The simplex solution

Dr Sean Sullivan, Executive Director of Pharmaceutical Sciences at Vical Inc. discusses the progress of his research into the development of an innovative vaccine to treat the herpes simplex virus 2

Vaccinations begin on day 15 and a total of three intramuscular vaccinations are given two weeks apart. Swabs are taken the last 14 days and assayed for viral genomes by PCR to evaluate viral shedding. The vaccine combining plasmids expressing glycoprotein D (gD) and tegument proteins UL46 and UL47, and formulated with Vaxfectin® (Vical’s cationic lipid adjuvant), has shown a statistically significant reduction in viral lesion recurrence in several experiments. A reduced viral shedding has also been observed.

How accurately will these guinea pig models translate to human clinical studies?

Preclinical animal models are used for evaluating different vaccine prototypes, including various genes, adjuvants and delivery systems, as well as dosing schedules. A response to truncated gD glycoprotein adjuvanted with alum has been shown (by others) in both the guinea pig model and human clinical trials. Furthermore, plasmid DNA expressing gD was combined with tegument proteins that also contain T-cell epitopes recognised by circulating human T lymphocytes. The combination of the tegument protein plasmid DNA with the gD plasmid DNA showed significant suppression of viral recrudescence and shedding, thus demonstrating a proof of concept and warranting advancement to clinical development. The results from the guinea pig model serve to identify antigens and adjuvants for testing in human clinical trials.

What progress has Vical made in DNA vaccine development and manufacturing?

Vical is a vaccine development company with multiple product candidates in late-stage clinical trials. The most advanced is Allovectin®, a plasmid-based immunotherapeutic approach. Completion of a Phase 3 clinical trial for first-line treatment of Stage III and IV melanoma patients. Allovectin® showed promising results in overall response rate and survival endpoints in Phase 2, and has shown an excellent safety profile in several clinical trials.

Vical is developing TransVax™, a therapeutic vaccine against cytomegalovirus (CMV) for the transplant population. In CMV seropositive patients, reactivation occurs in approximately 60 per cent of hematopoietic stem cell transplant recipients. Despite the use of pre-emptive antiviral therapy, CMV reactivation can lead to CMV disease and mortality and the treatment itself is relatively toxic in this setting. A Phase 2 clinical trial demonstrated statistically significant reduction across a range of CMV viral load endpoints, and we are currently applying those results to the design of a Phase 3 trial expected to begin by year-end 2011.

Vical is developing a separate vaccine designed to prevent CMV infection in women of childbearing age. CMV infection during pregnancy can result in viral transmission to the unborn child, which often causes deafness or mental retardation. A Phase 1 clinical protocol has been approved by the FDA.

Vical has also conducted several Phase 1 clinical trials for pandemic influenza vaccines – two for avian influenza (H5N1) and one for swine influenza (H1N1) to demonstrate the speed of development with plasmid DNA vaccines and advance the technology platform for future emerging disease outbreaks. These also were the first clinical trials showing safety and immunogenicity with Vaxfectin® formulated plasmid DNA.

Vical’s plasmid DNA manufacturing process has improved through experience in cGMP production of Phase 1, 2, and 3 clinical lots for Vical’s programmes and others such as NIH (HIV, West Nile virus, and Ebola virus) and the Naval Medical Research Center (dengue virus, and malaria). Vical’s current facility has sufficient capacity for the commercial launch of its two lead products, Allovectin® and TransVax™.
A cure for herpes?

Current estimates show that, on average, 500,000 new cases of herpes are recorded in the U.S. each year, and this figure could be as high as 2 million. With no effective vaccination yet available, an innovative response is required.

**HERPES SIMPLEX VIRUS 2 (HSV-2)** is a highly infectious virus that produces genital herpes. In the developed world, roughly one in five adults is infected with HSV-2; however, the prevalence of this virus is even greater in developing nations. It is believed that 80 per cent of those with the virus are asymptomatic but possibly contagious, but 20 per cent will develop genital lesions. This is due to the neuroinvasive nature of the HSV-2, which persists in the body by becoming latent and hiding from the immune system in the cell bodies of nerves. In many cases, the infection can lay dormant for long periods after the initial infection, before occurring in sporadic episodes of viral outbreaks. In these outbreaks, the virus in a nerve cell becomes active and is transported via the nerve’s axon to the skin, where virus replication and shedding occur, producing new sores and lesions. This shedding could be responsible for causing as many as 70 per cent of new cases.

**VACCINATION SHORTFALLS**

To date, no viable vaccination has been produced on a clinical scale. However, antiviral treatments have been shown to have some effect on reducing asymptomatic shedding, reducing the likelihood of shedding occurrence by as much as 10 per cent.

Herpes vaccination programmes have been limited by the broad-based immune response that they can produce, making it particularly difficult to achieve a reliable equilibrium of safety and immunogenicity in humans. This has been further exacerbated by the recent discovery that the strategy of neutralising antibodies – the primary approach used to date – is insufficient for the development of prophylactic vaccinations.

Dr Sean Sullivan is at the vanguard of a new effort to develop therapeutic vaccinations to prevent the recurrence of viral lesions and shedding in HSV-2 infected patients. He and his colleagues at Vical Inc. have adopted a new methodology using proprietary plasmid DNA vaccine technology, which they hope will overcome the obstacles experienced in HSV-2 vaccination development programmes in the past.

**INNOVATIVE SOLUTION**

This approach requires the expression of a viral antigen from plasmid DNA to be administered directly into the muscles or skin of the patient, which Sullivan believes offers several advantages: “Intramuscular or intradermal administration of plasmid DNA alone can produce an immune response. This can be further increased by formulating the plasmid DNA with an adjuvant, such as Vical’s proprietary cationic lipid system, Vaxfectin®”.

This approach also offers a number of other considerable advantages over the HSV-2 vaccine studies to date, as manufacturing is simplified and independent of the antigen, meaning that more than one antigen can be included in the vaccine. This can be achieved by combining multiple antigen-expressing plasmid DNAs into a single formulation, which increases its scope for application and may minimise resistance. Furthermore, unlike manufactured protein antigens, which can become denatured during the manufacturing process, the protein expressed in the patient’s body can retain its native configuration, dramatically increasing the likelihood of neutralising antibody production – fundamental for addressing the development and spread of the virus. In addition, the production of antigens within the cells also leads to strong cellular immune responses.

Vical’s plasmid DNA vaccine technology has been specifically developed to focus on three areas to maximise the drugs’ success and efficacy. Firstly, they have sought to optimise the plasmid DNA expression system to ensure the greatest possible expression of protein antigen. Moreover, Sullivan and his colleagues have identified a novel adjuvant, Vaxfectin®, to enhance both humoral and cell-mediated immune responses to the expressed antigen. Finally, the researchers are working to further develop the manufacturing process that yields pharmaceutical grade plasmid DNA on a commercial scale, which would provide sufficient stocks for full-scale production, and which could also aid in cost reduction. Phase 1 clinical trials of other Vaxfectin®-formulated DNA vaccines, in conjunction with safety and toxicity studies have already shown Vaxfectin® to be a safe and well tolerated adjuvant, providing a basis for further studies.
Expressing the full length gD glycoprotein has the potential to produce not only strong neutralising antibody responses, but also T-cell responses against multiple T-cell epitopes.

A VICAL CONTRIBUTION

Vical is an independent organisation that specialises in the research and development of biopharmaceutical products for the prevention and treatment of prevalent serious or life-threatening diseases. They operate at the forefront of vaccine development through their patented DNA delivery technologies, and are currently seeking to utilise these to instigate a paradigm shift in the production and delivery of DNA vaccines and cancer immunotherapies.

THE FUTURE

The progress made on the vaccine to date has been very promising, and Sullivan and his colleagues are looking to build upon this success in the near future. The next stage is to complete the assembly of a preclinical data package, before submitting an investigational new drug application for a Phase 1 trial, which will take between 12 to 18 months. While there is always uncertainty about the development and clinical testing of new drugs, Sullivan is hopeful that his approach will yield results: “A timeline for deployment of a global vaccine is difficult to predict. Vical’s advantage in developing a therapeutic vaccine is that the clinical proof of concept should be more rapid and the size of the clinical trials for a therapeutic vaccine should be somewhat smaller than those conducted to date for prophylaxis”.

HSV-2 glycoprotein D (gD) vaccine showed modest decreases in lesion recurrence in infected individuals,” explains Sullivan. “Expressing the full length gD glycoprotein has the potential to produce not only strong neutralising antibody responses, but also T-cell responses against multiple T-cell epitopes.”

Analysis of circulating T-cells from HSV-2 infected patients has already identified multiple T-cell epitopes for HSV-2 tegument proteins. Subsequently, preclinical results have shown that the combination of plasmid DNA expressing tegument proteins, such as UL46 and UL47 – which are responsible for cell replication and evasion of immune response – with the gD glycoprotein, can help to suppress viral recurrence.

This offers genuine hope for the estimate 500 million people living with HSV-2 worldwide at present. Furthermore, it is hoped that any successes in this field will also transfer to the less prevalent and less severe HSV-1 strain of the virus. While a definitive and applicable vaccine is still some way off, this is genuinely promising and exciting research.