In a perfect world, a vaccine would rapidly provide life-long, robust immunity against a disease after a single dose with minimal side effects. Currently available vaccines fall short of this goal – stimulating the pursuit of various technological approaches towards creating ideal vaccines.

By Kevin P Killeen and Ronald W Ellis at AVANT Immunotherapeutics

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removal of virulence genes from development of live attenuated vaccines involves the
revert to pathogenicity, ironically causing the symptoms
Moreover, because a live vaccine can replicate, it could
attenuating a live vaccine microorganism sufficiently to
disease. Many live vaccines can elicit a long-lasting
attenuating a live vaccine microorganism sufficiently to
reversal of these live vaccine candidates. This has
anterior and typhoid fever (currently in clinical
delivery systems. VLPs mimic viral structures and can
release slowly over time or in a pulsatile fashion, allowing
formulations can be used to create vaccines that are
in a way that stimulates mucosal immunity. Certain
formulations can be used to create vaccines that are
released slowly over time or in a pulsatile fashion, allowing
vaccine potentially to be administered in a single dose.

SUBUNIT, INACTIVATED VACCINES
Killed and recombinant subunit vaccines are generally well
tolerated and provide another layer of safety in that they
cannot replicate in the host. Such vaccines are usually
more technologically feasible to produce, especially given
the broad range of technical approaches including whole-
pathogen vaccines, protein or peptide subunit vaccines,
and carbohydrate and polysaccharide-based vaccines.

The disadvantage of inactivated or subunit vaccines is
that their immunogenicity usually requires enhancement
via adjuvants and/or antigen delivery systems in order to
stimulate protective immune responses. Moreover,
multiple doses or ‘boosters’ are also required to confer long-term protection.

DNA VACCINES
The idea behind DNA vaccine technology is that human
cells taking up DNA encoding a vaccine antigen(s) would
secret or express those antigens on the cell surface in a
way that would trigger an immune response. Initial
strategies involved the injection of a solution of naked
DNA encoding a vaccine antigen. While DNA vaccines
have been clinically evaluated for infectious disease targets,
their ability to elicit specific antibodies has been sporadic
and limited, often requiring a traditional antigen-based
vaccine to ‘boost’ the DNA prime. Thus, DNA delivery
technologies have not yet achieved effective vaccination.

DELIVERY SYSTEMS AND ROUTES OF ADMINISTRATION
Delivery systems can mediate activities that increase
vaccine effectiveness. They can enhance in vivo vaccine
stability and facilitate the efficient presentation of vaccines
in a way that stimulates mucosal immunity. Certain
formulations can be used to create vaccines that are
released slowly over time or in a pulsatile fashion, allowing
the vaccine potentially to be administered in a single dose.

A promising approach is the use of virus-like particles
(VLPs), which possess potential advantages over other
delivery systems. VLPs mimic viral structures and can
efficiently induce both antibody and cellular immunity.
They are non-replicating and well tolerated, and have
shown to be effective when administered
parenterally and mucosally. Moreover, VLPs can be
produced in a variety of expression systems, including
bacteria and yeast as well as cell culture. A second-
generation use of VLPs is as a ‘carrier’ – displaying
antigens from viral or bacterial pathogens on the VLP
surface, resulting in a highly pronounced antigenic
display and consequent enhancement of the immune
response to the foreign antigen.
Several technologies are under development for delivering vaccines by routes other than injection. An oral, killed cholera vaccine has been commercialised, and some live bacterial vectors can be administered orally. A live intranasal influenza vaccine has been licensed, although its utilisation to date has been limited. An inactivated influenza vaccine was also developed for intranasal administration; however, its use was discontinued due to reports of serious adverse events, likely related to the adjuvant used in its formulation. Further, vaccine patch technology – which delivers the vaccine transcutaneously – awaits clinical proof-of-principle.

**VACCINE MANUFACTURING ISSUES**

In addition to being safe, effective and user-friendly, an ideal vaccine should be practical and cost-effective to scale up and manufacture. The challenges inherent in vaccine manufacture are well-illustrated by efforts to improve the production of influenza vaccines. For 60 years, influenza vaccine has been made by growing virus in embryonated chicken eggs, which is time-consuming and labour-intensive, involving millions of eggs and long lead-times for vaccine production. Efforts to produce vaccine for each year’s flu season are constrained to three flu strains and must be commenced one year in advance, increasing the risk that the vaccine made will not protect against the viral strains in circulation upon immunisation.

Cell culture manufacture and DNA vaccine approaches may provide faster and more easily scaled-up alternatives to influenza vaccine production in eggs. Moreover, the use of reverse genetics – whereby RNA from circulating virus is reverse-transcribed into DNA, which is then used instead of live virus to transfect cell cultures to generate vaccine – has the potential to reduce the time lag between the identification of circulating viral strains and the availability of an appropriately protecting vaccine. To date, however, adoption of these strategies has been challenging. Converting to cell-culture production methods requires a high capital investment with accompanying higher cost of goods and no clear clinical advantage, and reverse genetics has not yet been widely implemented.

**NEW OPPORTUNITIES FOR VACCINES**

Traditionally, vaccines have been used mostly to protect against viral and bacterial diseases. However, thanks to scientific advances in immunology and other areas, new vaccine development efforts are tackling a variety of diseases never before thought amenable by vaccination. These include chronic illnesses such as Alzheimer’s disease, autoimmune diseases like multiple sclerosis, atherosclerosis and cholesterol management. Vaccine approaches are also in development against addictions to drugs such as cocaine and nicotine. New technologies also may improve allergy vaccines, which now require many doses and have limited effectiveness. Moreover, there is a growing realisation that vaccines offer opportunities to prevent not only acute disease but also the long-term sequellae of chronic infection.

Significant progress has already been made in the development of vaccines to prevent certain cancers, as illustrated by hepatitis B vaccines, first approved 20 years ago to prevent infection that can progress to liver cancer, and the recently approved HPV vaccine to prevent the leading cause of cervical cancer. Therapeutic vaccines are also in advanced stages of clinical development for major cancers including melanoma, prostate and breast.

**REGULATORY CHALLENGES**

Challenges remain with respect to the exorbitant costs of and regulatory hurdles to vaccine approval and commercialisation. The US FDA has demanded huge studies to address some vaccine safety issues to their satisfaction, as illustrated by the ~70,000-patient Phase 3 trials conducted for the rotavirus vaccines Rotarix® and RotaTeq®. This presents particular challenges to vaccine developers’ ability to bring certain products to the US, where there may be only a relatively small market compared with the rest of the world. Including R&D costs, manufacture and clinical trials, a failed Phase 3 trial can cost hundreds of millions of dollars with the vaccine candidate having never reached the marketplace. Thus, the FDA is considering how such vaccine products might be licensed without imposing regulatory burdens and prohibitive costs that could influence developers to avoid the US market due to daunting development and clinical costs. Similarly, current debates over the regulation of biogeneric/biosimilar products affect vaccines as well as therapeutic biologics.

**CONCLUSION**

There is no single perfect solution or technology platform on which all vaccines of the future should be based, but rather an increasing portfolio of technologies and approaches that can be blended to respond to specific vaccine needs. The opportunities and pay-off for successful vaccine development are clearly very large – and they should continue to grow in the coming years, particularly as increased causalities become understood between certain infectious diseases and long-term chronic illnesses.

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