Vaccines

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Vaccines are, without question, one of the most cost-effective and socially acceptable health interventions yet developed[1] and expanding vaccine coverage is a key enabling strategy for achieving the Millennium Development Goals[2]. As a challenge, the expanded and effective use of existing vaccines sits alongside the development of new and improved vaccines for preventing diseases which continue to have a major impact on humanity – diseases such as HIV/AIDS, tuberculosis and malaria. Because vaccine development is stringently controlled by regulatory authorities and the costs of producing new vaccines have increased significantly[3], responsibility for new vaccine development now typically rests with the larger pharmaceutical companies who have the resources and risk appetite to support the clinical testing program that is essential for licensure. Where this doesn't occur, development of so-called 'orphan' vaccines is supported by the major philanthropic agencies, often in collaboration with institutes such as the International Vaccine Institute in Korea. Animal vaccines are similarly becoming concentrated within global animal health companies.

But the glass is half-full – we should celebrate the fact that many of the common diseases which are associated with significant human mortality or morbidity at a global level are now well-addressed by vaccines. Where vaccines haven't yet been developed, the reasons are often clear, if not the solutions. For example, in HIV, there is the fundamental problem of antigenic variation, coupled with a poor understanding of how protection is effected. In tuberculosis, the underlying immunodeficiency(s) (for example, loss of CD4+ T cells through HIV co-infection) which allows the bacterium to escape what are often effective immune mechanisms that localise the bacterium and weaken vaccine responses. In some circumstances, for example, pneumococcal vaccination, effective vaccines have been developed but these vaccines are serotype-specific and the circulating serotypes may vary from, or replace those, found in the vaccine. This is especially important in preventing pneumococcal disease in Indigenous Australian communities where the circulating serotypes are often a poor match for the prevailing conjugate vaccines. The veterinary sector is faced by different challenges. Here the issues are price and administration consistent with intensive and extensive animal husbandry practices, and this has led to vaccine formulations that comprise multiple vaccine immunogens that protect against a wide variety of pathogens.

This issue of *Microbiology Australia* will present case studies from some of Australia's leading microbiologists who are engaged in the development of new vaccines. Australia plays an important role in the development of new human and veterinary vaccines. Some vaccines, such as those which prevent cervical cancer and Q fever were innovated in Australia. Australia, with its comparatively sophisticated health system, is a preferred country in which to test vaccines developed for Western markets; the phase III program for the new dengue fever vaccine (discussed below) was initiated in Australia.

The short articles address the current developmental paradigm, that is, in order to rationally develop and implement a vaccine, the following elements are required, that:

1. *The disease and pathogen are understood* – is the disease common? How is the pathogen transmitted? Is it a disease of the young or old? Is the pathogen identical? Is there a limited number of serotypes? **Lin-Fa Wang** will describe his and other group's work that identifies new viral pathogens and provide a brief review on the current strategies and future trend for rapid pathogen discovery.

2. *The immune response that prevents reinfection is understood* – a vaccine that must induce a specific antibody against a conformational antigen may need to be fundamentally different from a vaccine that must induce cytotoxic T cells (CTLs). **Stephen Kent** will discuss some of the immunological strategies that are being tested in novel HIV vaccines.

3. If specific antigens are to be used, *the antigen selected from the pathogen should be invariant, or where it is variant, there should be a limited number of circulating variants* – the days of developing new human 'bacterin'-type vaccines are behind us. Regulatory authorities are demanding highly pure, well-characterised products and commercial vaccine developers require patents to protect their substantial investments and it is often the vaccine antigen that provides for part of this protection. The antigen can either be isolated from the pathogen or, more likely, be produced by one of the many biotechnological processes including recombinant yeast fermentation, recombinant viruses or host (for example, egg)-adapted viruses. **Michael Good** will discuss how the variation in a key Streptococcal antigen has been overcome to yield a vaccine against rheumatic fever.

4 *The formulation of antigen is developed such that the desired response is elicited* – the role of adjuvants is critical in this aspect of the paradigm if the vaccine does not comprise a live attenuated pathogen. Different adjuvants and formulations elicit different responses from CTL responses to high titre antibody levels from single-dose vaccines and vaccine developers have combined classical empiricism with a much deeper understanding of how adjuvants work to produce antigen-adjuvant combinations that elicit specific and durable responses. **Martin Pearse** will discuss recent developments in adjuvant biology. **Tony Cunningham** will relate the chequered experience of herpes simplex virus vaccination to date.

5. *The vaccine is tested for safety, and then efficacy under field conditions* – the size of efficacy trials will depend on the frequency of disease. Some of the rotavirus efficacy trials required more than 50,000 participants. **Cameron Simmons** will discuss the progress through clinical trials of the new dengue virus vaccine and **Robin Anders** will discuss progress towards developing effective malaria vaccines.

6. *The vaccine is implemented because governments or other sponsors have the necessary infrastructure and financial resources to pay for implementation* – vaccines may be proven in clinical studies, may be known to prevent disease and save lives but their implementation will depend on financing. For vaccines to provide herd immunity, an appropriate percentage of the population must be vaccinated to keep the reproductive number less than one (that is, Ro<1). The level of coverage required is often beyond that which occurs when individuals elect to pay to receive a vaccine. Most developed countries have well-established vaccine programs; these are typically absent in poorer developing countries requiring support from foreign governments or philanthropy. **Glenn Browning** will examine the mechanisms for increasing the use of veterinary vaccines and **Marshall Lightowlers** will discuss the resourcing of new vaccines that address important zoonoses. **Ian Gust** will examine how the development of 'orphan vaccines' can be supported, that is, those vaccines for which the commercial returns do not justify the development costs and risks.

With smallpox and polio, vaccine use has been integral to global or geographical eradication of the pathogen and the same may well be true, in time, for diphtheria and Hib, and possibly typhoid fever. The disappearance of many infectious scourges of humankind has coincided with a mounting pressure against ongoing widespread vaccination, and the appearance of anti-vaccination lobby groups that have a significant internet presence. It is important that the arguments brought forward by these groups are challenged with careful, logical responses to ensure that the vaccine barrier that protects human populations is not weakened.

References

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Biography

Dick Strugnell is Professor of Microbiology at the University of Melbourne. He has spent 30 years researching the immune responses induced by bacteria and how immune responses can be used to prevent bacterial infections through vaccination. Most of these studies have been conducted in animal models of infection. His interest in the rational, commercial development of vaccines grew from working at Wellcome Biotech in the UK, and from his time as Deputy Director of the CRC for Vaccine Technology, where he worked with Anne Kelso to establish VacTX Pty Ltd, a spin-off company of the CRC-VT. Dick is supported by NHMRC Program and Project Grants and pursues interests in the molecular microbiology of *Klebsiella pneumoniae* (with Trevor Lithgow, Monash University) and particularly the immunobiology of *Salmonella* Typhimurium (with Sammy Bedoui and Odilia Wijburg, University of Melbourne).