated pro-inflammatory innate cells) were strongly correlated with higher and low antibody responses to HBV, respectively. This signature, including serum cytokine profiling and flow cytometric correlates of response, predicted the antibody response to HBV with up to 65% accuracy [78]. This study demonstrates that a systems biology approach can be used to predict age-related immune response to vaccination.

## Obesity and Immune Responses to Vaccines

Obesity is another major public global health concern. In the US, 68% of adults and nearly 32% of children and adolescents are now overweight or obese [79]. Weight gains across all countries have been demonstrated to be associated with increasing socioeconomic status. Obesity has been shown to be a predictor of impaired immunogenicity (e.g., decreased antibody response) to hepatitis B, tetanus toxoid, rabies, and influenza vaccines [80–83], and as such can be considered a marker, or state, of immunosuppression at its extremes. These data suggest that obesity is correlated with poorer vaccine-induced immune responses in humans, and further research is required to understand the immune mechanisms that are altered in obesity.

As individuals age, their circulating leptin levels rise with a concomitant reduction in leptin signaling; this results in leptin resistance, which is a finding associated with obesity [84]. Leptin resistance has been shown to adversely affect the immune response in obese subjects, including responses to influenza virus [85, 86]. For example, obese individuals demonstrate decreased activation of influenza-specific CD8<sup>+</sup> T cells compared to healthy-weight persons, including decreased production of IFN- $\gamma$  and granzyme B, suggesting that influenza vaccination may not be as effective in the obese population as in healthy-weight individuals [87]. Given only moderate seroprotection of influenza and other vaccines in obese older adults [83], and the importance of developing improved influenza vaccines [75],

systems biology studies designed to identify the mechanisms for improved immune response are needed. In fact, data from vaccine studies could be used to inform directed and rational development of personalized vaccines that optimally stimulate innate and adaptive immune responses in males and females and overcome immune deficiencies induced by obesity [88]. Careful vaccine studies comparing lean and obese persons could provide foundational data used to improve vaccine-induced protection in the obese, a subpopulation with an elevated risk for serious vaccine-preventable illnesses and suboptimal vaccine-induced protective responses [10].

## Adversomics

Adversomics utilizes tools—much like those used in vaccinomics—to identify, characterize, and predict adverse, or maladaptive, immune responses to vaccines [6, 89, 90]. The promise of adversomics would be to develop or identify either predictors or immune signatures of maladaptive immune responses that lead to harm rather than benefit, and to better understand the generation and mechanisms of such maladaptive immune responses.

We have asked the question, as have other scientists, “does it make sense in the 21<sup>st</sup> century to give the same vaccine, dose, and at the same frequency to everyone, regardless of age, weight, gender, race, genotype, and medical condition?” For example, we give adult males and females the same dose, and the same number of doses of vaccines, ignoring the findings that females nearly always have superior humoral immune responses to males for all vaccines studied, and yet experience significantly more side effects—more adverse events, of greater duration, and of higher intensity [47, 55, 60].

While the field is young in implementation, research has already revealed associations between specific genes or SNPs and adverse immune outcomes. For example, associations between cytokine gene expression and fever after smallpox vaccine have been identified [91]. Other studies have demonstrated correlations between smallpox vaccine-induced fevers and IL-1A and IL-18 SNPs [92]. Other smallpox vaccine-induced adverse events such as fever, rash, and enlarged lymph nodes have been significantly associated with MTHFR, IRF1, and IL-4 SNPs haplotypes [93]. While smallpox vaccine is not used in the general population, such studies stand as examples of the usefulness of vaccinomic approaches. Finally, other recent studies have identified generic fever gene networks (TNF-alpha) after vaccine administration [94], and relationships between MMR vaccine administration and SNPs in IFI44L, CD46, SCN1A, 2A, and TMEM16 (ANO3) genes [95].

## Challenges in Personalized Vaccinology

Despite the tremendous success of vaccines, vaccinologists face several current challenges, including difficulty in developing vaccines for hypervariable viruses (HIV, rhinovirus, hepatitis C virus, coronavirus) and complex pathogens (malaria, Mycobacterium tuberculosis); newly emerging pathogens, such as Zika virus (ZIKV); complications imposed by aging and immunosenescent populations; inadequate understanding of the neonatal and newborn immune systems; increasingly immune deficient or immunocompromised populations due to HIV, cancer, or medications; sex-based differences

in vaccine response and adverse-event rates; enhanced scrutiny of vaccine safety; and as noted global increases in age and weight. In addition, vocal and active anti-vaccine groups whose messages are not easily countered by facts or scientific studies have materially and detrimentally affected vaccine coverage rates [96–98]. Vaccinomic approaches can be utilized to better understand these issues; this information can then be used to inform new approaches, new understandings, and new vaccine candidates.

Just as new technologies have created exciting new opportunities in personalized medicine, they have brought with them novel challenges in addition to those mentioned above. In order for the full potential of personalized vaccines to be achieved, we must overcome additional challenges, such as the need for the following:

- Larger genotype:phenotype datasets (often in the many thousands to ten thousands)
- Integrating increasingly diverse high-throughput, high-dimensional data types
- Biomarkers that can reliably distinguish which product to give which people based on the likelihood of response or of an adverse side effect
- Vaccines with different mechanisms of action may require a move away from humoral correlates of protection for licensure; in this regard, correlates of protection based on cellular immune outcomes are likely to play an important role in future vaccines
- More sophisticated biostatistical and bioinformatics approaches that can identify patterns and causative networks within terabyte levels of extremely high dimensional data types
- From the economic side: methods of technology transfer and funding mechanisms to move novel vaccines developed through vaccinomic approaches into low and middle-income countries who often most need specific vaccines (malaria, others)

We have seen the shift from “vaccinology 1.0,” which is the empirical “Isolate-Inactivate-Inject” paradigm, to “vaccinology 2.0”—the use of recombinant technology and novel adjuvants. However, even this paradigm is limited by our incomplete mechanistic understanding of adjuvants and innate immunity. As we adopt approaches such as those listed above, we envision a movement of the field into an era of “vaccinology 3.0,” during which we expect to see the use of vaccinomics and systems-level approaches to develop new vaccines; innovative vaccine-antigen packaging methods; and adjuvant development targeted at the innate response pathways best suited for a given pathogen.

A common reaction to this paradigm of personalized vaccinology is questioning cost and economics. At one level, such considerations are simply “too soon” in the development of the science to effectively answer. However, like progress being made in individualized medicine, it is likely that being able to provide the right vaccine to the right patient—for the right reasons and at the right dose—will lead to improved medical outcomes and reduced costs at the population level.



## Vaccine Development

Personalized vaccinology is the goal of applying the concept of personalized medicine to vaccines. Rapid strides in omics technologies and foundational work applying systems biology, computational immunology and reverse vaccinology have facilitated modern approaches to vaccine design and development enabling us to create vaccine formulations for new and re-emerging pathogens. Egg-based influenza vaccines take > 6 months to create. The recent licensure of cell culture-based influenza vaccines demonstrate that rapid, scalable processes can now be implemented in order to create vaccine against emerging influenza strains (e.g., H1N1, H5N1, H7N9, H9N2, H7N8) within weeks. [99] that can be safely administered to individuals with egg allergies is one example [100]. The Ebola outbreak in Liberia, Sierra Leone, and Guinea in 2015 provides another example [101]. DNA vaccines, virus-like particle vaccines, and replicating/non-replicating viral vector vaccines have all been created and tested. Among the most promising are a replication-competent, recombinant vesicular stomatitis virus vector expressing the glycoprotein of Ebola Zaire (rVSV-ZEBOV), [102] a variety of adenovirus-vectored vaccines expressing Ebola glycoprotein, [103, 104] a modified vaccinia virus Ankara-based vaccine encoding the Ebola Zaire glycoprotein (MVA-BN-Filo), [105, 106] and DNA-based vaccines—one expressing glycoproteins from both Zaire and Sudan, and the other expressing the Marburg glycoprotein [107]. Although the rVSV-based vaccine elicits high titers of neutralizing Ab, it is contraindicated in children and those with compromised immune systems. Viral vector vaccines present the problem of developing robust immunity to the vector as well as the target immunogen, limiting their usefulness to a single vaccination. The availability of vaccines in multiple vector backbones opens up the possibilities for prime-boost vaccination strategies for Ebola, similar to those that have been applied to HIV, malaria, and tuberculosis [108–111]. In this regard, a prime-boost regimen using the MVA-based vaccine as the booster vaccination has shown considerable promise [101].

Another example of modern vaccine development being applied to a new pathogen can be seen with the response to Zika virus. A purified, formalin-inactivated vaccine (ZIKV PIV) has been developed by the Walter Reed Army Institute of Research (WRAIR) [112] and is being evaluated in several clinical trials (NCT02963909, NCT02952833, NCT02937233), while other inactivated vaccines are in preclinical development [113]. Two variants of a plasmid DNA vaccine containing the prM-ENV proteins have been developed by NIAID and one of the formulations is currently in a phase I clinical trial (NCT02840487) [114]. Inovio Pharmaceuticals developed their own plasmid DNA vaccine (also expressing prM-ENV), which is currently in two clinical trials (NCT02809443, NCT02887482). RNA-based vaccines [115] and a variety of subunit and viral vector-based vaccines are also in development [113, 116, 117]. DNA and RNA-based vaccines can be rapidly made at minimal costs compared to other formulations and are fairly stable, without the cold-chain requirements of live virus-based vaccines.

Subunit vaccines are typically safer than whole virus-based products, which represents an active area of investigation not only for pathogens with no existing vaccines, but also for improving on established vaccines. Our group and others have identified pathogen-derived epitopes as preliminary steps in the development of safe, stable, and effective peptide- and

protein-based vaccines for smallpox, influenza, measles, tuberculosis, staphylococcus, and myriad other viral and bacterial pathogens [38, 118–122].

Parallel efforts by different groups to create new vaccines result in a spectrum of potential products that can be uniquely tailored to specific population groups. Live viral vaccines rapidly inducing robust immunity can be used in healthy individuals where time is of the essence (e.g., in outbreak scenarios), while inactivated or subunit vaccines can be used in vulnerable populations such as pregnant women or those with immunocompromising conditions, or in young children where the presence of maternal Ab interferes with whole virus vaccines. Vaccines based on different viral vector backbones can be combined into effective prime-boost regimens. Vaccines with specific adjuvants may be most appropriate for the elderly in order to overcome immunosenescence, or in the very young in order to compensate for immune system immaturity.

## Conclusion

We, along with increasing numbers of other scientists, believe that personalized vaccinology will revolutionize the practice of vaccinology to the benefit of human health. As part of the development of this field of science, vaccinomics and adversomics will allow us to develop molecular immune signatures of adaptive and maladaptive immune responses to vaccines, develop early biomarkers of vaccine response in vaccine trials, identify who should get what vaccine and at what dose, and increase safety and public confidence in vaccines by reducing the likelihood of serious adverse events related to vaccines. In many ways, however, personalized vaccinology is most challenged by the difficulty in moving the field away from the post-WWII population-level paradigm of “one dose of every vaccine for everyone,” toward an individualized or personalized approach based on the unique factors relevant to a given individual. In his book, *The Structure of Scientific Revolutions* [123], Thomas Kuhn recognized that “we wrongly believe scientific progress is a process of *linear accretion of knowledge*, that science is predicated on the belief that the scientific community understands what the world is like, and that we suppress or resist ‘*fundamental novelties*’ because they are seen as subversive to our firmly held beliefs of what the world is like.” Later in his book, he suggests that “new advances always have and always will reveal that science and medicine includes bodies of belief incompatible with beliefs we hold today, and that advancements come when we reject a *time-honored* scientific theory in favor of another incompatible with it.” These cognitive biases have, in our opinion, been manifest in our discussions with scientific colleagues as we developed this field of science. Schopenhauer, the German philosopher, suggested that new discoveries are at first ridiculed, then opposed, and finally accepted as self-evident. Vaccinomics and adversomics appear to be moving from the ridiculed and opposed steps, and into the not-yet quite self-evident phase of the continuum.

Part of the challenge is that often the concept of personalized vaccinology suggests to the reader that a unique vaccine will be developed for each individual. While that is one tactic being used in the cancer-vaccine field, it is neither necessary nor practical for the prevention of infectious diseases. Rather, the personalized vaccinology approach would suggest the development of specific vaccines based on factors that relate to overcoming the potential for

poor immunogenicity and the potential for adverse events. An excellent example is influenza vaccines. A mere decade or so ago, only a trivalent injectable influenza vaccine was available. Quadrivalent vaccines were unavailable. For with one exception, everyone received the same vaccine and dose, regardless of age, weight, immunosuppression state, etc. At the current time in the US, multiple influenza vaccines are available so that the right vaccine, for the right patient, can be given at the right time. For example, LAIV can be used in younger subjects, or the needle-phobic. High-dose or MF-59 adjuvanted vaccines can be chosen for the elderly. Recombinant vaccines can be chosen for those with egg allergy, and so on. This is the approach that should be taken with all vaccines. In some cases it may mean merely adjusting the dose based on weight, gender, or age. In other cases it may mean utilizing an adjuvanted or non-adjuvanted vaccine based on immune status. Other examples include the recently licensed MF59 adjuvanted influenza vaccine (Fluad®), which has demonstrably higher immunogenicity and efficacy than its non-adjuvanted counterparts, [124–126] or the highly effective AS01-adjuvanted zoster glycoprotein E vaccine, which does not contain live virus and may be more broadly suitable for administration to older individuals [72, 73].

Thus, the movement toward a new paradigm of vaccine practice, based on a personalized approach, is occurring in the 21<sup>st</sup> century based on new scientific knowledge, market demand, safety considerations, immunogenicity concerns, public health trends (age, obesity, other), and the simultaneous pull of individualized medicine in other medical arenas. The net result is likely to be higher vaccine coverage rates, increased public confidence in vaccines, improved immunogenicity and adverse event rates, and a reduction or elimination in the morbidity and mortality related to vaccine-preventable diseases. As a result, we anticipate a new era of personalized “*Predictive Vaccinology*,” whereby we abandon a “one size and dose fits all vaccine approach” in order to design and develop new vaccines, and acquire the ability to make the following predictions for each individual: whether to give a vaccine based on likelihood of response (and perhaps need); the likelihood of a significant adverse event to a vaccine; and the number of doses likely to be needed to induce a protective response to a vaccine [63].

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## References

1. Chung AW, Kumar MP, Arnold KB, Yu WH, Schoen MK, Dunphy LJ, et al. Dissecting Polyclonal Vaccine-Induced Humoral Immunity against HIV Using Systems Serology. *Cell*. 2015 Nov 05; 163(4):988–98. [PubMed: 26544943]
2. Newell EW, Sigal N, Bendall SC, Nolan GP, Davis MM. Cytometry by time-of-flight shows combinatorial cytokine expression and virus-specific cell niches within a continuum of CD8+ T cell phenotypes. *Immunity*. 2012; 36(1):142–52. [PubMed: 22265676]

3. Porpiglia E, Samusik N, Van Ho AT, Cosgrove BD, Mai T, Davis KL, et al. High-resolution myogenic lineage mapping by single-cell mass cytometry. *Nat Cell Biol.* 2017 May; 19(5):558–67. [PubMed: 28414312]
4. Li S, Sullivan NL, Roupheal N, Yu T, Banton S, Maddur MS, et al. Metabolic Phenotypes of Response to Vaccination in Humans. *Cell.* 2017 May 18; 169(5):862–77. e17. [PubMed: 28502771]
5. 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.
6. Poland GA, Kennedy RB, McKinney BA, Ovsyannikova IG, Lambert ND, Jacobson RM, et al. Vaccinomics, adversomics, and the immune response network theory: Individualized vaccinology in the 21st century. *Seminars in Immunology.* 2013 Jun 4; 25(2):89–103. [PubMed: 23755893]
7. Poland GA. Pharmacology, vaccinomics, and the second golden age of vaccinology. *Clin Pharmacol Ther.* 2007; 82(6):623–6.
8. Poland GA, Ovsyannikova IG, Kennedy RB, Lambert ND, Kirkland JL. A systems biology approach to the effect of aging, immunosenescence and vaccine response. *Current Opinion in Immunology.* 2014 May 9.29C:62–8.
9. Castiblanco J, Anaya JM. Genetics and vaccines in the era of personalized medicine. *Curr Genomics.* 2015 Feb; 16(1):47–59. [PubMed: 25937813]
10. Painter SD, Ovsyannikova IG, Poland GA. The weight of obesity on the human immune response to vaccination. *Vaccine.* 2015 Aug 26; 33(36):4422–9. [PubMed: 26163925]
11. Goronzy JJ, Weyand CM. Understanding immunosenescence to improve responses to vaccines. *Nature immunology.* 2013 May; 14(5):428–36. [PubMed: 23598398]
12. Poland GA, Ovsyannikova IG, Jacobson RM. Vaccine immunogenetics: bedside to bench to population. *Vaccine.* 2008; 26:6183–8. [PubMed: 18598732]
13. Pulendran B. Learning immunology from the yellow fever vaccine: innate immunity to systems vaccinology. *Nat Rev Immunol.* 2009; 9(10):741–7. [PubMed: 19763148]
14. Rappuoli R, Black S, Lambert PH. Vaccine discovery and translation of new vaccine technology. *Lancet.* 2011; 378(9788):360–8. [PubMed: 21664687]
15. Nakaya HI, Li S, Pulendran B. Systems vaccinology: learning to compute the behavior of vaccine induced immunity. *Wiley Interdiscip Rev Syst Biol Med.* 2012; 4(2):193–205. [PubMed: 22012654]
16. Fitzmaurice K, Hurst J, Dring M, Rauch A, McLaren PJ, Gunthard HF, et al. Additive effects of HLA alleles and innate immune genes determine viral outcome in HCV infection. *Gut.* 2014 Jul 4; 64(5):813–9. [PubMed: 24996883]
17. Jarduli LR, Sell AM, Reis PG, Sippert EA, Ayo CM, Mazini PS, et al. Role of HLA, KIR, MICA, and cytokines genes in leprosy. *Biomed Res Int.* 2013; 2013:989837. [PubMed: 23936864]
18. Ali S, Chopra R, Aggarwal S, Srivastava AK, Kalaiarasan P, Malhotra D, et al. Association of variants in BAT1-LTA-TNF-BTNL2 genes within 6p21.3 region show graded risk to leprosy in unrelated cohorts of Indian population. *Human Genetics.* 2012 May; 131(5):703–16. [PubMed: 22071774]
19. Martin MP, Carrington M. Immunogenetics of HIV disease. *Immunological Reviews.* 2013 Jul; 254(1):245–64. [PubMed: 23772624]
20. Ovsyannikova IG, Haralambieva IH, Vierkant RA, O’Byrne MM, Jacobson RM, Poland GA. The association of CD46, SLAM, and CD209 cellular receptor gene SNPs with variations in measles vaccine-induced immune responses--a replication study and examination of novel polymorphisms. *Human Heredity.* 2011; 72(3):206–23. [PubMed: 22086389]
21. Ovsyannikova IG, Haralambieva IH, Vierkant RA, O’Byrne MM, Poland GA. Associations between polymorphisms in the antiviral TRIM genes and measles vaccine immunity. *Human Immunology.* 2013 Jun; 74(6):768–74. [PubMed: 23416095]
22. Ovsyannikova IG, Haralambieva IH, Vierkant RA, O’Byrne MM, Jacobson RM, Poland GA. Effects of vitamin A and D receptor gene polymorphisms/haplotypes on immune responses to measles vaccine. *Pharmacogenetics and Genomics.* 2012; 22(1):20–31. [PubMed: 22082653]

23. Wu TW, Chen CF, Lai SK, Lin HH, Chu CC, Wang LY. SNP rs7770370 in HLA-DPB1 loci as a major genetic determinant of response to booster hepatitis B vaccination: results of a genome-wide association study. *J Gastroenterol Hepatol*. 2015 May; 30(5):891–9. [PubMed: 25389088]
24. Davila S, Froeling FE, Tan A, Bonnard C, Boland GJ, Snippe H, et al. New genetic associations detected in a host response study to hepatitis B vaccine. *Genes and Immunity*. 2010 Apr; 11(3): 232–8. [PubMed: 20237496]
25. Pan L, Zhang L, Zhang W, Wu X, Li Y, Yan B, et al. A genome-wide association study identifies polymorphisms in the HLA-DR region associated with non-response to hepatitis B vaccination in Chinese Han populations. *Human Molecular Genetics*. 2014 Nov 28; 23(8):2210–9. [PubMed: 24282030]
26. Lambert ND, Haralambieva IH, Kennedy RB, Ovsyannikova IG, Pankratz VS, Poland GA. Polymorphisms in HLA-DPB1 are associated with differences in rubella-specific humoral immunity after vaccination. *Journal of Infectious Diseases*. 2015; 211(6):898–905. [PubMed: 25293367]
27. Cummins NW, Weaver EA, May SM, Croatt AJ, Foreman O, Kennedy RB, et al. Heme oxygenase-1 regulates the immune response to influenza virus infection and vaccination in aged mice. *FASEB Journal*. 2012; 26(7):2911–8. [PubMed: 22490782]
28. Ovsyannikova IG, Kennedy RB, O’Byrne M, Jacobson RM, Pankratz VS, Poland GA. Genome-wide association study of antibody response to smallpox vaccine. *Vaccine*. 2012; 30(28):4182–9. [PubMed: 22542470]
29. Kennedy RB, Ovsyannikova IG, Pankratz VS, Haralambieva IH, Vierkant RA, Jacobson RM, et al. Genome-wide genetic associations with IFN $\gamma$  response to smallpox vaccine. *Human Genetics*. 2012; 131(9):1433–51. [PubMed: 22661280]
30. Poland GA, Ovsyannikova IG, Jacobson RM. Immunogenetics of seasonal influenza vaccine response. *Vaccine*. 2008; 26S:D35–D40.
31. Ovsyannikova IG, Pankratz VS, Vierkant RA, Pajewski NM, Quinn CP, Kaslow RA, et al. Human leukocyte antigens and cellular immune responses to anthrax vaccine adsorbed. *Infection and Immunity*. 2013 Jul; 81(7):2584–91. [PubMed: 23649091]
32. Ovsyannikova IG, Jacobson RM, Dhiman N, Vierkant RA, Pankratz VS, Poland GA. Human leukocyte antigen and cytokine receptor gene polymorphisms associated with heterogeneous immune responses to mumps viral vaccine. *Pediatrics*. 2008; 121(5):e1091–e9. [PubMed: 18450852]
33. Kennedy RB, Ovsyannikova IG, Haralambieva IH, Lambert ND, Pankratz VS, Poland GA. Genetic polymorphisms associated with rubella virus-specific cellular immunity following MMR vaccination. *Human Genetics*. 2014 Aug 7; 133(11):1407–17. [PubMed: 25098560]
34. Poland, GA., Ovsyannikova, IG., Jacobson, RM. The Jordan Report. U.S. Department of Health and Human Services; 2012. Vaccinomics and Personalized Vaccinology.
35. Ovsyannikova IG, Pankratz VS, Vierkant RA, Jacobson RM, Poland GA. Consistency of HLA associations between two independent measles vaccine cohorts: a replication study. *Vaccine*. 2012; 30(12):2146–52. [PubMed: 22285888]
36. Haralambieva IH, Kennedy RB, Ovsyannikova IG, Whitaker JA, Poland GA. Variability in Humoral Immunity to Measles Vaccine: New Developments. *Trends Mol Med*. 2015 Dec; 21(12): 789–801. [PubMed: 26602762]
37. Ovsyannikova IG, Johnson KL, Muddiman DC, Vierkant RA, Poland GA. Identification and characterization of novel, naturally processed measles virus class II HLA-DRB1 peptides. *Journal of Virology*. 2004; 78(1):42–51. [PubMed: 14671086]
38. 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. *Journal of Proteome Research*. 2005; 4:2243–9. [PubMed: 16335972]
39. Homan EJ, Bremel RD. Are cases of mumps in vaccinated patients attributable to mismatches in both vaccine T-cell and B-cell epitopes?: An immunoinformatic analysis. *Hum Vaccin Immunother*. 2014; 10(2):290–300. [PubMed: 24275080]
40. Akira S, Takeda K, Kaisho T. Toll-like receptors: critical proteins linking innate and acquired immunity. *NatImmunol*. 2001; 2(8):675–80.

41. Schnare M, Barton GM, Holt AC, Takeda K, Akira S, Medzhitov R. Toll-like receptors control activation of adaptive immune responses. *Nat Immunol.* 2001; 2(10):947–50. [PubMed: 11547333]
42. Ovsyannikova IG, Haralambieva IH, Vierkant RA, Pankratz VS, Poland GA. The role of polymorphisms in toll-like receptors and their associated intracellular signaling genes in measles vaccine immunity. *Human Genetics.* 2011; 130(4):547–61. [PubMed: 21424379]
43. Ovsyannikova IG, Dhiman N, Haralambieva IH, Vierkant RA, O’Byrne MM, Jacobson RM, et al. Rubella vaccine-induced cellular immunity: evidence of associations with polymorphisms in the Toll-like, vitamin A and D receptors, and innate immune response genes. *Human Genetics.* 2010; 127:207–21. [PubMed: 19902255]
44. Young KR, Nzula S, Burt DS, Ward BJ. Immunologic characterization of a novel inactivated nasal mumps virus vaccine adjuvanted with Protollin. *Vaccine.* 2014 Jan 3; 32(2):238–45. [PubMed: 24252699]
45. Klein SL, Jedlicka A, Pekosz A. The Xs and Y of immune responses to viral vaccines. *Lancet Infect Dis.* 2010; 10(5):338–49. [PubMed: 20417416]
46. Klein SL, Poland GA. Personalized vaccinology: one size and dose might not fit both sexes. *Vaccine.* 2013 May 28; 31(23):2599–600. [PubMed: 23579257]
47. Engler RJ, Nelson MR, Klote MM, VanRaden MJ, Huang CY, Cox NJ, et al. Half- vs full-dose trivalent inactivated influenza vaccine (2004–2005): age, dose, and sex effects on immune responses. *Arch Intern Med.* 2008; 168(22):2405–14. [PubMed: 19064822]
48. Couch RB, Winokur P, Brady R, Belshe R, Chen WH, Cate TR, et al. Safety and immunogenicity of a high dosage trivalent influenza vaccine among elderly subjects. *Vaccine.* 2007; 25(44):7656–63. [PubMed: 17913310]
49. Stanberry LR, Spruance SL, Cunningham AL, Bernstein DI, Mindel A, Sacks S, et al. Glycoprotein-D-adjuvant vaccine to prevent genital herpes. *New England Journal of Medicine.* 2002; 347:1652–61. [PubMed: 12444179]
50. Kennedy RB, Ovsyannikova IG, Pankratz VS, Vierkant RA, Jacobson RM, Ryan MA, et al. Gender effects on humoral immune responses to smallpox vaccine. *Vaccine.* 2009; 27(25–26): 3319–23. [PubMed: 19200827]
51. Furman D, Hejblum BP, Simon N, Jovic V, Dekker CL, Thiebaut R, et al. Systems analysis of sex differences reveals an immunosuppressive role for testosterone in the response to influenza vaccination. *Proceedings of the National Academy of Sciences of the United States of America.* 2014 Jan 14; 111(2):869–74. [PubMed: 24367114]
52. Veit O, Niedrig M, Chapuis-Taillard C, Cavassini M, Mossdorf E, Schmid P, et al. Immunogenicity and safety of yellow fever vaccination for 102 HIV-infected patients. *Clinical Infectious Diseases.* 2009 Mar 1; 48(5):659–66. [PubMed: 19191654]
53. Kanesa-Thanan N, Sun W, Ludwig GV, Rossi C, Putnak JR, Mangiafico JA, et al. Atypical antibody responses in dengue vaccine recipients. *Am J Trop Med Hyg.* 2003 Dec; 69(6 Suppl):32–8. [PubMed: 14740953]
54. Lorenzo ME, Hodgson A, Robinson DP, Kaplan JB, Pekosz A, Klein SL. Antibody responses and cross protection against lethal influenza A viruses differ between the sexes in C57BL/6 mice. *Vaccine.* 2011 Nov 15; 29(49):9246–55. [PubMed: 21983155]
55. Klein SL, Hodgson A, Robinson DP. Mechanisms of sex disparities in influenza pathogenesis. *Journal of Leukocyte Biology.* 2012 Jul; 92(1):67–73. [PubMed: 22131346]
56. Cook IF, Barr I, Hartel G, Pond D, Hampson AW. Reactogenicity and immunogenicity of an inactivated influenza vaccine administered by intramuscular or subcutaneous injection in elderly adults. *Vaccine.* 2006; 24(13):2395–402. [PubMed: 16406171]
57. Fang JWS, Lai CL, Chung HT, Wu PC, Lau JYN. Female children respond to recombinant hepatitis B vaccine with a higher titre than male. *Journal of Tropical Pediatrics.* 1994; 40:104–7. [PubMed: 8015023]
58. Klein SL, Pekosz A. Sex-based biology and the rational design of influenza vaccination strategies. *The Journal of Infectious Diseases.* 2014 Jul 15; 209(Suppl 3):S114–9. [PubMed: 24966191]
59. Klein SL, Marriott I, Fish EN. Sex-based differences in immune function and responses to vaccination. *Trans R Soc Trop Med Hyg.* 2015 Jan; 109(1):9–15. [PubMed: 25573105]

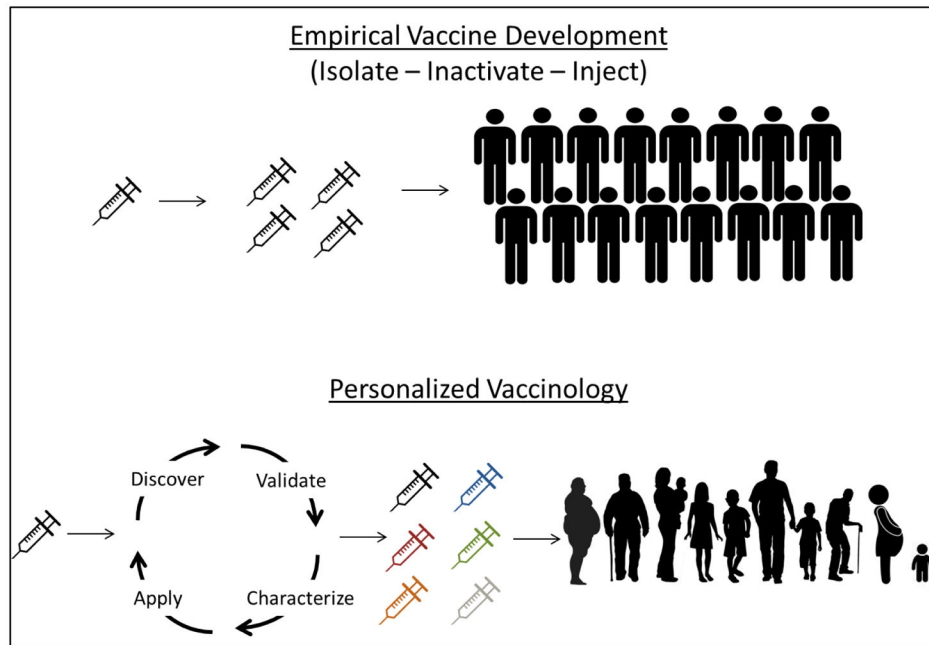
60. Beery AK, Zucker I. Sex bias in neuroscience and biomedical research. *Neurosci Biobehav Rev*. 2011 Jan; 35(3):565–72. [PubMed: 20620164]
61. Klein SL. Immune cells have sex and so should journal articles. *Endocrinology*. 2012 Jun; 153(6):2544–50. [PubMed: 22434079]
62. Ovsyannikova IG, Salk HM, Kennedy RB, Haralambieva IH, Zimmermann MT, Grill DE, et al. Gene signatures associated with adaptive humoral immunity following seasonal influenza A/H1N1 vaccination. *Genes and Immunity*. 2016 Aug 18; 17(7):371–9. [PubMed: 27534615]
63. Poland GA, Kennedy RB, Ovsyannikova IG. Vaccinomics and personalized vaccinology: Is science leading us toward a new path of directed vaccine development and discovery? *PLoS Pathogens*. 2011; 7(12):e1002344. [PubMed: 22241978]
64. Poland GA, Ovsyannikova IG, Jacobson RM. Personalized vaccines: the emerging field of vaccinomics. *Expert Opin Biol Ther*. 2008; 8(11):1659–67. [PubMed: 18847302]
65. Weng NP. Aging of the immune system: how much can the adaptive immune system adapt? *Immunity*. 2006; 24(5):495–9. [PubMed: 16713964]
66. Gomez CR, Boehmer ED, Kovacs EJ. The aging innate immune system. *Current Opinion in Immunology*. 2005; 17(5):457–62. [PubMed: 16084711]
67. Lambert ND, Ovsyannikova IG, Pankratz VS, Jacobson RM, Poland GA. Understanding the immune response to seasonal influenza vaccination in older adults: a systems biology approach. *Expert Rev Vaccines*. 2012; 11(8):985–94. [PubMed: 23002979]
68. Allman D, Miller JP. The aging of early B-cell precursors. *Immunological Reviews*. 2005; 205:18–29. [PubMed: 15882342]
69. Franceschi C, Bonafe M, Valensin S, Olivieri F, De LM, Ottaviani E, et al. Inflamm-aging. An evolutionary perspective on immunosenescence. *Ann NY Acad Sci*. 2000; 908:244–54. [PubMed: 10911963]
70. Zhang Y, Wallace DL, de Lara CM, Ghattas H, Asquith B, Worth A, et al. In vivo kinetics of human natural killer cells: the effects of ageing and acute and chronic viral infection. *Immunology*. 2007; 121(2):258–65. [PubMed: 17346281]
71. Qian F, Wang X, Zhang L, Chen S, Piecychna M, Allore H, et al. Age-associated elevation in TLR5 leads to increased inflammatory responses in the elderly. *Aging Cell*. 2012; 11(1):104–10. [PubMed: 22023165]
72. Cunningham AL, Lal H, Kovac M, Chlibek R, Hwang SJ, Diez-Domingo J, et al. Efficacy of the Herpes Zoster Subunit Vaccine in Adults 70 Years of Age or Older. *The New England Journal of Medicine*. 2016 Sep 15; 375(11):1019–32. [PubMed: 27626517]
73. Lal H, Cunningham AL, Godeaux O, Chlibek R, Diez-Domingo J, Hwang SJ, et al. Efficacy of an adjuvanted herpes zoster subunit vaccine in older adults. *The New England Journal of Medicine*. 2015 May 28; 372(22):2087–96. [PubMed: 25916341]
74. Behzad H, Huckriede AL, Haynes L, Gentleman B, Coyle K, Wilschut JC, et al. GLA-SE, a synthetic toll-like receptor 4 agonist, enhances T-cell responses to influenza vaccine in older adults. *The Journal of Infectious Diseases*. 2012 Feb 1; 205(3):466–73. [PubMed: 22147791]
75. Gallaher WR. Towards a sane and rational approach to management of Influenza H1N1 2009. *Virology*. 2009; 6(1):51. [PubMed: 19422701]
76. Querec TD, Akondy RS, Lee EK, Cao W, Nakaya HI, Teuwen D, et al. Systems biology approach predicts immunogenicity of the yellow fever vaccine in humans. *Nat Immunol*. 2009; 10(1):116–25. [PubMed: 19029902]
77. Nakaya HI, Wrarmert J, Lee EK, Racioppi L, Marie-Kunze S, Haining WN, et al. Systems biology of seasonal influenza vaccination in humans. *Nat Immunol*. 2011; 12(8):786–95. [PubMed: 21743478]
78. Fourati S, Cristescu R, Loboda A, Talla A, Filali A, Railkar R, et al. Pre-vaccination inflammation and B-cell signalling predict age-related hyporesponse to hepatitis B vaccination. *Nat Commun*. 2016 Jan 08; 7:10369. [PubMed: 26742691]
79. Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of childhood and adult obesity in the United States, 2011–2012. *JAMA*. 2014 Feb 26; 311(8):806–14. [PubMed: 24570244]

80. Weber DJ, Rutala WA, Samsa GP, Santimaw JE, Lemon SM. Obesity as a predictor of poor antibody response to hepatitis B plasma vaccine. *JAMA*. 1985 Dec 13; 254(22):3187–9. [PubMed: 2933532]
81. Eliakim A, Schwindt C, Zaldivar F, Casali P, Cooper DM. Reduced tetanus antibody titers in overweight children. *Autoimmunity*. 2006; 39(2):137–41. [PubMed: 16698670]
82. Banga N, Guss P, Banga A, Rosenman KD. Incidence and variables associated with inadequate antibody titers after pre-exposure rabies vaccination among veterinary medical students. *Vaccine*. 2014 Feb 12; 32(8):979–83. [PubMed: 24394442]
83. Talbot HK, Coleman LA, Crimin K, Zhu Y, Rock MT, Meece J, et al. Association between obesity and vulnerability and serologic response to influenza vaccination in older adults. *Vaccine*. 2012 Jun 6; 30(26):3937–43. [PubMed: 22484350]
84. Zhang Y, Scarpance PJ. The role of leptin in leptin resistance and obesity. *Physiol Behav*. 2006; 88(3):249–56. [PubMed: 16782141]
85. Karlsson EA, Sheridan PA, Beck MA. Diet-induced obesity impairs the T cell memory response to influenza virus infection. *J Immunol*. 2010; 184(6):3127–33. [PubMed: 20173021]
86. Ovsyannikova IG, White SJ, Larrabee BR, Grill DE, Jacobson RM, Poland GA. Leptin and leptin-related gene polymorphisms, obesity, and influenza A/H1N1 vaccine-induced immune responses in older individuals. *Vaccine*. 2014 Feb 7; 32(7):881–7. [PubMed: 24360890]
87. Sheridan PA, Paich HA, Handy J, Karlsson EA, Hudgens MG, Sammon AB, et al. Obesity is associated with impaired immune response to influenza vaccination in humans. *International Journal of Obesity*. 2012 Aug; 36(8):1072–7. [PubMed: 22024641]
88. White SJ, Taylor MJ, Hurt RT, Jensen MD, Poland GA. Leptin-based adjuvants: an innovative approach to improve vaccine response. *Vaccine*. 2013 Mar 25; 31(13):1666–72. [PubMed: 23370154]
89. Poland GA, Ovsyannikova IG, Jacobson RM. Adversomics: the emerging field of vaccine adverse event immunogenetics. *Pediatr Infect Dis J*. 2009; 28(5):431–2. [PubMed: 19395950]
90. Whitaker JA, Ovsyannikova IG, Poland GA. Adversomics: a new paradigm for vaccine safety and design. *Expert Review of Vaccines*. 2015 May; 2:1–13.
91. McKinney BA, Reif DM, Rock MT, Edwards KM, Kingsmore SF, Moore JH, et al. Cytokine expression patterns associated with systemic adverse events following smallpox immunization. *J Infect Dis*. 2006; 194(4):444–53. [PubMed: 16845627]
92. Stanley SL Jr, Frey SE, Taillon-Miller P, Guo J, Miller RD, Koboldt DC, et al. The immunogenetics of smallpox vaccination. *J Infect Dis*. 2007; 196(2):212–9. [PubMed: 17570108]
93. Reif DM, McKinney BA, Motsinger AA, Chanock SJ, Edwards KM, Rock MT, et al. Genetic basis for adverse events after smallpox vaccination. *Journal of Infectious Diseases*. 2008; 198(1):16–22. [PubMed: 18454680]
94. Hur J, Ozgur A, Xiang Z, He Y. Identification of fever and vaccine-associated gene interaction networks using ontology-based literature mining. *J Biomed Semantics*. 2012 Dec 20; 3(1):18. [PubMed: 23256563]
95. Feenstra B, Pasternak B, Geller F, Carstensen L, Wang T, Huang F, et al. Common variants associated with general and MMR vaccine-related febrile seizures. *Nature Genetics*. 2014 Dec; 46(12):1274–82. [PubMed: 25344690]
96. Poland GA, Jacobson RM. The clinician's guide to the anti-vaccinationists' galaxy. *Human Immunology*. 2012; 73(8):859–66. [PubMed: 22504410]
97. Poland GA, Jacobson RM, Ovsyannikova IG. Trends affecting the future of vaccine development and delivery: The role of demographics, regulatory science, the anti-vaccine and consumer culture and vaccinomics. *Vaccine*. 2009; 27(25–26 Special Issue SI):3240–4. [PubMed: 19200833]
98. Poland GA, Jacobson RM. Understanding those who do not understand: a brief review of the anti-vaccine movement. *Vaccine*. 2001; 19:2440–5. [PubMed: 11257375]
99. Milian E, Julien T, Biaggio R, Venereo-Sanchez A, Montes J, Manceur AP, et al. Accelerated mass production of influenza virus seed stocks in HEK-293 suspension cell cultures by reverse genetics. *Vaccine*. 2017 Jun 08; 35(26):3423–30. [PubMed: 28495315]
100. Hegde NR. Cell culture-based influenza vaccines: A necessary and indispensable investment for the future. *Hum Vaccin Immunother*. 2015; 11(5):1223–34. [PubMed: 25875691]



101. Pavot V. Ebola virus vaccines: Where do we stand? *Clinical immunology*. 2016 Dec.173:44–9. [PubMed: 27910805]
102. Regules JA, Beigel JH, Paolino KM, Voell J, Castellano AR, Hu Z, et al. A Recombinant Vesicular Stomatitis Virus Ebola Vaccine. *The New England Journal of Medicine*. 2017 Jan 26; 376(4):330–41. [PubMed: 25830322]
103. De Santis O, Audran R, Pothin E, Warpelin-Decrausaz L, Vallotton L, Wuerzner G, et al. Safety and immunogenicity of a chimpanzee adenovirus-vectored Ebola vaccine in healthy adults: a randomised, double-blind, placebo-controlled, dose-finding, phase 1/2a study. *The Lancet Infectious Diseases*. 2016 Mar; 16(3):311–20. [PubMed: 26725450]
104. Zhu FC, Hou LH, Li JX, Wu SP, Liu P, Zhang GR, et al. Safety and immunogenicity of a novel recombinant adenovirus type-5 vector-based Ebola vaccine in healthy adults in China: preliminary report of a randomised, double-blind, placebo-controlled, phase 1 trial. *Lancet*. 2015 Jun 6; 385(9984):2272–9. [PubMed: 25817373]
105. Milligan ID, Gibani MM, Sewell R, Clutterbuck EA, Campbell D, Plested E, et al. Safety and Immunogenicity of Novel Adenovirus Type 26- and Modified Vaccinia Ankara-Vectored Ebola Vaccines: A Randomized Clinical Trial. *JAMA*. 2016 Apr 19; 315(15):1610–23. [PubMed: 27092831]
106. Zhou Y, Sullivan NJ. Immunology and evolution of the adenovirus prime, MVA boost Ebola virus vaccine. *Current Opinion in Immunology*. 2015 Aug.35:131–6. [PubMed: 26247875]
107. Kibuuka H, Berkowitz NM, Millard M, Enama ME, Tindikahwa A, Sekiziyivu AB, et al. Safety and immunogenicity of Ebola virus and Marburg virus glycoprotein DNA vaccines assessed separately and concomitantly in healthy Ugandan adults: a phase 1b, randomised, double-blind, placebo-controlled clinical trial. *Lancet*. 2015 Apr 18; 385(9977):1545–54. [PubMed: 25540891]
108. Excler JL, Plotkin S. The prime-boost concept applied to HIV preventive vaccines. *AIDS*. 1997; 11(Suppl A):S127–37. [PubMed: 9451976]
109. Amara RR, Villinger F, Altman JD, Lydy SL, O'Neil SP, Staprans SI, et al. Control of a mucosal challenge and prevention of AIDS by a multiprotein DNA/MVA vaccine. *Science*. 2001 Apr 06; 292(5514):69–74. [PubMed: 11393868]
110. Schneider J, Gilbert SC, Blanchard TJ, Hanke T, Robson KJ, Hannan CM, et al. Enhanced immunogenicity for CD8+ T cell induction and complete protective efficacy of malaria DNA vaccination by boosting with modified vaccinia virus Ankara. *Nature Medicine*. 1998 Apr; 4(4): 397–402.
111. McShane H, Brookes R, Gilbert SC, Hill AVS. Enhanced immunogenicity of CD4 + T-cell responses and protective efficacy of a DNA-modified vaccinia virus Ankara prime-boost vaccination regimen for murine tuberculosis. *Infection and Immunity*. 2001; 69(2):681–6. [PubMed: 11159955]
112. Abbasi J. First Inactivated Zika Vaccine Trial. *Jama*. 2016 Dec 27.316(24):2588.
113. Durbin AP. Vaccine Development for Zika Virus-Timelines and Strategies. *Semin Reprod Med*. 2016 Sep; 34(5):299–304. [PubMed: 27607566]
114. Barouch DH, Thomas SJ, Michael NL. Prospects for a Zika Virus Vaccine. *Immunity*. 2017 Feb 21; 46(2):176–82. [PubMed: 28228277]
115. Pardi N, Hogan MJ, Pelc RS, Muramatsu H, Andersen H, DeMaso CR, et al. Zika virus protection by a single low-dose nucleoside-modified mRNA vaccination. *Nature*. 2017; 543(7644):248–251. [PubMed: 28151488]
116. Abbink P, Larocca RA, De La Barrera RA, Bricault CA, Moseley ET, Boyd M, et al. Protective efficacy of multiple vaccine platforms against Zika virus challenge in rhesus monkeys. *Science*. 2016 Aug 4; 353(6304):1129–32. [PubMed: 27492477]
117. Kim E, Erdos G, Huang S, Kenniston T, Falo LD Jr, Gambotto A. Preventative Vaccines for Zika Virus Outbreak: Preliminary Evaluation. *EBio Medicine*. 2016 Nov.13:315–20.
118. Kennedy RB, Poland GA. The identification of HLA class II-restricted T cell epitopes to vaccinia virus membrane proteins. *Virology*. 2010; 408(2):232–40. [PubMed: 20961593]
119. Johnson KL, Ovsyannikova IG, Mason CJ, Bergen HR III, Poland GA. Discovery of naturally processed and HLA-presented class I peptides from vaccinia virus infection using mass spectrometry for vaccine development. *Vaccine*. 2009; 28(1):38–47. [PubMed: 19822231]

120. Johnson AJ, Kennedy SC, Lindestam Arlehamn CS, Goldberg MF, Saini NK, Xu J, et al. Identification of mycobacterial RplJ/L10 and RpsA/S1 proteins as novel targets for CD4+ T cells. *Infection and Immunity*. 2017; 85(4):e01023–16. [PubMed: 28115505]
121. Hajjigharamani N, Nezafat N, Eslami M, Negahdaripour M, Rahmatabadi SS, Ghasemi Y. Immunoinformatics analysis and in silico designing of a novel multi-epitope peptide vaccine against *Staphylococcus aureus*. *Infect Genet Evol*. 2017 Mar;48:83–94. [PubMed: 27989662]
122. Loeffler FF, Pfeil J, Heiss K. High-Density Peptide Arrays for Malaria Vaccine Development. *Methods Mol Biol*. 2016; 1403:569–82. [PubMed: 27076154]
123. Kuhn, TS. *The structure of scientific revolutions*. Chicago: The University of Chicago Press; 1996.
124. Camilloni B, Basileo M, Valente S, Nunzi E, Iorio AM. Immunogenicity of intramuscular MF59-adjuvanted and intradermal administered influenza enhanced vaccines in subjects aged over 60: A literature review. *Hum Vaccin Immunother*. 2015; 11(3):553–63. [PubMed: 25714138]
125. Nolan T, Bravo L, Ceballos A, Mitha E, Gray G, Quiambao B, et al. Enhanced and persistent antibody response against homologous and heterologous strains elicited by a MF59-adjuvanted influenza vaccine in infants and young children. *Vaccine*. 2014 Oct 21; 32(46):6146–56. [PubMed: 25223266]
126. Van Buynder PG, Konrad S, Van Buynder JL, Brodtkin E, Krajden M, Ramler G, et al. The comparative effectiveness of adjuvanted and unadjuvanted trivalent inactivated influenza vaccine (TIV) in the elderly. *Vaccine*. 2013 Dec 9; 31(51):6122–8. [PubMed: 23933368]



**Figure 1. Personalized Vaccinology Paradigm**

Current vaccine development is largely empirical. Vaccines are tested by trial and error, are mass produced, and given to the entire population using the same antigen dose, route of administration, number of vaccinations, and at the same age.

In contrast, the new vaccine-development paradigm begins with the “Discovery” of new knowledge by integrating unbiased, comprehensive analysis of the genome, transcriptome, proteome, metabolome, microbiome, and immunome—along with the assessment of multiple measures of immune function—in order to understand and evaluate perturbations of the immune system. Findings are then “Validated” in replication cohorts or additional model systems. The new knowledge is then “Applied” to the creation of new vaccine formulations that can undergo additional testing to start a new round of “Discovery,” or can move into clinical trials in order to develop vaccine products engineered to elicit (or avoid) specific effects on the immune system. Each product is tailored to specific subgroups such that robust, protective immunity can be elicited in the old and young, lean and obese, or male and female, while avoiding inappropriate immune responses due to genetics, metabolism, race, gender, malnutrition, immunosuppression, and other host factors or underlying conditions.