

Human Vaccines: News

Successful combination: Existing drugs boost cancer vaccine responses

Vaccines against many types of cancers are in development and in clinical trials, some showing great promise. But there are still many obstacles along the way to success. Two recent studies have looked at ways to overcome these, focusing on combining experimental cancer vaccines with existing drugs.

Researchers from the Perelman School of Medicine and the Abramson Family Cancer Research Institute at the University of Pennsylvania (PA, USA) found that daclizumab improved the survival of breast cancer patients taking a cancer vaccine by 30%, compared to those patients not taking daclizumab. This proof-of-concept study was recently published in the journal *Science Translational Medicine*.¹

Daclizumab is a CD25-blocking monoclonal antibody, approved by the US Food and Drug Administration (FDA) for use in kidney transplantation. The antibody can deplete regulatory T cells (Tregs), an important population of white blood cells (WBCs) that help turn off the immune system when the system's job is done. Tumor cells can exploit Tregs, drawing them to the tumor area like a protective shell, thereby preventing other tumor-fighting WBCs from getting to the core of the tumor. Depleting Tregs with the help of daclizumab is believed to help restoring the immune system's ability to fight tumors.

Tregs rely on the protein IL-2 for much of their function. They interact with IL-2 via the CD25 receptor on their surface, which is the target of daclizumab. In the presence of daclizumab, Tregs are deprived of IL-2, because it blocks the CD25 receptor. The team found that the lack of IL-2 forces Tregs to convert into normal T cells that no longer surround the tumor,

which allows other tumor-fighting WBCs to get access to the tumor.

In a phase I trial, ten patients with metastatic breast cancer received daclizumab prior to treatment with an experimental breast cancer vaccine developed and produced at the University of Pennsylvania. There were no detectable side effects, and the T-cell conversion in the patients on daclizumab lasted two months. The tumors did not shrink, but the tumors stopped growing in six out of ten patients. Furthermore, daclizumab patients had an increased survival of about seven months compared to patients who received the cancer vaccine only.

According to Dr. Vonderheide from the University of Pennsylvania, senior author of the study, all previous attempts to eliminate Tregs have been toxic and short-lived, but the effects of daclizumab were observed to be rapid, prolonged, and consistent. He notes: "Although we tested our approach in patients with breast cancer, we know that Tregs can block the immune response against most human cancers."

In another recent study, an experimental cancer vaccine, known as L-BLP25 (Stimuvax) was tested in combination with the drug letrozole, a standard hormonal therapy against breast cancer. Researchers from the University of California Davis (CA, USA) found that combining the vaccine with letrozole significantly increased survival in mice. Study results were recently published in the journal *Clinical Cancer Research*.²

Stimuvax is in phase III trials for lung cancer. The vaccine specifically targets Mucin 1 glycoprotein (MUC1), an antigen that is expressed in an altered form on cancer cells.

When introduced to the body, Stimuvax elicits an immune response by T-cells, which then recognize and destroy the tumor cells.

In the mouse study, the animals were injected weekly with the vaccine or a placebo for eight weeks. In addition to the vaccine or placebo, some mice were treated with either letrozole or tamoxifen, commonly used hormonal therapies against breast cancer. Although both drugs have similar actions—namely, blocking the effects of estrogen, thereby slowing or stopping the growth of some breast cancer cells—the benefits of the vaccine were greater in the mice treated with letrozole.

"We found that the vaccine and the hormonal drug letrozole were more effective when given together," said Dr. Michael DeGregorio, UC Davis professor of hematology and oncology and principal investigator of the study. "This adds critical evidence that immunotherapy with vaccines, which has traditionally been used to prevent infectious diseases, is also a promising new approach to combating cancer."

According to the authors, the current mouse study is the first to demonstrate that a hormonal therapy combined with a vaccine provides additive antitumor activity and survival benefit. DeGregorio's group also will test the vaccine with other conventional therapies and determine optimal dosing. Clinical trials in patients with breast cancer are in the planning stages.

References

1. Rech AJ, et al. *Sci Transl Med* 2012; 4:134ra62.
2. Mehta NR, et al. *Clin Cancer Res* 2012; 18:2861-71.

Inovio's universal avian flu vaccine generates protective antibody responses in phase 1

The US-based company Inovio Pharmaceuticals (PA, USA) recently announced promising results from a phase 1 study of its universal SynCon avian influenza vaccine candidate. The vaccine generated protective hemagglutination inhibition (HAI) titres against six different unmatched strains of H5N1.

Inovio's novel SynCon vaccine design process creates a single consensus gene sequence from one or more selected antigens (e.g. HA, NA and NP) of multiple existing virus strains within each targeted influenza subtype. The vaccine based on one or more of these new gene sequences is designed to achieve

cross-strain or universal protection against the natural and frequent mutations of influenza strains. A universal influenza vaccine would be a great step forward from today's seasonal vaccines, which only provide protection against a few targeted virus strains predicted to be of concern in the next flu season. Sometimes the

vaccines fail to be protective because the predicted strain(s) changes as the next flu season emerges, or—of even greater concern—subtypes can reassort, which is the usual cause of pandemic flu outbreaks.

In the current phase 1 trial, 17 patients completed a full H5N1 immunization regimen consisting of two intramuscular vaccinations with a synthetic DNA vaccine encoding three flu antigens (HA, NA and NP) followed by two intradermal vaccinations of only the HA antigen using Inovio's novel skin electroporation device. Vaccination was well tolerated. Of vaccinated subjects, 100% and 89% demonstrated

high-titered binding HAI responses against the more common Clade 1 A/Vietnam/1203/04 and Clade 2 A/Indo/5/05 strains, respectively, demonstrating vaccine-specific immune activation. The vaccine's ability to generate protective HAI responses against six distinct H5N1 virus strains (Clades 0, 1, 2.1, 2.2, 2.3.2 and 2.3.4) was also tested. Eight of 17 study subjects (47%) had an HAI titer of $\geq 1:40$, and twelve of 17 (71%) had an HAI titer of $\geq 1:20$ against at least one of the tested H5N1 viruses. Two vaccinated subjects demonstrated an HAI titer $\geq 1:20$ against all six strains tested.

Dr. J. Joseph Kim, Inovio's president and CEO, said: "Our goal has been to develop a truly universal influenza vaccine capable of providing years of protection across subtypes and strains. The protective levels of antibody responses generated by our universal H5N1 vaccine against diverse unmatched strains of this dangerous subtype provides proof of principle for our SynCon universal flu program and our other antibody-based vaccine products. We are planning further development initiatives for this program and look forward to forthcoming data from INO-3510, our universal vaccine for the influenza H5N1 and H1N1."

Update on NewLink's HyperAcute cancer immunotherapy products

The company NewLink Genetics Corporation (IA, USA) recently presented updates on its cancer vaccines, HyperAcute Pancreas (algenpantucel-L) and HyperAcute Lung (tergenpumatumucel-L).

NewLink's HyperAcute cancer immunotherapy product candidates (i.e. HyperAcute Pancreas or HyperAcute Lung) are composed of irradiated, live, allogeneic human cancer cells modified to express the gene for alpha (1,3) galactosyl transferase (α -GT), an enzyme that is responsible for the incorporation of a non-human form of carbohydrate called alpha (1,3) galactosyl carbohydrates (α -gal). This exposure to α -gal stimulates the human immune system to attack and destroy the immunotherapy cells on which α -gal is present by activating complement, an important component of the immune system capable of cell destruction. After destruction, NewLink believes that the resulting cellular fragments bound by anti- α -gal antibodies are processed by the immune system to elicit an enhanced multifaceted immune response to tumor-associated antigens common to both the immunotherapy and the patient's tumor cells.

HyperAcute Pancreas is based on two allogeneic pancreatic cancer tumor cell lines modified to express the gene for α -GT. In a multicenter, open-label, dose-finding phase 2 trial in 70 patients, the use of HyperAcute Pancreas in addition to the standard-of-care (SOC) chemoradiotherapy was evaluated. The vaccine was given intradermally in up to twelve treatments

over six months, extended by six maintenance treatments over a further six months.

The 12-month overall survival (OS) rate was 86%, which is a 37% increase in survival compared to the predicted 12-month OS of 63% in SOC patients. Increases in OS at two and three years were 59% and 121%, respectively. The vaccine demonstrated good tolerability and a favorable safety profile.

Dr Jeffrey M. Hardacre, the study's Principal Investigator, from the University Hospitals Seidman Cancer Center and Case Western Reserve University, Cleveland, OH stated, "As a surgeon who regularly treats patients suffering from pancreatic cancer, and being accustomed to the dismal prognosis for these patients, I am highly encouraged with the exceptional overall survival data from this study." The vaccine is now in a pivotal phase 3 trial, which will involve up to 722 patients and will also be led by Dr. Hardacre.

The second HyperAcute product is a therapeutic cancer vaccine for the treatment of non-small cell lung cancer (NSCLC), made up of cells from three allogeneic lung tumor cell lines, again modified to express the gene for α -GT. Results from a phase 1B/2 study of HyperAcute Lung showed a direct correlation between immune response and survival in NSCLC patients. In addition, patient survival compared favorably to that seen in patients receiving other second-line chemotherapy agents, suggesting encouraging clinical benefit.

Seventeen patients were treated in the phase 1 part of the study, and 37 patients were treated in the phase 2 part. Patients had metastatic or recurrent NSCLC and had failed first-line chemotherapy. All phase 2 patients received an injection every two weeks for up to eight scheduled doses. Serum samples were collected before and after immunization and then at two-month follow-up visits. Twenty-eight of the phase 2 patients were evaluable for clinical response. Among these patients, median OS was 11 months. Eight patients (29%) demonstrated stable disease after 16 weeks of treatment, including one patient that initially progressed and later regressed, surviving over 40 months. Eighteen patients with pre-immunization and post-immunization serum samples were tested for elevations in interferon- γ response to drug. Eleven of these 18 responded with increased interferon- γ , and the overall survival of these patients was 22 months. The increase in overall survival of patients with increased interferon gamma compared to non-responders was statistically significant. HyperAcute Lung showed a good safety and tolerability profile.

"The overall survival data is particularly remarkable when compared to current standard-of-care, which primarily utilizes cytotoxic chemotherapy agents with their associated debilitating side effects," commented Dr Nick Vahanian, President, Chief Medical Officer at NewLink Genetics.

Ghana and Rwanda expand national immunization programs

Two African countries, Ghana and Rwanda, have recently introduced rotavirus vaccines to their national immunization programs in a bid to fight diarrheal infections caused by rotavirus, a significant cause of childhood mortality. Ghana also introduced the pneumococcal vaccine at the same time.

In Ghana, pneumonia and diarrheal diseases each account for approximately 10% of deaths in children under five years of age. At a ceremony in Accra (Ghana) in April 2012 marking the introduction of the two life-saving vaccines, Dr. Ernestina Naadu Mills, First Lady of Ghana, said: "I am happy to announce that vaccines against pneumonia will from today be available at all health centers and hospitals. Children will be given three doses of the vaccine at 6, 10 and 14 weeks of age. Also, rotavirus vaccines will be administered to children aged 6 and 10 weeks."

Many international guests attended the ceremony, such as GAVI CEO Dr. Seth Berkley, who said: "Ghana has taken the lead...it has taken a bold and courageous decision and today's simultaneous launch marks yet another ambitious and encouraging step to make life-saving

vaccines rapidly and efficiently available to children who need them wherever they may be born. The world is watching as Ghana has set an example for everyone else."

Over the past years, Ghana has made big progress in increasing immunization coverage, from 4% with just one antigen in 1985 to a national coverage of 90% with nine antigens in 2012.

In May Rwanda followed the example of Ghana and also expanded its national immunization program. Merck's live oral pentavalent rotavirus vaccine ROTATEQ will be routinely administered to all infants in Rwanda. The Government of Rwanda Ministry of Health expects that more than 100,000 children will receive the vaccine during 2012.

In Rwanda, diarrheal infections rank third among causes of death in children under 5 years of age. Nearly 22% of all Rwandan children between 6 and 11 months and 25% of children between 12 to 23 months suffer from diarrheal infections. Samples tested from October 2010 to March 2012 showed that nearly half of the infections were caused by rotavirus.

Dr Mark Feinberg, chief public health and science officer at Merck Vaccines, said: "Rwanda is committed to the vaccination of their children and their accomplishments to date have been impressive. Given the impact of rotavirus gastroenteritis in children, working to help reduce severe rotavirus disease represents a critically important public health goal and we're pleased to be able to work with the GAVI Alliance to make ROTATEQ available to Rwanda and other GAVI-eligible countries worldwide."

International organizations, such as the WHO, GAVI Alliance, the Gates Foundation and PATH, have recognized the importance of rotavirus vaccination. Since 2009 the Strategic Advisory Group of Experts, the principle advisory group to the WHO for vaccines and immunization, has recommended the inclusion of rotavirus vaccination in all national immunization programs. GAVI Alliance and other stakeholders are working to make rotavirus vaccines available in the poorest countries of the world.

News studies: Combining PROSTVAC with conventional cancer therapy

The therapeutic prostate cancer vaccine PROSTVAC is being tested in combination with other already available drugs. A phase 2 clinical trial evaluates the use of PROSTVAC in combination with Quadramet, a commercially available skeletal-targeted radiopharmaceutical. In another study, the effect combining PROSTVAC and flutamide, a standard hormone therapy for prostate cancer, will be tested.

According to the National Cancer Institute (NCI), one in six men will be diagnosed with prostate cancer in his lifetime. While the majority of prostate cancer patients are diagnosed with disease that has not spread beyond the prostate, between 30 and 40% of those patients will have disease progression within ten years after having received initial treatment as shown by a rise in prostate specific antigen (PSA) level. Patients in this instance who have a rising PSA level without evidence of disease spread on imaging tests are commonly treated with hormone therapy. Even with hormonal therapy, PSA levels can still rise.

The experimental vaccine PROSTVAC is a viral vector-based vaccine, modified to produce a PSA protein whose presence helps focus the body's immune response against the prostate tumor. The vaccine has shown promise in previous trials in patients with metastatic castration-resistant prostate cancer (mCRPC), and is also being investigated in combination with conventional cancer drugs.

Bavarian Nordic recently presented interim data from a phase 2 clinical trial of PROSTVAC combined with Quadramet (samarium-153 EDTMP, or Sm-153), conducted by the NCI. The multi-center trial is intended to randomize 68 patients to Sm-153 alone (Arm A) or with PROSTVAC (Arm B). Interim analysis suggests that the combination of PROSTVAC and Sm-153 in patients with mCRPC is well tolerated with similar toxicity profile to Sm-153 alone. The early indication of improved time-to-tumor progression (TTP) warrants continued study accrual.

"A randomized, placebo-controlled phase 2 study of PROSTVAC reported an 8.5-month

improvement in median overall survival in men with metastatic, castrate resistant prostate cancer. Based upon these encouraging results, we recently initiated our pivotal, global phase 3 clinical study, PROSPECT," stated Dr Anders Hedegaard, President & CEO of Bavarian Nordic. "To learn more about the potential usefulness of PROSTVAC in other settings, PROSTVAC is being studied by the National Cancer Institute in combination with Sm-153, and we are encouraged by these interim results," he added.

Another study has recently been launched to evaluate the effect of combining PROSTVAC with flutamide, a standard hormone therapy for prostate cancer. Investigators at the Cancer Institute of New Jersey (CINJ) and the NCI examine the potential of this combination for treating prostate cancer resistant to hormone therapy and not visible on imaging tests such as a CT scan and a bone scan. The effects will be compared to those seen in patients who are receiving hormone therapy alone. Patients will be randomly assigned to receive

the vaccine or no vaccine. Those assigned not to receive the vaccine originally will be given it at a later date if PSA levels are rising, as part of a crossover design.

Promising phase 1 data for the first “cross-kingdom” vaccine

The US company NovaDigm Therapeutics recently presented positive data for its NDV-3 vaccine program from a second phase 1 study. NDV-3 is being developed for the prevention and treatment of diseases caused by *Candida* and *Staphylococcus aureus*, including methicillin-resistant *S. aureus* (MRSA). A single dose of NDV-3 with or without alum adjuvant was safe, well-tolerated and induced strong antibody and T-cell immune responses.

The prophylactic vaccine candidate NDV-3 contains the recombinant *Candida* surface protein Als3, which is structurally similar to the microbial surface components recognizing adhesive matrix molecule adhesin, clumping factor, from *S. aureus*. Preclinical studies have shown that NDV-3 confers a high survival rate following a challenge with highly virulent doses of one of several species of *Candida* or against one of several strains of *S. aureus*, including methicillin-resistant *S. aureus* (MRSA). These data

provided the foundation for vaccine development against both *S. aureus* and *Candida*, which collectively cause 200,000 bloodstream infections resulting in 40-50 thousand deaths annually in the US alone.

The current double-blind, placebo-controlled phase 1 trial included 160 healthy adults, and evaluated the safety, tolerability and immunogenicity of a single dose of three different formulations and two routes of administration. A dose of the vaccine containing 300 µg of Als3 was administered intramuscularly with and without alum adjuvant to assess the impact of the adjuvant. In the third vaccinated group, a dose of NDV-3 containing 30 µg of Als3 was administered intradermally without alum adjuvant. The vaccine was safe and well tolerated in all three vaccine groups compared to the saline placebo group. All three vaccine groups showed increases in serum and vaginal IgG and IgA1 antibodies

by Day 7 following vaccination, which peaked at Day 14. The demonstration of vaginal antibody responses to NDV-3 may be important in preventing vaginal yeast infections caused by *Candida albicans*, which is the objective of a planned phase 2 efficacy study. The majority of subjects that received NDV-3 also demonstrated significant Als3-stimulated production of the T-cell cytokines IL-17A and IFN-γ between 7 and 14 days post-vaccination relative to subjects receiving placebo.

“The data from our second phase 1 study confirms positive results from our initial phase 1 study and shows that those receiving adjuvant-free NDV-3 had robust immune responses, as did those receiving NDV-3 with alum adjuvant,” said Dr. Timothy Cooke, CEO of NovaDigm. “These results position us to begin phase 2 efficacy studies with an optimized vaccine formulation and a Phase 1 safety database of 200 adults.”

First worldwide clinical study of a Parkinson disease vaccine

The worldwide first clinical trial for the development of a Parkinson Disease (PD) vaccine has recently been initiated in Vienna (Austria). The vaccine PD01A, developed by the Austrian company AFFiRIS, represents the first agent worldwide aiming at disease modification of PD rather than addressing symptomatic improvement only. The vaccine candidate is being tested in a phase 1 trial in about 30 PD patients. The primary endpoints of the trial are safety and tolerability.

Since the approval of L-DOPA some 50 years ago, any other therapeutic intervention for Parkinson followed the same concept: the substitution of the neurotransmitter dopamine. Accordingly, all medications for Parkinson so far can impact on the symptoms only, but none of them modify the course of disease. AFFiRIS candidate vaccine has the

potential to treat the cause of PD for the first time, and this potential prompted the US Michael J. Fox Foundation to generously support the development of PD01A with \$1.5 million. It is one of the few projects outside of the US considered worthy of support by the foundation.

Based on today's scientific understanding, PD is caused by deposits of pathological forms of the protein alpha-Synuclein (alpha-syn). A reduction of these aggregates is believed to have a beneficial impact on disease progression. PD01A is designed to do just that by training the immune system to generate antibodies directed against alpha-syn, to neutralize its toxic impact.

Based on the company's own patent positions, AFFiRIS develops tailor-made peptide vaccines for Alzheimer disease, atherosclerosis,

PD, hypertension and several other conditions. Alzheimer is the current lead indication.

Dr Frank Mattner, CSO of AFFiRIS, explains: “PD01A is based on our AFFITOME®-technology, which already identified our lead vaccine developments in the field of Alzheimer. This technology delivers not only a single vaccine for the treatment of a certain disease but a whole pool of product candidates with excellent safety profiles and exactly fine tuned specificities. Therefore, we apply our strategy of “clinical maturation,” meaning that we investigate several vaccines against a certain disease in clinical testing to ensure that the best vaccine for humans will be developed.”

Oral TB vaccine shows promise in phase 2 trial

Immunitor recently presented preliminary data from a phase 2 clinical trial of the oral *Mycobacterium vaccae* therapeutic vaccine V7 at the Keystone Symposium “Drug Resistance and Persistence in Tuberculosis,” which took place in May 2012 in Uganda. The vaccine has the potential to shorten current long-term complicated and often-toxic TB treatment regimens.

The placebo-controlled phase 2 trial (imm02) was conducted in Ukraine and included 106 patients with tuberculosis (TB), including individuals with re-treated TB, multidrug resistant (MDR) TB and TB with HIV co-infection. Participants of the study received a daily dose of heat-killed *Mycobacterium vaccae* as a pill. The V7 vaccine was found to be safe; no adverse effects or reactivation of TB were observed. Concurrent administration of low doses of *M. vaccae* with either first- or second-line TB drugs resulted in clearance of

M. tuberculosis in sputum smears of 78% of vaccinated patients, compared to only 19% in the control group. Sputum conversion occurred within only one month of treatment. No difference was seen when drug-sensitive, easy-to-treat TB was compared to treatment-failed TB, MDR-TB or HIV-TB. The proportion of converted patients and time to conversion were identical.

These preliminary study results support findings from a previous V7 trial in Argentina, published last year in the journal *Immunotherapy*.¹

“Remarkable anti-TB activity resulting from daily dosing with oral *M. vaccae* supports [an] earlier study in Argentina, which has been conducted in drug-sensitive TB patients. The goal of Immunitor was to confirm findings from the original developers of this vaccine and, in so doing, eventually develop an easy-to-administer TB vaccine that could potentially do both,

treat and prevent the disease. Our results indicate that conventional TB therapy can be shortened significantly and further investigation in a larger population is needed,” said Dr Dmytro Butov, the Principal Investigator of this study.

M. vaccae is the only TB vaccine that has been through phase 3 trials in the last 90 years. It is currently sold in China as an adjunct immunotherapy for TB by Anhui Longcom Biologic Pharmacy Co., Ltd. Except for the two oral vaccination studies in Argentina and Ukraine, all prior studies were based on injectable formulation. *M. vaccae* offers obvious advantages and potential for use in developing countries where TB and HIV are rampant: it is inexpensive, made from a readily available source, and can potentially be given orally.

Reference

1. Dlugovitzky D, et al. *Immunotherapy*. 2011; 3:57-68.