International Journal for Parasitology xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

International Journal for Parasitology

journal homepage: www.elsevier.com/locate/ijpara

Invited Review

Genome-based vaccine design: the promise for malaria and other infectious diseases

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ARTICLE INFO

Article history:
Received 15 June 2014
Received in revised form 30 July 2014
Accepted 31 July 2014
Available online xxxx

Keywords:
Vaccine
Rational vaccine design
Genome-based
Malaria
Infectious diseases
'Omics'

ABSTRACT

Vaccines are one of the most effective interventions to improve public health, however, the generation of highly effective vaccines for many diseases has remained difficult. Three chronic diseases that characterise these difficulties include malaria, tuberculosis and HIV, and they alone account for half of the global infectious disease burden. The whole organism vaccine approach pioneered by Jenner in 1796 and refined by Pasteur in 1857 with the "isolate, inactive and inject" paradigm has proved highly successful for many viral and bacterial pathogens causing acute disease but has failed with respect to malaria, tuberculosis and HIV as well as many other diseases. A significant advance of the past decade has been the elucidation of the genomes, proteomes and transcriptomes of many pathogens. This information provides the foundation for new 21st Century approaches to identify target antigens for the development of vaccines, drugs and diagnostic tests. Innovative genome-based vaccine strategies have shown potential for a number of challenging pathogens, including malaria. We advocate that genome-based rational vaccine design will overcome the problem of poorly immunogenic, poorly protective vaccines that has plagued vaccine developers for many years.

1. Vaccines – the global need

The term 'vaccine' is derived from *Variolae vaccinae*, literally smallpox of the cow, and was coined by Edward Jenner in 1798 in an article describing the protective effect of cowpox against smallpox (Jenner, 1798; Cohen et al., 1961; Baxby, 1999; Tuells, 2012). Since then, vaccines have been established as one of the most efficient and cost-effective interventions for the control and eradication of disease, and the prevention of morbidity and mortality worldwide. No other modality has had such a major effect on reducing mortality and improving public health, except for water sanitation (World Health Organization, 2006). Moreover, vaccinology is the only science that has eradicated an infectious disease (Andre, 2003), with the landmark achievement in 1977 of the eradication of smallpox (Fenner, 1982), a disease that plagued humankind and shaped our history since earliest civilisation (Fenner et al., 1988). It is anticipated that poliomyelitis will soon be eradicated, although some challenges remain (Pallansch and Sandhu, 2006).

Infectious diseases are responsible for one-third of all deaths worldwide, killing at least 15 million people each year (http://www.who.int/healthinfo/global_burden_disease/gbd/en/). They are clearly established as the leading cause of death of children globally and are responsible for 64–68% of deaths in children under 5 years of age, approximately 5 million children each year (Black et al., 2010; Liu et al., 2012). It is estimated that at least 3 million deaths per year are prevented by licensed vaccines currently in use (World Health Organization, 2007, 2009). Mass smallpox vaccination of children became compulsory in the United Kingdom (UK) in 1853 and vaccines are now available for most viral and bacterial diseases common in children including diphtheria (1923), whooping cough (1926), tetanus (1937), influenza (1942), pertussis (1949), polio (1958 and 1961), measles (1963), mumps (1967), rubella (1969), bacterial meningitis (1974), pneumonia (1983), varicella (1995) and rotavirus (1998) (http://www.who.int/immunization/policy/position_papers/en/).However, many of these existing vaccines are underutilised and the World Health Organization has estimated that 2.5 million children under the age of 5 years die from vaccine-preventable diseases each year, more than 6800 child deaths every day (World Health Organization, 2007). There are also many serious pathogens for which effective vaccines are not yet available including hepatitis C virus (HCV), human immunodeficiency virus (HIV), Dengue, respiratory

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http://dx.doi.org/10.1016/j.ijpara.2014.07.010
0020-7519/

syncytial virus (RSV) and cytomegalovirus (CMV); bacteria (e.g. *Mycobacterium tuberculosis* (TB), Group A streptococcus (GAS), Group B *Streptococcus* (GBS), *Staphylococcus aureus*, *Meningococcus* Group B (MenB), *Shigella*, pathogenic *Escherichia coli*); and parasites (e.g. *Plasmodium*, *Leishmania*, *Schistosoma*, *Trypanosoma*) and these are estimated to claim in excess of 3 million more lives each year (World Health Organization, 2005, 2007).

It is noteworthy that despite the demonstrated success of vaccines in preventing illness caused by viral and bacterial pathogens, there are not yet any licensed vaccines for parasitic infections of humans or for any chronic infections by complex pathogens (World Health Organization, 2006; Moorthy and Kieny, 2010). The pathogens causing these diseases have adapted to long-term coexistence with the human immune system and have evolved sophisticated immune evasion strategies. Many express hundreds or thousands of potential antigenic targets, often in distinct phases of their life cycles, so it is perhaps not surprising that vaccine efforts to develop vaccines based on only a limited number of antigens, often selected on an ad hoc basis and without knowledge of the antigenic repertoire of the organisms, have not been successful.

Moreover, all currently licensed vaccines for infectious diseases are prophylactic, preventing the effects of a future infection by the target pathogen, and there are no licensed therapeutic vaccines for any chronic or acute infectious disease. The only therapeutic vaccine approved by the United States Food and Drug Administration (US FDA) is for a certain type of metastatic prostate cancer (Provenge®, DendreonCorp, USA; approved in 2010). Prophylactic vaccines have been developed to prevent human papilloma virus (HPV) and hepatitis B virus (HBV) which cause chronic infections and in some cases cancer (Plotkin, 2008; Levine and Esparza, 2009). However, effective vaccines against the three pathogens responsible for more than half of the global burden of infectious diseases (malaria, HIV, TB) (World Health Organization, 2006) will need to be therapeutic, given the chronicity of these infections in endemic regions.

2. History of vaccines

The field of vaccinology originated on 14 May 1796 when Edward Jenner inoculated an 8 year old boy named James Phipps with vaccinia virus contained in pus from lesions on the hand of a milkmaid with cowpox and showed that Phipps did not become infected with smallpox when subsequently variolated (inoculated, or in today's parlance – challenged, with smallpox). Jenner's seminal study predated formal evidence for the germ theory of disease (microbial origin) obtained by Louis Pasteur in 1857 and Robert Koch in 1876 (D'Argenio and Wilson, 2010) which provided the foundation of empirical vaccine development. A century after Jenner's observation, proof-of-concept was established with the development by Louis Pasteur of an attenuated vaccine for chicken cholera in 1879, an anthrax vaccine in 1881, and a rabies vaccine in 1885 http://www.historyofvaccines.org).

These and subsequent "first generation" vaccines (e.g. Bacillus Calmette Guerin (BCG)) consisted of live-attenuated pathogens (typhoid, pertussis, measles, mumps, rubella) or inactivated killed pathogens (polio, rabies, cholera, hepatitis A, bubonic plague) and were developed according to the classical "isolation, inactivation and injection of disease-causing pathogen" approach to vaccine development established by Pasteur, and using Koch's postulates as a general guide.

In the second half of the 20th Century, significant advances in many fields including cell culture (enabling the growth of viruses in vitro), polysaccharide chemistry, recombinant DNA technology and immunology, allowed the development of "second generation" vaccines which comprised purified pathogen components such as protein antigens or polysaccharides (e.g. polio, measles, mumps, rubella, chickenpox, tetanus, diphtheria, anthrax, influenza, hepatitis A, hepatitis B, rotavirus, influenza, pneumonia and human papillomavirus (Hilleman, 1999; Finco and Rappuoli, 2014; Rhee, 2014). Maurice Hilleman is widely recognised as a pioneer and the most prolific developer of vaccines in this period, developing more than 40 vaccines (Hilleman, 1999; http://www.historyofvaccines.org).

It was in this era that Jonas Salk, who developed the first (inactivated) vaccine against polio, defined vaccinology as "the application of the basic requirements for effective immunisation" which include (i) stimulation with a sufficient quantity of antigen, (ii) use of a suitably specific antigen, and (iii) the induction of an appropriate immune response for the prevention of the pathological consequences of infection; also noting that vaccinology "requires an understanding of the etiologic agents, the pathogenic mechanisms, and the epidemiology of the individual diseases" (Salk and Salk, 1977). The majority of currently-licensed vaccines consist of either killed (inactivated) or live attenuated pathogens, or pathogen-related biomolecules including toxoids or polysaccharides (Grimm and Ackerman, 2013; U.S. Food and Drug Administration, 2014). It is notable that most currently licensed vaccines target pathogens with a relatively low degree of antigen variability and work mainly by eliciting functional antibodies (De Gregorio and Rappuoli, 2012).

For many significant pathogens, the generation of broadly protective vaccines has remained elusive. Such pathogens often present technical obstacles to the vaccinologist that include their inability to be cultured in vitro (e.g. *Mycobacterium leper*, papilloma virus type), have antigenic hypervariability (e.g. serogroup B meningococcus, HIV, HCV), or whose life cycles have an intracellular phase that puts them out of the reach of antibodies and therefore require a cellular immune response - controlled predominantly by T cells (e.g. malaria, tuberculosis); furthermore, traditional approaches to vaccine design and development do not allow the rapid development of new vaccines for pandemic agents (Finco and Rappuoli, 2014). Most second generation vaccines do not target these types of pathogens or elicit the correct types of responses and we have reached a point where most of the low-hanging fruit has been taken. These challenges are significant and explain why we have reached the end of the age of second generation vaccine development.

Advances in genomics and other "omics" over the past two decades have given rise to a "third generation" of vaccines (e.g. Meningococcus group B, group A streptococcus, group B streptococcus, *S. aureus*, *E. coli*, *Clostridium difficile*) based on technologies such as reverse vaccinology pioneered by Rappuoli (2000), structural biology and synthetic vaccines (Delany et al., 2014; Finco and Rappuoli, 2014). This activity has resulted in vaccines that protect against an increased range of vaccine-preventable diseases, that are multivalent and target different serotypes, or highly purified vaccines with an improved safety profile, and replace the more reactogenic whole cell vaccines (Rappuoli et al., 2011). These advances, combined with knowledge gained from successes with vaccine development against acute diseases in the 20th Century, provide the foundation for the development of vaccines that have thus far proved elusive, including those that are therapeutic (for chronic diseases), require cellular immunity for protection, for pregnant women and elderly or immunocompromised people, or for new indications such as autoimmune disease and cancer (Poland and Barrett, 2009; Rappuoli et al., 2011). They also enable more efficient pathways for vaccine development and new technologies for assessment of vaccine safety, which are especially pertinent given increased public scrutiny of adverse events associated with vaccination and stringent regulatory requirements for vaccine approval (Rappuoli et al., 2011).

On May 8, 1980, the World Health Assembly certified the world free of naturally occurring smallpox, representing a landmark

Please cite this article in press as: Doolan, D.L., et al. Genome-based vaccine design: the promise for malaria and other infectious diseases. Int. J. Parasitol. (2014), http://dx.doi.org/10.1016/j.ijpara.2014.07.010