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The unconventional side of vaccines

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The unconventional side of vaccines

Guest Column

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When we talk about vaccines, most people think of an injection to prevent childhood infectious disease. However, in recent years the uses to which vaccines are being put has expanded dramatically. Hence, vaccines that are currently in development, target prevention or treatment of a wide range of non-

infectious diseases, including allergy, diabetes, high blood pressure, heart disease, asthma, obesity, Alzheimer's disease and cancer.

At the novelty end of the spectrum, vaccines are being developed to treat conditions such as smoking and drug addiction. With these new vaccine applications, have come new challenges, such as how to break self-tolerance and how to induce immune responses against non-protein small molecules? Our Adelaide-based company, Vaxine, has been at the forefront of this revolution in non-traditional vaccine development, with current programs encompassing cancer, allergy, diabetes and Alzheimer's vaccines, in addition to a large array of more traditional infectious disease vaccines.

All vaccine function by the administration of a target substance called an antigen, which is typically a protein but can also be a sugar or a lipid. These antigen then trigger an immune response against itself resulting in the production of antibodies that bind the antigen and remove it from the body. Vaccine antigens can also activate T lymphocytes (T cells), which then are able to attack any cells that are expressing the antigen on their surface.

While the immune system has primarily evolved to attack and neutralize invading pathogens, this does not mean that it cannot respond against other molecules including those derived from our own tissues. This is the basis of cancer vaccines, which typically involve injection of antigens expressed by the tumour, together with an immune potentiator called an adjuvant, to try and trigger an immune response against the cancer.

To be successful a cancer vaccine must break self-tolerance, some thing that is hard to do as the body normally tries to avoid responding against itself in order to avoid autoimmune disease. To get around this problem cancer vaccines typically include a powerful inflammatory adjuvant that drives the immune system to respond to the antigen even although it may represent self. Another technique for administering cancer vaccines is to incubate the relevant antigen with dendritic cells in vitro, to allow uptake of the antigen and then injecting the antigen-labeled cells back into the patient. This is the basis of Provenge, currently the only approved human cancer vaccine that was developed by Dendreon, for treatment of patients with prostrate cancer.

For Provenge the patients' blood cells are incubated with a fusion protein (PA2024) consisting of two parts, the antigen prostatic acid phosphatase which is present in 95 percent of prostate cancer cells, and an immune signaling factor GM-CSF as an adjuvant. The fact that Provenge is the only approved therapeutic cancer vaccine out of hundreds that have been tested in clinical trials shows just how hard the cancer vaccine field is. However, a large amount of knowledge has been accrued over the years about the mode of action of cancer vaccines and hence it might be predicted that more effective cancer vaccines will evolve over time and hence this remains an exciting and promising area of unconventional vaccine development.

Another promising area of unconventional vaccine development is allergy. In the US, approximately 20 percent of the population or 65 million people have an allergy. Allergy to grasses represent close to 50 percent of all allergies, with allergies to animals representing around 30 percent and food allergies comprising of 10 percent. Allergy desensitization therapy involves administration of progressively higher doses of allergen with the subject requiring lifelong boosters.

Recent attempts have been made to simplify desensitization to just a short course of two-to-three vaccinations using an adjuvant to induce long-term immunity. Our company, Vaxine, is developing a promising allergy vaccine against life threatening anaphylaxis from insect sting allergies, incorporating the proprietary delta inulin adjuvant, Advax, with promising results in an ongoing human clinical trial of bee venom allergy.

Allergy Therapeutics has developed a vaccine called Pollinex Quattro, based on MPLA, for the treatment of ragweed allergy. Cytos Biotechnology has developed CYT003-QbG10, an allergen-independent immunodrug, which in phase I clinical trials in allergic asthma and rhino-conjunctivitis was well tolerated and is now in phase II clinical development for allergic asthma. CYT003 comprises the virus-like particle Qb, filled with a synthetically produced bacterial DNA that activates the immune system via TLR9. Overall, the application of new delivery and adjuvant technologies to allergy vaccines represents a relatively low-risk, high-return, approach within the unconventional vaccine area.

Considerable effort has also gone into developing vaccines that protect against Alzheimer's disease. The first vaccine against Alzheimer's disease was Elan Pharmaceuticals' AN-1792 vaccine, which successfully reversed amyloid-Î² deposits and memory loss in transgenic mice. But in humans, AN-1792 was somewhat of a disaster with Elan having to halt a large clinical trial after some patients developed meningo-encephalitis. A phase II trial of bapineuzumab, Elan's passive anti-amyloid-Î² antibody infusion showed little clinical benefit and at high doses caused brain swelling and associated microbleeds in some patients.

Despite all these setbacks the immense potential value of the Alzheimer's disease market keeps bringing new players into this arena. For example, Cytos is developing CAD106, Austria-based AFFiRiS has a vaccine called AD02 based on their Affitome technology, which uses a pool of peptides, and researchers from Karolinska Institute in Sweden recently showed their CAD10 amyloid-Î² vaccine induced antibodies in 74 percent of subjects aged between 50-to-80 years. Hence, despite the setbacks, progress is being made and a vaccine against Alzheimer's may emerge soon.

Parkinson's disease is another incurable disorder that affects the brain and the nervous system, leading to problems with movement and cognition. AFFiRiS has just begun clinical testing of a therapeutic vaccine to treat Parkinson's disease. The vaccine known as PD01A, uses Affiris' Affitome technology, which uses a pool of peptides that mimic the alpha-synuclein and thereby induces antibodies against alpha-synuclein mutant forms that clump together in the brain of patients.

Several vaccines are in development against autoimmune diseases, such as multiple sclerosis (MS) and rheumatoid arthritis. Opexa Therapeutics is developing Tcelna, as a personalized MS therapy. Tcelna is manufactured using ImmPath, Opexa's proprietary method to induce T-cells against selected peptides from myelin basic protein, myelin oligodendrocyte glycoprotein and proteolipid protein. Cytos is developing a vaccine for therapy of rheumatoid arthritis, which induces neutralizing antibodies against the inflammatory mediator, TNF-alpha.

A range of vaccines have been developed for prevention of type 1 diabetes (T1D). Diamyd Medical reported phase II success with their alum-adjuvanted glutamic acid decarboxylase vaccine, Diamyd, but stumbled when a larger Phase III study did not meet the primary efficacy endpoint of preserving beta cell function. A phase II study, DiAPREV-IT, of Diamyd in children at risk of developing T1D is ongoing. A long running study in Melbourne, Australia, of nasal insulin for T1D prevention is struggling with recruitment, showing how tough T1D clinical studies can be. Several immunoregulatory vaccines have also been shown to protect against type 1 diabetes in animal models, including the approved live BCG vaccine (bacillus Calmette-Guerin) or work by our own group showing similar results can be achieved with the approved inactivated Q fever vaccine (Qvax).

Therapeutic vaccines against type 2 diabetes and/or obesity are also in development. Cytos's CYT013-IL1bQb, is designed to induce antibodies against interleukin (IL)-1. Cytos also developed CYT009-GhrQb, an obesity vaccine based on production of neutralizing antibodies to ghrelin, a peptide that enhances appetite and food intake, but failed to show efficacy in clinical studies. Braasch Biotech is attempting to develop an anti-obesity vaccine by immunizing with chimeric somatostatin proteins to induce neutralizing antibodies and thereby enhancing endogenous growth hormone and insulin-like growth factor 1.

Vaccines against atherosclerosis are also in development. AVANT Immunotherapeutics developed a vaccine that works by eliciting neutralizing antibodies to cholesteryl ester transfer (CETP) raising high density lipoprotein. AFFiRiS also has an atherosclerosis vaccine in pre-clinical development that induces antibodies against CETP.

Hypertension is another common chronic disease against which vaccines are being developed. Cytos has CYT006-AngQb, which induces an antibody response against angiotensin II, an important regulator of blood pressure. While clinical trials were successful, the effect was modest leaving this program in limbo.

Another area of research in vaccines is against drug addiction. Nabi Biopharmaceuticals has developed NicVAX that is currently in phase III clinical trials for nicotine addiction. Cytos' Nic-002 vaccine did not achieve its primary end point of smoking cessation. Celtic Pharma is developing TA-Nic, which is in phase I. Hence despite some early setbacks, research continues into anti-smoking vaccines.

The above descriptions are not meant to be exhaustive listing of unconventional vaccines in development, but rather are selected snapshots to demonstrate the extreme diversity of vaccines currently under development for non-infectious indications. Whilst activity remains strong, many late-stage clinical trial failures highlight that there is much that still needs to be known at the basic science level about induction of immune responses against unconventional antigens.

We are excited by the fact that our own proprietary vaccine enhancement platform known as Advax, shows great promise across a broad range of unconventional as well as conventional antigens. Hence we look to a future when vaccines will be used to treat a broad range of non-infectious as well as infectious diseases. The lessons learned during the development of unconventional vaccines may also help in the identification of new strategies to develop successful vaccines against the likes of HIV and chronic hepatitis B.