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The rational design of vaccines

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This review provides an insight into the various opportunities for vaccine intervention, analysis of strategies for vaccine development, vaccine ability to modulate immune responses and resultant rational vaccine design. In addition, wider aspects are considered, such as biotechnological advances, advances in immunological understanding and host–pathogen interactions. The key question addressed here is, with all our research and understanding, have we reached a new echelon in vaccine development, that of rational design?

The goal of any vaccination is the induction of an appropriate and effective immune response, but precisely what constitutes an effective immune response for many diseases is still unclear. Specific levels of antibody are considered protective in vaccine efficacy for vaccines against hepatitis, diphtheria and tetanus; for example, anti-hepatitis surface antigen antibody levels >10 mIU/ml, anti-diphtheria antibody levels >100 mIU/ml and anti-tetanus antibody levels >100 mIU/ml are quoted as protective levels of antibody in humans [1,2]. However, for many other diseases, correlations of efficacy are less obvious or yet to be agreed. By definition of perceived need, we are most acutely aware of the requirement of effective vaccines against infectious agents, pathogens ancient, re-emergent and new, yet the opportunities for manipulation of immune responses offer potential in the prevention and treatment of a far larger diversity of diseases. From these, immunomodulation in cancer, allergy and autoimmune disease are also considered here.

Recent developments have brought vaccines against infectious diseases to the forefront of the scientific community. The 'wake up call' that came from SARS (severe acute respiratory syndrome) has undoubtedly fuelled present fears of a flu pandemic. The 1918 Spanish flu pandemic provides an extreme historical precedent, causing an estimated 50 million deaths after infecting one billion people worldwide [3]. As to the impact of such an outbreak, today there is serious concern over the capacity of the existing infrastructure to limit fatalities by providing suitable healthcare [4]. Although development of a suitable vaccine can take a minimum of six months, in an organized and prepared scenario this could provide the major weapon that will ultimately contain such a catastrophe.

The latest polio outbreaks look set to delay the long hope for eradication of this disease [5]. In the UK, the substitution of the live oral polio vaccine with an inactive vaccine should provide a step towards safe cessation of polio vaccination when the time is right. The live vaccine has the capacity to generate infectious polio virus through mutation, and altered immunological properties of mutants present concern about virus spread in immunized as well as non-immunized populations [6,7].

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Taken as a whole, vaccine research and development encompasses a wide diversity of potential applications, developmental strategies and opportunities. The ongoing elucidation of immunological mechanisms of pathogen recognition and adjuvant action, as well as the knowledge of pathogen mediated mechanisms of immune evasion and gene expression, have transformed our understanding of immunology and disease in recent years. In this complex but increasingly focussed environment of vaccine development, are there opportunities for new solutions for vaccine design? And can new and refined approaches succeed where more conventional approaches appear to have failed?

Vaccines against key diseases

Infectious diseases

There are several reasons as to why the bacillus Calmette–Guérin (BCG) vaccine against tuberculosis (TB) is perceived as ineffective, including manipulation of immune responses (as for virulent TB [8,9]) and, interestingly, variation between propagated strains of BCG [10]. In the case of TB, recent literature has correlated the production of interleukin 4 (IL-4) and IL-4δ2 (a splice variant of IL-4 and an IL-4 antagonist) with the propensity of a latently infected host to succumb to active tuberculosis. The production of IL-4δ2 is correlated with the control of the disease [11]. Focus on the type of immune response needed to engender protection against TB seems to be orientated (convincingly) towards suppression of IL-4 and the long standing dogma advocating the importance of Th1 type cytokines (such as interferon gamma, IFN-γ) in TB resistance [12,13].

In the case of HIV, only one HIV candidate vaccine has completed clinical trials Phases I, II and III in more than 20 years of the epidemic. The Phase III trial was based on the use of recombinant envelope proteins, with the aim of evoking virus neutralizing antibodies. However, results from this were disappointing.

Currently available vaccines are mostly effective against viral diseases that are normally cleared during natural infection [influenza, smallpox, polio and all three viruses in the measles, mumps and rubella (MMR) immunisation]. HIV, in common with Epstein–Barr virus, cytomegalovirus, hepatitis (B and C) and herpes simplex virus, normally establishes chronic infection. Opinion is divided as to what type of immune response is required in the control of HIV. Neutralizing antibodies might be efficient in blocking virus particles but poorly effective against cell-associated virus, whereas some cytotoxic T lymphocytes (CTLs) are effective against virally infected cells but not against free virus particles. Latent infection facilitates immune evasion and the rate of mutation inherent in HIV also facilitates evasion (by escape from responding T cells [14]). Promising vaccine strategies will likely depend upon highly conserved epitopes and upon vaccine strategies that induce potent immune responses capable of driving cytotoxicity and producing broadly effective neutralizing antibodies [15].

Allergy and autoimmune diseases

Allergic and autoimmune diseases represent undesired hypersensitive immune responses to normally harmless environmental antigens, in the case of allergy, or normally tolerated self-proteins, in the case of autoimmunity. The understanding of the pathogenesis of allergic and autoimmune diseases has led to several proposed associations and causes for these diseases. It has been shown that high-affinity T cells can out-compete lower-affinity T cells during responses to antigen *in vivo* [16]. Competition between T cells provides the basis for the argument that maintaining a balanced peripheral immune system might also be a side effect of normal competition for shared resources within an intact immune system [17], a mechanism proposed to be responsible for the increased occurrence of these diseases, where hypersensitivity is normally passively controlled by expansion of immune cells specific for prevalent infectious agents. Autoimmunity can have strong associations with exposure to crossreactive proteins, and genes encoding major histocompatibility complex (MHC) are strongly associated with some autoimmune diseases, but this is markedly less so for allergy. Allergy and autoimmunity are thought to differ by virtue of their regulation through central and peripheral tolerance. Genetic predisposition and environmental exposure are believed to play key roles in the development of asthma and atopy [18], with the significant increase in the incidence of these disorders thought to provide evidence for the involvement of various environmental factors, especially in developed countries [19].

The rationale for immunological therapeutic intervention is strongly supported by the present lack of curative treatments for autoimmune and allergic disorders, a growing unmet need, where the largely palliative treatment is not without problems [20].

Evidence that pathology associated with allergy and autoimmunity is reversible is provided by transient and long-term resolution of disease as well as by the success of specific allergen immunotherapy, where subcutaneous or sublingual administration of the sensitizing protein(s) modifies immunity and reduces allergen sensitivity [20].

Cancer

Serological identification of antigens by recombinant expression cloning has led to the identification of a multitude of new tumour antigens [21]. It is thought that most or all paraneoplastic neurological disorders (neurological disorders remote from the site of a malignant neoplasm or its metastases) are immune mediated [22] and this has been cited as evidence for the involvement of specific immune responses in cancer suppression [23]. Indeed, failure to find the relevant antigen in the cancer of a patient should prompt a search for a second cancer

TABLE 1

The main players: oncogenic infectious agents and their associated malignancies

Oncogenic infectious agents	Associated malignancies
Human papillomaviruses	Cervical carcinoma
Human polyomaviruses	Mesotheliomas, brain tumours
Epstein–Barr virus	B-cell lymphoproliferative diseases and nasopharyngeal carcinoma
Herpesvirus	Kaposi's sarcoma and primary effusion lymphomas
Hepatitis B and hepatitis C viruses	Hepatocellular carcinoma
Human T-cell leukemia virus-1	T-cell leukemias
Helicobacter pylori	Gastric carcinoma

[24]. Immunotherapy has recently achieved much interest as a possible addition to chemotherapeutic treatment [25] and this could open up a new and innovative avenue for clinical trials. Effective chemotherapy against *Schistosoma mansoni* with praziquantel is dependent on the presence of antibodies recognizing schistosome glycoprotein epitopes [26]. Another interesting approach is the therapeutic vaccination against cancer by targeting anti-apoptotic molecules [27].

Infectious agents are implicated as causes of cancer and contribute to a variety of malignancies worldwide. Some of the major players in this role are shown in Table 1 and they account for several of the most common malignancies and up to 20% of malignancies around the globe [28]. As such, these agents offer increased potential for prevention of cancer by prophylactic vaccination.

Passive immunisation

Administration of antisera as a treatment against snake venom dates back to the 1890s and the work of Albert Calmette. Although this article largely focuses on active immunisation and the generation of host antibodies by the host immune system itself, the strategy of passive immunisation is worth consideration, as epitopes identified using modern molecular biology techniques might be targeted by the use of passively administered monoclonal antibodies. Examples of immunotherapy using monoclonal antibodies are Campath® (alemtuzumab), manufactured by Genzyme for the treatment of B-cell chronic lymphocytic leukaemia, and Rituxan® (Rituximab), a chimeric murine–human monoclonal antibody that targets the CD20 antigen found on the surface of normal and malignant B lymphocytes and used in the treatment of non-Hodgkin's lymphoma. This strategy is not restricted to cancers; for example Remicade®, a chimeric monoclonal antibody specific for tumour necrosis factor α (TNF-α, is used in the treatment of autoimmune disease.

Vaccine development strategies

Historical outline

The implementation of rational design was first evident when Pasteur reproducibly manufactured attenuated cultures of chicken cholera vaccines, thereby routinely preventing cholera in vaccinated chickens. Extrapolation of this strategy for anthrax vaccines in livestock in the 1880s was a success with significant economic benefits. Despite the elucidation of an attenuated vaccination strategy against rabies and other inactivated whole-organism vaccines towards the end of the nineteenth century, it wasn't until the cell-culture revolution in 1950–1980 that attenuated viral vaccines really took off, together with the isolation and use of extracts and subunits of infectious agents. Pasteur's approaches of attenuation and inactivation still today provide the two poles of vaccine technology [29]. A chronology of important developments and achievements in vaccine research and implementation is shown in Figure 1. Recent developments in vaccine technology and application include combination vaccines, new adjuvants and delivery systems, reverse vaccinology and vaccines against noninfectious diseases. The history of vaccine development is very much related to technological advances [30].

Exploiting vaccine delivery systems and adjuvants

Subunit vaccines can be produced in bulk, safely and reproducibly, using recombinant DNA technology. Much research has already been accomplished in the development of suitable carrier systems able to engender enhanced immune responses to entrapped peptide and protein epitopes. The identification of potentially useful antigens is greatly facilitated by improved molecular biology techniques, such as microarray technology (discussed further below), but the elucidation of their full potential might rely on the development of effective delivery systems and adjuvants. Many adjuvants are based on microbial components but others, traditionally aluminium salts and more recently emulsions and surfactant based formulations, exploit different mechanisms of action. Particulate delivery can be mediated by polymer [often poli(lactide-co-glycolide)] microparticles, immunostimulatory complexes, liposomes and virosomes [31]. Possible advantages of particulate delivery are that antigen and coadjuvant can be delivered to the same cell and particulates have excellent potential for targeting cells of the immune system [32]. The extensive diversity of adjuvants and delivery systems is more comprehensively reviewed elsewhere [31–34] and this review will, where appropriate, focus on the application and other aspects of this technology.

Date	Event or vaccine introduction	Major development
1796	Edward Jenner uses cowpox vaccine against smallpox	Related animal virus used to prevent disease in humans; can be seen as the birth of 'vaccinology'
1870s	Chicken cholera vaccine created by Pasteur	First live attenuated bacterial vaccine
1880s	Rabies and anthrax vaccines	Chemical attenuation; first live attenuated viral vaccine (rabies) (Pasteur)
1890s	Typhoid, cholera, plague vaccines	Inactivation of whole organisms
1920s	Whole cell pertussis vaccine (inactivated); attenuated BCG; Tetanus and diphtheria toxoid vaccines	*In vitro* passage; Use of inactivated toxins
1930s	Inactivated influenza vaccine; attenuated yellow fever	Chick embryo and tissue culture (yellow fever)
1940s	Japanese encephalitis; also war support for vaccine development	Use of pathogen derived extracts and subunits; DPT (tri-valent diphtheria/pertussis/tetanus) recommended by the AAP for routine use
1950s	Inactivated polio virus vaccine (IPV)	The cell culture 'revolution' between the 1950s and 1980s provided the foundation for the attenuated viral vaccines in use today
1960s	Live oral polio (OPV) and measles virus vaccines licensed	
1970s	Pneumococcal and meningococcal vaccines; licensure of rubella vaccine (earlier in the USA); adenovirus vaccines; Influenza	Use of capsular polysaccharides; last indigenous case of smallpox (Somalia), cessation of smallpox vaccination; use of ressortants (influenza)
1980s	Hepatitis B vaccine; *H. influenzae* type b protein conjugated polysaccharide; typhoid	Hepatitis B vaccines produced by recombinant DNA technology replaced the (plasma derived) vaccine licensed earlier; development of auxotrophic vaccines (typhoid)
1990s	Varicella, lyme disease vaccines; dtap (diphtheria, tetanus, acellular pertussis) licensed; supersedes whole-cell DPT; various combination vaccines licensed	Development of safer vaccines (Dtap); elucidation of the possibility of DNA vaccines
	Rotavirus vaccine recommended, licensed and withdrawn in less than two years (1998-99 USA)	
2000 onwards	Live influenza vaccine; bovine-human rotavirus vaccine; polio: centers for Disease Control recommends use of IPV instead of OPV; withdrawal of lyme disease (Lymerix) vaccine; penta-valent DtaP/HepB/IPV (Pediarix) licensed; serious consideration of biowarfare vaccines (e.g. smallpox); papillomavirus vaccines against cancer	

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FIGURE 1

A historical outline of important developments and achievements in vaccine research. The figure outlines many of the important developments and achievements that have underpinned the development of successful vaccines from 1796. The variolation against Smallpox is believed to originate in China or India, later spreading to the Middle East, Africa, Turkey and Great Britain.

The 300 million doses of influenza vaccine needed annually worldwide require more than 350 million chicken eggs and six or more months. The development of cell-culture technology that could replace the egg-based manufacturing process might facilitate faster production of much-higher antigen yields [4]. Live vaccines generally possess a natural adjuvant capability that is built on the evolved ability of our immune system to recognize many facets of potentially dangerous microbes and they have contributed immeasurably to the control of disease. Although some live vaccines might have undesirable characteristics, such as the mutation of polio virus and persistence of viruses such as varicella zoster virus, their use has been, and indeed remains, able to significantly reduce the impact of associated diseases [35,36]. Viruses and bacteria as carriers of heterologous antigens and genes have received considerable attention over previous decades, and generation of auxotrophic mutants, as well as the use of other replication incompetent vectors and of reassortant viruses generated by the addition of RNA segments to viruses with segmented genomes, such as influenza and rotavirus, indicates the potential inherent in these efficient types of vaccine. In an interesting utilization of viral replication, a self-replicating RNA vector encoding a model antigen (β-gal), which was shown to protect mice against subsequent tumour challenge with colon carcinoma cells engineered to express β-gal, was also shown to effectively induce apoptosis in transduced cells [37]. The observed apoptosis also facilitated enhanced uptake by dendritic cells and was likely mediated by the presence of double-stranded RNA in replication of the virally derived genome. Double-stranded RNA is recognized by Toll-like receptor (TLR) binding. Different TLRs recognize different surface and intracellular components of microorganisms. The interaction between a TLR and a microbial component triggers the activation of the innate immune system and

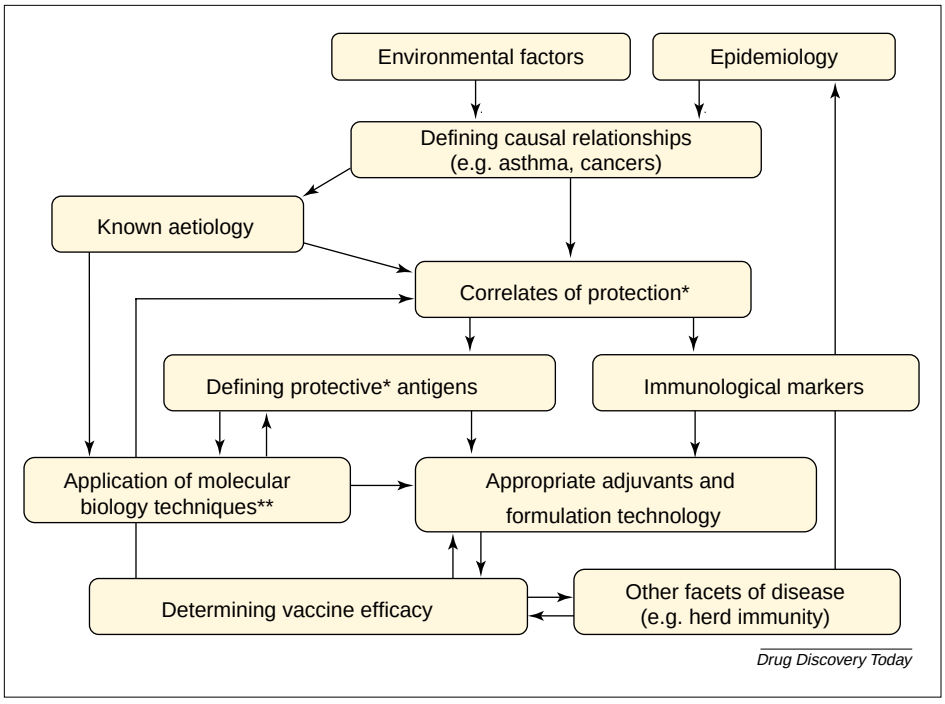

FIGURE 2

Important factors in the rational design of vaccines and the cyclical generation of knowledge. The level of involvement of any of these factors depends on the aetiological agent of disease. For example, the level of protection required in a population (herd immunity) will be different and this could allow theoretical flexibility in vaccine efficacy. The application of molecular biology techniques can be crucial in the identification of new candidate antigens and subsequent determination of vaccine efficacy using adjuvants can feed knowledge back to correlates of protection in terms of immunological markers. This knowledge can then be used in choice of appropriate adjuvants and formulation. The key implication projected by this schematic is that for the greatest challenges in vaccine development the cyclical generation of knowledge provides a strong role for rational design.
* Can be protective or therapeutic. ** Including reverse vaccinology and associated technologies.

the initiation of acquired immunity [38]. The elucidation of these pathways sheds light on mechanisms of adjuvant action and provides a basis for the inclusion of such potent agents and their analogues in vaccine design.

The role of rational design

Looking for associations

It is important to consider how we classify or view rational design in the context of vaccines. A picture springs to mind of the rapid analysis of pathogens, the identification and allocation of immunological interactions for specific genes, as well as the generation of a superimposed choreography of the infection or disease process, resulting in the identification of credible candidate target antigens. Following this, appropriate formulation with adjuvants and delivery systems might elicit immune responses of the type and magnitude predictive of providing protection or therapeutic action. The truth is that we are still very far from this idyll.

Recent articles have intimated the minor contribution of our knowledge of immunology to the development of vaccines [39,29]. However, the development of improved and large-scale cellular immunity techniques for the analysis of immune responses, such as ELISPOT for cytokine induction, tetramer staining for peptide specific CTLs, along with analysis of the immunological basis for the efficacy of successful vaccines, facilitates the role of immunology in predicting the appropriate context for antigen delivery. Extensive characterisation of adjuvant action and the potential to target desired immune responses through the exploitation of this knowledge is key for rational vaccine design [29,31,32,39,40]. The interaction between different elements involved in rational vaccine design is outlined in Figure 2.

The use of microarray technology can allow identification of virulence genes and vaccine targets [41] and is one of the most powerful tools for the study of the transcriptome, the complete set of transcripts of an organism. Indeed, in conjunction with proteomics and comparative genome analysis, interpretation of whole-genome sequences through bioinformatics (or genomic mining) can be used to assign putative gene functions to each open reading frame on the basis of homology to known proteins [42]. Systematic identification of potential antigens of a pathogen using this information, without the need for cultivation of the pathogen, is termed 'reverse vaccinology' [43] and represents a significant departure towards the idyll of rational vaccine design described above, at least in terms of dissection of potential pathogen-related antigens.

A new era of vaccine design?

Knowledge of pathogen interactions during infection can provide an invaluable insight into potentially successful targets for vaccines. For example, knowledge of gene expression in *Mycobacterium tuberculosis* enables us to see why vaccines based on early secreted proteins, such as Ag85 and ESAT-6, can generate effective pre-exposure vaccines and helps us to predict that an effective post-exposure vaccine will utilize dormancy induced proteins, such as α-crystallin, heat shock protein 'HspX' [44].

In the case of HIV, the implication of lipid rafts in viral entry and budding processes might have provided a rationale for the evaluation of peptides, based on highly conserved caveolin-1 binding domains of HIV-1 glycoprotein gp41 in candidate vaccine formulations [45]. Encouragingly, this has resulted in peptides capable of the elicitation of neutralizing antibody responses able to inhibit different clades of HIV-1. It is thought that the poor ability of some specific antibodies to neutralize primary isolates is due, at least in part, to steric factors that limit antibody access to the gp120 epitopes [46].

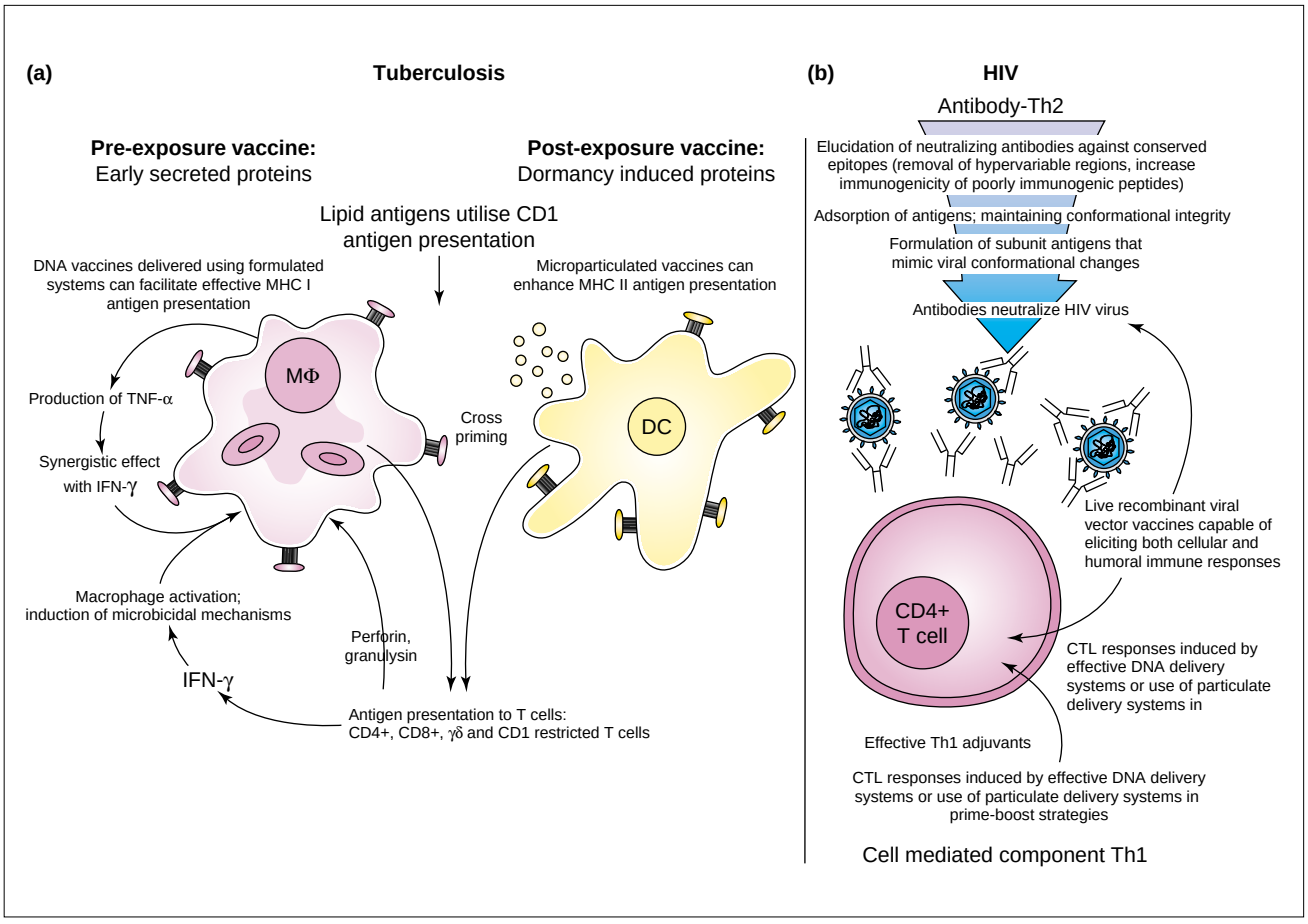

FIGURE 3

Proposed opportunities for vaccination against TB and HIV. In both cases, the utilization of adjuvants capable of driving the required type of immune response can be used. This can be based on our current understanding of TLR interaction, and studies that manipulate this understanding might also serve to elucidate complex interactions during infection and disease. **(a)** According to recent models, antigen specific CD4+ T cells, CD8+ T cells, γδ T cells and CD1 restricted T cells, all participate in protection against *M. tuberculosis* infection in response to antigen presentation by macrophages (MΦ) and dendritic cells (DC), probably also involving crosspriming, where mycobacterial antigens are transferred from infected MΦ to DC. It is unlikely that the induction of IFN-γ or the production of inducible nitric oxide synthase alone is enough to control TB infection, and evidence indicates that there might be another role for CD4+ T cells. The development of pre- and post-exposure vaccines will likely require antigens expressed by *M. tuberculosis* under pre- and post-exposure conditions, respectively. Interestingly, nonpolymorphic CD1 restricted T cells are thought to have evolved as a result of prolonged interaction with mycobacteria, indicating the extent of the impact of mycobacteria on its mammalian host. **(b)** For vaccines against HIV, it seems increasingly likely that strategies will depend upon highly conserved epitopes and on vaccine strategies that induce potent immune responses capable of driving cytotoxicity, as well as broadly reactive, highly effective neutralizing antibodies. Target antigens might very probably be different for each of these strategies. Figure adapted, with permission, from Ref. [32].

Antibodies against the caveolin-1 binding domains are rare in many HIV infected individuals, possibly because of the presence of hypervariable immunodominant epitopes or the location and lack of exposure of conserved regions. The proposed opportunities for vaccines against HIV and TB are summarized in Figure 3; the rationale for elicitation of successfully neutralizing antibodies against HIV is centred upon increasing the immunogenicity of poorly immunogenic peptides, modification and/or removal of hypervariable regions and mimicking viral conformational changes.

One of the hottest areas of interest regarding new vaccine development surrounds the Phase III efficacy trials and prospective licensure of two vaccines against human papillomavirus (HPV) [47]. The vaccines, one from Merck and one from GSK, are effectively vaccines against cervical cancer; the (now) unequivocal link between this common virus, which rarely causes serious disease in itself, and cervical cancer found credence as long ago as the 1970s. The production of both vaccines (the Merck vaccine produced in yeast administered with an aluminium adjuvant and the GSK vaccine in baculovirus with the adjuvant AS04; aluminium and bacterial lipid already approved for use in Europe) has its basis in work that elucidated the production and self-assembly of virus-like particles of the HPV outer L1 and L2 coat proteins [48,49] in various cell types.

Vaccines against most *Neisseria meningitidis* serogroups have been developed using traditional approaches. However, group B meningococcus has represented a particular challenge because of the sequence variation of surface proteins and crossreactivity of the capsular polysaccharide

with host polysialic acid [50]. In this case, reverse vaccinology was convincingly applied to overcome these problems by alternative means [51]. Screening of DNA fragments, discarding likely cytoplasmic protein sequences and known *Neisseria* antigens, extensive cloning and expression of identified candidate genes allowed selection of antigens that were found not only to offer significant potential for protection against group B meningococcus but also to facilitate crossprotection against heterologous strains.

Also worth mentioning is the technique of molecular breeding or gene shuffling, where reassembled chimeric genes are created from a selection of homologous gene sequences. The related sequences are denatured, annealed and subsequently extended in what is in effect a self-priming polymerase chain reaction (PCR) that takes advantage of crossovers, deletions, insertions, inversions and point mutations, as occurs in natural evolution (hence the term 'molecular breeding'). Proteins and genes with enhanced activity are then selected for inclusion in further rounds of molecular breeding. This has a proven application for the generation of enzymes with markedly enhanced activity [52] and the enhancement of the functions of a diverse range of proteins, such as green fluorescent protein [53] and IFN-α [54]. This technique is thought to be superior to other methods that employ random mutagenesis, such as error-prone PCR (hence the phrase 'the rational basis for irrational design' [55]), but the screening of candidate antigen genes is necessarily expensive in terms of resources and time if it is compared for example to the screening of an enzyme. Their potential has been noted with relevance to allergy vaccines [56], as pre-existing immunity is the therapeutic target and screening of allergen variants might be somewhat more practicable.

Conclusions

Bringing together developmental strategies with the knowledge gleaned from host pathogen interactions represents a highly evolved design strategy. Although each individual molecular biology technique appears to have something to contribute to vaccine development, it is the holistic application of a combined approach that is closest to a premeditated and planned rational vaccine design. Pathogens such as *Streptococcus pneumoniae*, *Porphyromonas gingivalis*, *Staphylococcus aureus*, *Chlamydia pneumoniae* and *Bacillus anthracis* have all been investigated using bioinformatics techniques in the context of reverse vaccinology [43], with continued interesting results. In terms of antigen identification, the National Institute of Allergy and Infectious Diseases (NIAID) recently announced initiation of the Large-Scale Antibody and T Cell Epitope Discovery Program; utilizing complementary methods for epitope discovery, it is designed to identify immune epitopes from selected infectious agents and will make this information freely available to scientists worldwide through the Immune Epitope Database and Analysis Resource (IEDB), currently under development [57].

Recent discoveries have resulted in a wealth of options, when considering what we can do in terms of vaccine design and production. Mechanisms of adjuvant action have been elucidated, pattern recognition receptors including Toll-like receptors, NOD1, NOD2, scavenger receptors, mannose and other receptors are becoming increasingly well defined [38] and intracellular events related to these, such as activation of transcription factors and expression of inflammatory cytokines, shed further light on how these ligands and adjuvants that bind to pattern recognition receptors mediate their immunological actions. The ability of infectious agents to induce rapid, innate immune responses to molecular patterns provides the basis for adjuvant immunotherapy of cancers. Studies, such as the recent work examining the adjuvant activity of BCG cell-wall skeleton, peptidoglycan and lipopolysaccharide by the induction of genes in dendritic cells [58], will very possibly help to achieve definition of efficient effector output with minimal toxicity.

The easier and safer production of vaccines and vaccine components facilitated by modern biological techniques underpins a rational approach that is an integral part of the rational design of vaccines. The extensive knowledge of immunological mechanisms and host pathogen interactions is able to contribute to the design of effective vaccines in addition to the elucidation of the mechanisms of action of many candidate vaccine agents. In fact, rational design of vaccines represents a driving force born in the first revelations that components from or relating to a microbial pathogen can be used to protect against that disease and present throughout development of vaccines in the modern era, honing our understanding and preparing the way for the next steps in the battle to combat today's significant pathogens and diseases, such as cancer, HIV, tuberculosis and malaria. In this era, we begin to explore the very limits of immunotherapeutic and prophylactic intervention and the tools that have been developed to elucidate gene expression and function might have at last begun to find their application in our most significant of challenges.

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