Ticks and Tick-borne Diseases 7 (2016) 573–585

Contents lists available at ScienceDirect

Ticks and Tick-borne Diseases

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

A review of reverse vaccinology approaches for the development of vaccines against ticks and tick borne diseases

A.E. Lew-Tabor[a,b,*], M. Rodriguez Valle[a]

[a] The University of Queensland, Centre for Animal Science, Queensland Alliance for Agriculture and Food Innovation, Carmody Rd., St. Lucia 4072, QLD, Australia
[b] Murdoch University, Centre for Comparative Genomics, Murdoch 6150, WA, Australia

ARTICLE INFO

Article history:
Received 7 September 2015
Received in revised form
24 November 2015
Accepted 12 December 2015
Available online 18 December 2015

Keywords:
Reverse vaccinology
Ticks
Tick borne diseases
Veterinary
Vaccines

ABSTRACT

The field of reverse vaccinology developed as an outcome of the genome sequence revolution. Following the introduction of live vaccinations in the western world by Edward Jenner in 1798 and the coining of the phrase 'vaccine', in 1881 Pasteur developed a rational design for vaccines. Pasteur proposed that in order to make a vaccine that one should 'isolate, inactivate and inject the microorganism' and these basic rules of vaccinology were largely followed for the next 100 years leading to the elimination of several highly infectious diseases. However, new technologies were needed to conquer many pathogens which could not be eliminated using these traditional technologies. Thus increasingly, computers were used to mine genome sequences to rationally design recombinant vaccines. Several vaccines for bacterial and viral diseases (*i.e.* meningococcus and HIV) have been developed, however the on-going challenge for parasite vaccines has been due to their comparatively larger genomes. Understanding the immune response is important in reverse vaccinology studies as this knowledge will influence how the genome mining is to be conducted. Vaccine candidates for anaplasmosis, cowdriosis, theileriosis, leishmaniasis, malaria, schistosomiasis, and the cattle tick have been identified using reverse vaccinology approaches. Some challenges for parasite vaccine development include the ability to address antigenic variability as well the understanding of the complex interplay between antibody, mucosal and/or T cell immune responses. To understand the complex parasite interactions with the livestock host, there is the limitation where algorithms for epitope mining using the human genome cannot directly be adapted for bovine, for example the prediction of peptide binding to major histocompatibility complex motifs. As the number of genomes for both hosts and parasites increase, the development of new algorithms for pan-genomic mining will continue to impact the future of parasite and ricketsial (and other tick borne pathogens) disease vaccine development.

Contents

* Corresponding author at: The University of Queensland, Centre for Animal Science, Queensland Alliance for Agriculture and Food Innovation, Carmody Rd., St. Lucia 4072, QLD, Australia. Tel.: +61 417737595; fax: +61 7 33462167.
E-mail address: a.lewtabor@uq.edu.au (A.E. Lew-Tabor).

http://dx.doi.org/10.1016/j.ttbdis.2015.12.012
1877-959X/

History of vaccinology

During the very early development of human society, the epidemics and pandemics were intrinsic threats to human health (http://www.historyofvaccines.org/content/timelines/all). There are documented examples of these doomed moments of humanity such as the Spanish flu pandemic in 1918 (Taubenberger, 2006; Taubenberger and Morens, 2006), and the smallpox (*Variola minor* and *Variola major*) epidemics in second century AD in Rome and London in 1665. Smallpox caused the deaths of approximately 400,000 people annually towards the end of the 18th century (Rolleston, 1933) and ~300–500 million deaths during the 20th century as reviewed by Behbehani (1983).

Animals are affected by important zoonotic diseases and can be transmitted to humans such as anthrax, typhus and influenza. Since the times of ancient Greece and Rome, civilisations have paid attention to animal diseases because of their significant impact on agriculture (Sallares, 1991). Hence, during the periodic smallpox epidemics in the 18th century, the ancient Chinese and Indian practices based on using cowpox pustules to prevent smallpox infection, were applied in Europe. The English physician Edward Jenner published the first scientific publication describing this variolation method. The terms 'vaccine' and 'vaccination' originated from *Variolae vaccinae* (smallpox of the cow) which Jenner named "cowpox" later known as Vaccinia virus (Haller et al., 2014; Jenner, 1798). To honour Dr Jenner, Louis Pasteur proposed in 1881 that these terms should be extended to all new protective inoculations (Pasteur, 1881). Additionally, he enunciated the theory behind vaccination after developing a methodology to attenuate the virulence of *Pasteurella multocida* (fowl cholera). Chickens exposed to attenuated *P. multocida* did not show disease symptoms after a second challenge with virulent *P. multocida*, hence Pasteur concluded:

> A local disorder, by a morbid modification more or less profound in a muscle, if it is a muscle which has been inoculated with the virus. The muscle is filled with microbes which are easily recognised because the attenuated microbes have almost the bulk, the form, and the appearance of the most virulent microbes. But why is not the local disorder followed by death? For the moment let us answer by a statement of facts. They are these: the local disorder ceases of itself more or less speedily, the microbe is absorbed and digested, if one may say so, and little by little the muscle regains its normal condition. Then the disease has disappeared" (Pasteur, 1881).

This type of reaction in the vaccinated host was characterised and later recognised as the 'immune response' (Ehrlich and Lazarus, 1905; Metchnikoff, 1905). Vaccines are produced by different procedures including: live, attenuated, inactivated/Killed, toxoid (inactivated toxin), and/or subunit/conjugate vaccines all of which aim to induce a long lasting immunological memory in order to respond quickly to the invading pathogen. Therefore, the control and prevention of diseases through vaccines have been utilised as an effective and economic method of pathogen control in human and animal health for more than two centuries (Greenwood, 2014).

Veterinary parasite vaccines

Parasites are responsible for important human, livestock and companion animal diseases which are controlled and treated mainly by chemotherapeutic products. However, the rate at which parasite species can develop resistance to chemicals has been challenging for both industrialised and developing countries particularly when it is the only available control method (Sutherland and Leathwick, 2011). Although a large number of vaccines against various pathogens including bacteria and viruses are readily available, the number of anti-parasite vaccines continued to be insufficient (Knox and Redmond, 2006). There are veterinary parasite vaccines available in the market, but in contrast there are no commercially available human anti-protozoal vaccines (Meeusen et al., 2007). These veterinary vaccines have been established using live organisms to induce protective immune responses, for example, the first commercial parasite vaccine developed was against the bovine lungworm *Dictyocaulus viviparus* (Jarrett et al., 1960). The avian coccidiosis vaccine contains oocysts selected from naturally occurring *Eimeria* strains that produce fewer merogenic cycles and are therefore safer to use (Shirley and Bedrnik, 1997). *Theileria parva* which causes east coast fever in cattle is also administered as a live vaccine which is then followed by drug treatment (long-acting tetracyclines). A solid protection (cell-mediated immunity) is conferred against homologous challenge, but this vaccination strategy can be expensive (Graham et al., 2006). A parasite vaccine registered for veterinary use was developed using mouse attenuated *Toxoplasma gondii* which removed its ability to form cysts (Suzuki and Remington, 1988). The S48 strain of *T. gondii* is the main component in the vaccine which results in long-lasting immunity (18 months) for susceptible ewes (Buxton et al., 1993). Tropical theileriosis in cattle is controlled using a live, attenuated *Theileria annulata* vaccine produced by continuous *in vitro* passaging of the intracellular macroschizont stage (Pipano and Shkap, 2000). *Babesia bovis* and *Babesia bigemina* are attenuated by continuous passage through splenectomised calves. These live vaccines were developed in Australia several decades ago and the infected blood from acute infections of splenectomised calves is still used in most countries to protect against babesiosis (Callow and Mellors, 1966; de Waal and Combrink, 2006). These babesiosis vaccines are often mixed with *Anaplasma marginale* ssp. *centrale* infected blood in those areas where the rickettsial pathogen *A. marginale* is enzootic–collectively known as 'tick fever' vaccines (Bock and de Vos, 2001). A recent review of babesiosis vaccines summarises a list of countries using these live tick fever vaccines including Argentina, Australia, Brazil, Colombia, Israel, Malawi, Mexico, South Africa and Uruguay (Florin-Christensen et al., 2014). *Neospora caninum* is associated with cattle abortion hence a crude adjuvated preparation of inactivated *N. caninum* tachyzoites is available in the United States to diminish abortions and to prevent parasite transmission (Innes et al., 2005; Romero et al., 2004). These live vaccines still pose problems due to antigenic variation to protect from heterologous challenge and the potential for 'reversion to virulence' as documented for babesiosis live vaccines (Barre et al., 2011; Bock et al., 1995).

Tick vaccines

Ticks are vectors of the causal agents for babesiosis, theileriosis, anaplasmosis and cowdriosis in domestic ruminants and Lyme borreliosis in humans. Hence, the tick and tick borne disease (TTBD) complex constitutes a global threat for livestock and human health (Jongejan and Uilenberg, 2004). *Rhipicephalus microplus* (cattle tick) is the most significant in terms of impact on livestock in particular the beef and dairy cattle industries of tropical and sub-tropical regions of the world (Jongejan and Uilenberg, 2004). The cattle tick is a vector of bovine tick fever (babesiosis and anaplasmosis) to susceptible cattle as well as other diseases such as equine piroplasmosis (*Theileria equi*). Globally, 80% of the world's cattle populations (1.3b) are at risk of TTBDs with the economic losses caused by ticks and tick-borne diseases estimated in 1996 as approximately US$13.9–18.7 billion per annum (de Castro, 1997). With 1.47b cattle globally (FAO) and taking into account inflation rates from 1996 to 2015 at 52.3%, the losses currently are more likely to be in the vicinity of US$22–30b per annum. The Australian cattle (beef and dairy)