Phase I clinical trial for prostate cancer vaccine

Medarex, Inc. (NJ, USA) and Cell Genesys, Inc. (CA, USA) have announced the initiation of a Phase I clinical trial for a candidate prostate cancer vaccine developed in 2003. During the clinical trial, patients with advanced prostate cancer will receive Cell Genesys’ GVAX® prostate cancer vaccine, in combination with Medarex’ human anti-CTLA-4 antibody, M DX-010. The study will be conducted by Winald Gerritsen from the University Hospital Vrije Universiteit Cancer Center (Amsterdam, The Netherlands).

The GVAX cancer vaccine is currently undergoing Phase III clinical trials for advanced prostate cancer and is also undergoing separate trials for use against a multitude of other cancers including melanoma, leukemia, pancreatic and lung cancer. The vaccine, comprised of genetically modified tumor cells, acts by stimulating an immune response against the tumor via the secretion of granulocyte-macrophage colony-stimulating factor. MDX-010 targets the immunosuppressing CTLA-4, a molecule found on the surface of T-cells, and subsequently acts to upregulate the immune response to cancer and other diseases.

The combination trial will involve approximately 45 patients with metastatic hormone-refractory prostate cancer. The study aims to assess the safety of the vaccine and determine the maximum tolerated dose, as well as the time to disease progression and overall survival of the patients.

The combination vaccine has demonstrated positive antitumor effects in previous Phase I clinical trials for ovarian cancer and melanoma, which were published in the Proceedings of the National Academy of Sciences in April 2003, and were also presented at the American Society of Clinical Oncology meeting in June 2004. In addition, preclinical analysis of animal models demonstrated that MDX-010 antibody therapy, followed by the GVAX vaccine, increased the levels of antitumor response.

Gerritsen discussed his optimism for the forthcoming trial, “The results of clinical trials to date for GVAX prostate cancer vaccine as a single agent and MDX-010 in combination with other vaccines have been encouraging, and we look forward to exploring the potential of this combination therapy in patients with prostate cancer.”

Joseph Vallner, President and CEO of Cell Genesys commented, “Previous studies in animal tumor models showed synergy for this combination of cancer vaccine and antibody therapy that we believe could potentially lead to increased antitumor activity in prostate cancer in human patients.”

Melanoma vaccine induces cancer-specific immunity

A recent paper published in the Proceedings of the National Academy of Sciences USA, reports the success of clinical trials for a therapeutic cancer vaccine being co-developed by the Ludwig Institute for Cancer Research (Melbourne, Australia) and the Australian biotechnology company CSL Ltd (Victoria, Australia). Results demonstrated that the vaccine was capable of inducing a comprehensive immune response in patients and appeared to delay cancer recurrence.

Jonathan Cebon, Head of the Joint Austin Health/Ludwig Institute Oncology Unit is excited about the results, “They show that it is possible to stimulate an integrated immune response that has the potential to attack cancer from a number of different angles. Being able to get antibodies, together with both types of T-cells, gives us enormous confidence that we are heading in the right direction to develop a clinically effective therapy.”

The study, which took place at the Austin Hospital and the Peter Mccallum Cancer Center in Melbourne, involved 46 melanoma patients, who had already undergone surgery for removal of the tumor mass. The researchers administered three monthly doses of the NY-ESO-1/ISCOMATRIX™ vaccine, which combines a cancer-specific protein, the NY-ESO-1 antigen, with an immune stimulant, the ISCOMATRIX adjuvant, from CSL Ltd. The results of the study demonstrated that the NY-ESO-1/ISCOMATRIX vaccine induced an immune response resulting in the production of CD4 and CD8 T-cells and antibodies to target the cancer-specific NY-ESO-1 antigen. Researchers also found that those patients immunized with the vaccine containing the NY-ESO-1 protein alone, had a weaker immune response compared with those who received the vaccine complex.

An additional finding was that the vaccine appeared to delay the recurrence of cancer. Out of 19 patients, 14 remained cancer free for 2 years after receiving the vaccine. In contrast, of the seven patients who received the placebo, five suffered a recurrence of cancer. The rate of recurrence was also higher in the group of patients who received parts of the vaccine complex compared with those who received the full NY-ESO-1/ISCOMATRIX vaccine. Cebon and colleagues suggest this is due to the protection conferred by the vaccine, “Experience tells us that relapse within the next 5 years is quite likely in this patient group. So we had a unique opportunity to gather preliminary data on the vaccine’s effect by comparing, over a relatively long period of time, the progress of the group that received the vaccine with the progress of the group that did not.”

Ian Davis, who led the researchers, warns that although the results are exciting, they must not be taken out of context.
context. Davis explains that the study was a retrospective analysis, and therefore, is likely to be less accurate than a prospective study. "In interpreting these data, we need to be mindful that there may be unforeseen variables that we didn't control for when we set up the trial. And of course this is a small number of patients."

Larger, randomized trials of the vaccine in advanced metastatic melanoma will now be carried out by The Cancer Vaccine Collaborative (CVC). The Phase II study planned for 2005, will take place at clinical trial centers in Australia, New Zealand and the U.K. These further studies are aiming to determine whether the vaccine is effective at producing a significant immunologic and clinical response against the cancer-specific antigen, and whether it can prevent recurrence of the disease.

Early results for streptococcal vaccine encouraging

Preliminary results for a streptococcal vaccine suggest that the candidate is effective in protection against streptococcal infections. If this proves to be true, then it will be a significant advance in the history of vaccine development, as streptococcal group A infections and the associated complications are a global health problem.

Recruitment for the Phase I trial of the vaccine took place in Baltimore (MD, USA) between October 1999 and February 2003. The study, published in a recent issue of the JAMA, was led by Karen Kotloff, University of Maryland School of Medicine (MD, USA) and involved 28 adult subjects between 18 and 50 years of age. The subjects were divided into three groups, and each individual received three intramuscular injections of either 50 µg (n = 8), 100 µg (n = 10) or 200 µg (n = 10) of group A streptococcal vaccine formulated with aluminum hydroxide.

Kotloff and colleagues summarized the results of their study, "Our findings, albeit in a small number of participants, suggest that in the full dose-range tested, the vaccine appears safe and well-tolerated and does not evoke antibodies that cross react with human tissue. We have identified a dose [200 µg] and schedule [0, 28 and 112 days] that appears to be capable of inducing immune responses that are likely to confer protection against multiple group A streptococcal M types."

First round immunizations for Phase II/III hepatitis B vaccine trial complete

The first stage of the Phase II/III clinical trials for a hepatitis B virus (HBV) prophylactic vaccine has been completed. All candidates have now been recruited to the double-blind study, which is being conducted at two study centers in Singapore and the first round of immunizations has been initiated. The study aims to compare the newly developed Dynavax Technologies' (CA, USA) HBV vaccine candidate with GlaxoSmithKline's currently available HBV vaccine, Engerix-B®. This new candidate HBV vaccine is based on the use of immunostimulatory sequences (ISSs), which are short DNA sequences that upregulate the immune response against disease and inflammation. The study is being conducted by Lim Seng Ge (National University Hospital, Singapore) and Chow Wan Cheng (Singapore General Hospital, Singapore) whose primary aim will be to determine the level of immunity conferred after the full dosing schedule has been completed. Results from a Phase II trial for Dynavax's hepatitis B prophylactic vaccine in young adults have previously demonstrated that it produced a more rapid antibody response with fewer injections compared with Engerix-B.

The 94 subjects participating in the forthcoming study are between 40 and 70 years of age and have not previously been immunized against HBV. The participants will receive three injections over a 6-month period and researchers will measure antibody levels 1 month after each injection to establish whether the vaccine has induced an immune response. The third and final injection is scheduled to be administered in early 2005, when the first interim data are expected to be released.

Dino Dina, President and CEO of Dynavax Technologies, said "If these data show that our HBV vaccine can provide superior protection against HBV infection for this sizeable segment of the population that historically respond poorly to currently marketed vaccines, we will initiate in the first half of 2005 Phase III studies that would confirm this efficacy on a larger scale. In parallel, we will test this vaccine more broadly in young adults and adolescents."

There are an estimated 350 million carriers of hepatitis B infection worldwide and therefore spread of the disease is a major cause for concern. The quest to develop an effective vaccine to protect against hepatitis caused by the virus is of paramount importance, especially in areas with large numbers of chronically infected people.

Currently approved HBV vaccines are capable of providing protection to approximately 95% of healthy adults, however, this immunity is only conferred if the full dosing schedule, comprising three inoculations, is completed. The US Centers for Disease Control and Prevention (CDC) estimate that only 53% of those who receive the first dose return for the second inoculation and only 30% of those receive the third dose, which dramatically reduces the effectiveness of the vaccine. Global annual sales of the HBV vaccines exceeded $1 billion in 2001, providing a significant financial incentive to develop a new, more effective vaccine.
**FluBlOk™ trial update**

FluBlOk™ is a recombinant influenza vaccine being developed by Protein Sciences Corp. (CT, USA). The vaccine contains three hemagglutinin proteins corresponding to the influenza virus strains selected by the World Health Organization (WHO) each year. FluBlOk is a genetically engineered vaccine produced in insect cells. Baculoviruses are injected into reactors that contain the insect cells and the viruses program the cells to produce the proteins from each of the three strains of influenza that are going to be included in the annual vaccination. These key proteins can then be extracted, purified and stored in buffered saline solution. The fact that no adjuvants or preservatives are used in the preparation of the vaccine is likely to account for the high tolerance and low incidence of adverse effects observed with FluBlOk.

Phase II trials of the vaccine were completed by October 2002, with crucial Phase III trials planned in the fall of 2004. Data from the Phase II trials demonstrated that the vaccine was well-tolerated and had fewer adverse affects associated with it than a licensed egg-derived vaccine containing the same antigens. The Phase IIb trial, conducted by The National Institute of Allergy and Infectious Diseases (NIAID), involved 399 elderly subjects. The results of the study, which was completed in November 2003, demonstrated that the new FluBlOk produced higher antibody titers than the 2003–2004 injectable vaccine. The optimal dose for the vaccine was also determined during the study, and 45 µg/antigen was selected as the dose to be used for future trials.

Dan Adams, president and CEO of Protein Sciences Corp., who presented some of the interim data at the Seventh Annual Conference on Vaccine Research said that 77 and 97% of patients who were inoculated with the two highest doses of FluBlOk had protective antibody titers. The clinical trials for this vaccine are expected to continue, with the company planning to launch the vaccine in preparation for the 2006–2007 flu season.

**Disappointing results for Kenyan AIDS vaccine trial**

Clinical trials for the first in a series of DNA vaccines specifically targeted against the most common strain of HIV in Kenya, subtype A, have produced poor results. This has previously been the most promising candidate in the struggle to develop a method of combating this disease. Unless subsequent data demonstrates dramatically improved responses, the International AIDS Vaccine Initiative (IAVI) says the study will have to be abandoned.

The vaccine was developed by researchers at the Medical Research Council Human Immunology Unit, University of Oxford (Oxford, UK) and the University of Nairobi (Kenya), specifically for use in Africa. The researchers developed the combination vaccine after observing that commercial sex workers in Nairobi have a natural resistance against HIV infection.

The preliminary results of the trials, launched in 2001, were presented at a conference in Lausanne, Switzerland in September 2004. The results demonstrated that of the 205 volunteers who received the vaccine, less than 20% produced an immune response. The IAVI requires 60% of the volunteers to elicit a significant immune response before they can consider the trials a success; the results obtained are therefore extremely disappointing.

Andrew McMichael, director of the Human Immunology Unit of the UK Medical Research Council said that he and his colleagues are still determined to continue to develop the vaccine, “With a project of this type you realistically have to expect to modify the vaccine as you go and that it might be a second- or third-generation vaccine which actually ends up being successful.” This is despite the negative approach taken by the IAVI, who say that despite the safety and tolerability of the vaccine demonstrated in the study, it has fallen far short of the expectations from preclinical studies. Chrispin Kambili, head of IAVI’s Kenyan office said, “Unless there are new immune response data that are dramatically different, IAVI will not develop the candidates further and will focus on its other research and development projects.”

The AIDS vaccine trial has cost more than $80 million to date and as results have been so disappointing, the IAVI has decided to abandon plans for further clinical trials in Rwanda and The Netherlands, as they do not feel that these studies would provide any new data. McMichael commented that if the IAVI withdraw funding from the project, his research team may seek other sources of financial support in order to continue the development of the vaccine.