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Human Vaccines and Immunotherapeutics: News

DNA vaccine for T1D promising in the clinic

A novel approach to treating type 1 diabetes (T1D) was recently presented in the journal *Science Translational Medicine*.[1] An international team of scientists, led by Dr Lawrence Steinman of Stanford University, engineered and successfully tested a DNA vaccine in patients suffering from T1D.

T1D features an intense autoimmune response that destroys the β-cells in the pancreatic islets of Langerhans, the site where insulin is produced and released. This pathogenic response is in part mediated by CD8+ T cells against various islet cell antigens including proinsulin, the molecular precursor to insulin and islet-specific glucose-6-phosphatase catalytic subunit-related protein. These $CD8^+$ T cells have been detected in the blood and in the pancreatic islets of individuals with T1D. A therapy for T1D that targets the specific autoimmune response in this disease, while leaving the remainder of the immune system intact, has long been sought and would be a great improvement to the current therapeutic situation, where T1D patients require lifelong treatment with daily insulin injections.

The DNA vaccine tested in this study consists of a plasmid encoding proinsulin (BHT-3021). It was engineered to reduce the immunogenicity of the encoded proinsulin by substituting CpG hexameric motifs, which stimulate the innate immune response, with GpG hexameric nucleotide sequences, known to modulate innate immunity. The researchers hypothesized that "reverse vaccination" with BHT-3021 would preserve β-cell function in T1D patients through reduction of insulin-specific $CD8^+$ T cells.

The vaccine was tested in 80 adult T1D patients, who had been diagnosed with the disease within the past five years. They were randomized to receive weekly intramuscular injections of BHT-3021 or placebo for 12 weeks, and then monitored for safety and immune responses. Study results showed that vaccination could preserve β-cell function in T1D patients. Levels of C-peptide rose, a marker of β-cell function, while proinsulin-reactive $CD8^+$ T cells were reduced, with no effect on other antigen-specific T-cell responses. The DNA vaccine caused no serious side effects.

By targeting the root cause of T1D, reverse vaccination could potentially change the course of events that lead to severe disease, and the approach might also be helpful for treating other autoimmune diseases.

Reference

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HPV vaccines halved infections in US teenage girls

After Australia recently reported positive results from its human papilloma virus (HPV) immunization campaign, US data show the effectiveness of HPV vaccines. The incidence of HPV infections by the strains included in Gardasil (Merck) and Cervarix (GlaxoSmithKline) fell by 56% among teenage girls in the vaccine era.

HPV vaccination was introduced into the routine immunization schedule in the US in late 2006 for females aged 11–12 y, with catch-up vaccination recommended for those aged 13–26 y. However, vaccination rates remain low, with 3-dose vaccine coverage of only 32% in 2010.

Since the reductions in the prevalence of vaccine types (HPV-6, -11, -16, and -18) are expected to be one of the first measures of vaccine impact, researchers from the Centers for Disease Control and Prevention (CDC) compared and analyzed HPV prevalence data from the vaccine era (2007–2010) and the prevaccine era (2003–2006) that were collected during National Health and Nutrition Examination Surveys. Among females aged 14–19 y, the vaccine-type HPV prevalence decreased from 11.5% in the prevaccine era to 5.1% in the vaccine era, representing a decline of 56%. The effectiveness of at least one dose was 82%. The study results were recently published in the *Journal of Infectious Diseases*.[2]

The decline of vaccine-type HPV prevalence in teenage girls was greater than anticipated, possibly because of the herd immunity effect. CDC officials see the result as compelling evidence that more people should receive the vaccine.

"Our low vaccination rates represent 50 000 preventable tragedies—50 000 girls alive today will develop cervical cancer over their lifetime that would have been prevented if we reach 80% vaccination rates. For every year we delay in doing so, another 4400 girls will develop cervical cancer in their lifetimes," said CDCP Director Dr Tom Frieden.

According to the CDCP, there are 27 000 cases of HPV-related cancer in the US annually. While more than two-thirds of these cases affect women, with cervical cancer being a particular threat, men are at risk too, with throat cancer being the most common form of cancer.

Reference

2. Markowitz LE, et al. J Infect Dis 2013; 208:385-93; PMID:23785124; http://dx.doi.org/10.1093/infdis/jit192

Modified DC immunotherapy against melanoma

Modified dendritic cells (DCs) that can recognize cancer-associated protein fragments have shown promise in a small clinical trial studying melanoma. A team of researchers, led by Dr Scott Pruitt from Duke University, used modified DC immunotherapy to selectively seek and destroy cancer via vaccination. Trial results were recently published in the *Journal of Clinical Investigation*.[3]

Many cancers, including melanoma, exclusively express constitutive proteasomes (cPs) and are unable to express immunoproteasomes (iPs). In contrast, mature DCs used for immunotherapy exclusively express iPs. Since proteasomes generate peptides presented by HLA class I molecules, the authors hypothesized that mature melanoma antigen-loaded DCs engineered to process antigens through cPs would be superior inducers of anti-melanoma immunity in vivo.

In order to test this hypothesis, the researchers studied 12 metastatic melanoma patients—four were vaccinated with regular DCs, five received DCs that were modified to recognize tumor antigens associated with cPs, and three underwent control treatment,

They found that immunotherapy with all types of DCs stimulated antigen-specific T-cell responses which peaked after 3–4 vaccinations, but patients who received the modified DCs showed fewer circulating melanoma cells and a longer-lasting immune response. Interestingly, of two patients with active disease who had both received the modified DCs, one had a partial clinical response, while the other, who exhibited diffuse dermal and soft tissue metastases, had a complete response.

Overall, these results suggest that the efficacy of melanoma DC-based immunotherapy can be enhanced when tumor antigen-loaded DCs used for vaccination express cPs, so that they recognize cP-produced tumor antigens.

Reference

3. Dannull J, et al. J Clin Invest 2013; 123:3135-45; PMID:23934126; http://dx.doi.org/10.1172/JCI67544

New study looks at clinical severity of human H7N9 infections

According to a new report in *The Lancet,*[4] the H7N9 avian influenza virus, first identified in humans earlier this year, kills 36% of infected people admitted to hospitals in China. Of course it is far more difficult to estimate how many die in the general population after becoming infected, since the most severe cases are also more likely to end up being hospitalized. The authors of the current study estimate an overall fatality rate of 0.2–2.8% for individuals showing symptoms of infection. This estimate suggests that the H7N9 virus is less deadly than the H5N1 bird flu first appearing in 2003, and more deadly than the 2009 H1N1 swine flu pandemic. Others infected with the virus may never show symptoms.

"There is almost always a large portion of asymptomatic (flu virus) cases, and cases where infected people do not seek treatment," says Dr Gabriel Leung, senior author of the study and head of the University of Hong Kong's School of Public Health.

Since its discovery in March 2013, 132 cases of H7N9 infection with 37 deaths have been confirmed. During the summer, H7N9 activity has slowed dramatically; only one case has appeared since May. Still, public health officials warn that number could significantly rise during the autumn influenza season. To prepare for this scenario, several manufacturers have advanced research on H7N9 vaccines.

Taiwan is the one country outside China to experience a case of H7N9 infection, and the leading Taiwanese vaccine manufacturer Adimmune has completed clinical trials for its H7N9 vaccine. This vaccine is expected to become available imminently. The US company Novavax has started a clinical trial of its monovalent virus-like particle (VLP) H7N9 vaccine, and Inovio, also based in the US, recently presented data showing that its H7N9 vaccine is 100% protective in animals. Other companies with H7N9 vaccine candidates under development include Greffex, Protein Sciences Corporation and Medicago (see *Human Vaccines and Immunotherapeutics News 9–6*[5]).

References

4. Yu H, et al. Lancet 2013; 382:138-45; PMID:23803487; http://dx.doi.org/10.1016/S0140-6736(13)61207-6
5. Riedmann EM. Hum Vaccin Immunother 2013; 9:1187-90; http://dx.doi.org/10.4161/hv.25576

Prevnar vaccines are valuable for healthcare systems

Pfizer's Prevnar vaccines have been very successful and, as shown by two recent studies, have been a boon for healthcare systems. One study shows that Prevnar 7 (PCV7), the precursor of Prevnar 13 (PCV13), was responsible for a large drop in hospital visits. The second study makes the case for Prevnar as a lifesaver in pandemic influenza outbreaks by limiting co-infections.

PCV13 prevents infections from 13 strains of *Streptococcus pneumoniae,* a bacterium causing pneumonia, ear infections and even fatal diseases such as pneumococcal meningitis. The vaccine is approved for use in infants and young children in more than 120 countries, and for use in adults over 50 y of age in more than 80 countries. Last month, Pfizer received approval from the European health regulator to expand the use of PCV13 to a wider population of adults aged 18 to 49 y.

A recent study in the *New England Journal of Medicine*[6] looked at the impact of PCV7 on hospital visits. The vaccine was introduced in the US childhood immunization schedule in 2000 and has substantially reduced the incidence of vaccine-serotype invasive pneumococcal disease in young children and unvaccinated older children and adults. Because of concerns about increases in disease caused by non-vaccine serotypes, the researchers wanted to determine the reduction in pneumonia-related hospitalizations among children and in older age groups. They found that PCV7 has prevented 168 000 hospitalizations a year in the US. With 73 000 prevented trips to the hospital, people over 85 y of age benefited most as a result of diminished circulation of vaccine-type strains. The vaccine also has prevented an estimated 47 000 pneumonia hospitalizations a year among infants under two years old.

In addition to the decline in hospitalizations, which potentially saves healthcare systems money, the vaccine is also helping in other ways such as preventing ear infections and outpatient visits. The six additional strains in PCV13, which has taken over from the 7 strain variant in most countries, should cut hospitalizations further.

Another recent study in the journal B*MC Infectious Diseases*[7] looked at the impact of

PCV13 in a pandemic similar to the 2009 H1N1 pandemic in the US. For the 1918 pandemic flu, it has previously been shown that secondary bacterial pneumonia directly caused many deaths. The authors predict that in an outbreak like the 2009 H1N1 pandemic, when 28–55% of autopsies found bacterial co-infections, PCV13 would have saved 3700 more lives than PCV7. The reduction in deaths, hospitalizations and long-term complications is predicted to generate cost savings of $1 billion. As in any prediction, the calculation is based on numerous assumptions, but it nonetheless gives a platform from which to discuss the value provided by PCV13.

References

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GAPVAC: New consortium in the fight of brain cancer

A new EU-funded consortium has been formed to develop fully personalized tumor vaccines for brain cancer patients. The Glioma Actively Personalized Vaccine Consortium (GAPVAC) consists of 14 organizations from the biotech industry and academia in Europe and US, which have agreed to join forces to develop a novel approach to fight cancer. The consortium will be led by *immatics* biotechnologies GmbH (Coordinator) and BioNTech AG (Vice Coordinator), both located in Germany.

The GAPVAC project is designed to create, manufacture and develop actively personalized vaccines (APVACs) tailored for each patient based on the individual aspects of the patient's tumor and immune system. GAPVAC will address the high unmet medical need in glioblastoma, an aggressive form of brain cancer with poor prognosis, where the limited treatments available today have minimal effect on overall survival. The aim of the project is to show that APVACs are well tolerated and immunogenic against cancer, and that this novel personalized approach is feasible.

Immatics and BioNTech will jointly take this personalized immunotherapy approach into clinical development. In a multi-national Phase 1 clinical trial planned to start in 2014, up to 30 newly diagnosed glioblastoma patients will be enrolled to receive a vaccine specifically prepared for each individual.

Immatics will use its unique antigen discovery engine XPRESIDENT to generate a warehouse of tumor-associated peptides (TUMAPs) from which the most suitable ones for each patient are selected based on transcriptomic and peptidomic analysis to create the first of two APVACs applied to the patient. BioNTech will add proprietary glioblastoma-expressed TUMAPs to the peptide warehouse. The APVAC on-demand manufacturing will be performed by the group of Prof Dr Hans-Georg Rammensee from the University of Tübingen (Germany). The complex peptide warehouse will be manufactured by BCN Peptides in Spain, an enterprise focused on peptide synthesis for clinical use. In addition, ten academic partners from Europe and the US have joined the consortium to apply the APVACs to their patients as well as contributing to the project with their own research.

The clinical trial will be accompanied by an extensive biomarker program led by *immatics* and the Association of Cancer Immunotherapy (CIMT), a non-profit organization dedicated to the advancement of cancer vaccines, to confirm the mechanism-of-action and to identify biomarker signature candidates predicting which patients are most likely to benefit from treatment with APVACs.

Dr. Harpreet Singh, CSO of *immatics* and Coordinator of the GAPVAC consortium, said: "GAPVAC represents an exciting step forward as the first project exploring actively personalized therapeutic cancer vaccines at a European level. Unlike other approaches, this consortium is looking at the specific characteristics of each patient's disease. If successful, this novel approach could create a completely new way to treat cancer. Such a unique approach is only possible by combining a variety of the latest technological innovations and by joining forces with superb biotechnology companies and academic institutions—by partners who share a dedication for the personalization of therapy for the benefit of cancer patients."

Cytomegalovirus vaccine to enter phase 3

The US biotech company Vical and the Japanese pharmaceutical company Astellas Pharma recently announced the initiation of a multinational phase 3 trial of the cytomegalovirus (CMV) vaccine ASP0113 (TransVax) in 500 hematopoietic cell transplant (HCT) recipients. The two companies entered into exclusive license agreements in 2011 to develop and commercialize TransVax, Vical's investigational therapeutic vaccine, designed to control CMV in transplant recipients. Astellas is conducting the trial, and Vical is providing development, regulatory and manufacturing support. A separate phase 2 trial of TransVax in solid organ transplant (SOT) recipients is planned for later this year.

CMV is a herpesvirus that infects more than half of all adults in the US by age 40, and is even more widespread in developing countries. A healthy immune system protects an infected person against CMV disease, but does not prevent or clear latent infection. Individuals whose immune systems are not fully functional, such as transplantees, are at high risk of CMV reactivation, potentially leading to severe illness or death.

Vical's investigational bivalent DNA vaccine TransVax contains plasmids encoding human CMV pp65 and gB for induction of cellular and humoral immune responses, and is formulated with a proprietary poloxamer-based delivery system. It has received orphan drug designation in the US and Europe for HCT and SOT patients.

"With the initiation of this trial, ASP0113 becomes the first investigational therapeutic CMV vaccine to reach phase 3 testing," said Dr Vijay Samant, President and CEO of Vical. "Therapeutic vaccines, designed to control disease in people with established and persistent infections, represent the highest hurdle in vaccinology. We are excited to achieve this

important milestone as we continue advancing ASP0113 toward commercialization."

The Phase 3 study is designed as a 1:1 randomized, double-blind, placebo-controlled trial which will enroll CMV seropositive subjects undergoing HCT procedures. The trial will use an adaptive design composed of two parts. The first part will enroll approximately 100 subjects, and the primary endpoint will be overall survival at one year. The second part will enroll approximately 400 subjects, and the primary endpoint will be either survival or a composite endpoint including survival and other variables, depending on the statistical analysis of results from the first part. Treatment and follow-up for each subject will continue for one year following enrollment.

Malaria vaccination using chemically attenuated parasites

Australian researchers are developing a novel malaria vaccine that has shown promising results in animals and is ready for human trials. Preclinical results, demonstrating that the vaccine induces protective immunity to multiple strains of malaria in mice, were recently published in the *Journal of Clinical Investigation*.[8]

Malaria is caused by the parasite *P. falciparum* and transmitted by mosquitos. Symptoms may include fever, headaches, and chills, and in severe cases can involve seizures and breathing difficulty. According to the WHO, ~660000 people are estimated to have died from malaria in 2010, the majority of which are children under the age of five years in developing countries. There are no licensed vaccines, and people at risk rely on preventions such insecticide-treated bed nets and spraying the home with pesticides to eliminate infected mosquitos.

Vaccine development for the blood stages of malaria has focused on the induction of antibodies to parasite surface antigens, most of which are highly polymorphic. An alternate strategy has evolved from observations that low-density infections can induce antibody-independent immunity to different strains. To test this strategy, the research team led by Dr Michael Good from Griffith University in Australia treated parasitized red blood cells from the rodent parasite *P. chabaudi* with a chemical that irreversibly alkylates parasite DNA, thereby blocking their ability to replicate. After injection to mice, DNA from the vaccine could be detected in the blood for more than 110 d, and a single vaccination induced profound immunity to different malaria parasite species. Immunity was mediated by $CD4^+$ T cells and was dependent on the red blood cell membrane remaining intact. Importantly, the authors showed that *P. falciparum* could also be attenuated by this chemical treatment.

Overall, these data demonstrate that vaccination with chemically attenuated parasites induces protective immunity and provide a compelling rationale for testing a blood-stage parasite-based vaccine targeting human Plasmodium species.

Reference

8. Good MF, et al. J Clin Invest 2013; 123:3353-62; http://dx.doi.org/10.1172/JCI66634