

Human Vaccines: News

HPV vaccine protects against pre-cancerous growths

Vaccination against certain types of human papillomavirus (HPV) provides sustained protection against genital warts and pre-cancerous growths of the cervix, according to a new study published on bmj.com.

HPVs are responsible for around 500,000 annual cases of cervical cancer globally and 10 million further cases of high grade cervical intraepithelial neoplasia, which are immediate precursors to malignant cancerous growths. In addition, it is estimated that 30 million women and men acquire anogenital warts or low-grade cervical growths each year.

While it is known that the quadrivalent vaccine for HPV (types 6, 11, 16 and 18) has the potential to prevent about 70% of cervical cancers and 90% of genital warts, its

contribution to preventing low-grade disease is still uncertain.

The international study, funded by Merck Research Laboratories, maker of the HPV vaccine Gardasil, enrolled 17,622 women aged 16–26 in two studies between December 2001 and May 2003. The women were enrolled from primary care centers and university- or hospital-associated health centers in 24 countries and territories worldwide. They were split at random into two groups—one group was given three doses of HPV vaccine (for types 6, 11, 16 and 18) at day 1, month 2, and month 6 of the study, while the other women were given a placebo.

Results showed that among previously unexposed women, the vaccine was highly

effective (96–100%) for preventing low-grade lesions attributable to HPV types 6, 11, 16 and 18 for up to four years. It also had considerable effectiveness against any lesion (regardless of HPV type), with a reduction of 30% of cervical low-grade growths, 48% of vulvar and 75% of vaginal low-grade growths. Genital warts were reduced by 83%.

The authors said the prolonged effectiveness of the vaccine in preventing low-grade lesions is important, and concluded: "These lesions occur shortly after infection and a reduction in these lesions will be the earliest clinically noticeable health gain to be realised by HPV vaccination."

Read the study at www.bmj.com/cgi/content/full/341/jul20_1/c3493

One vaccine for a range of cancers

A vaccine to help cure some of the most deadly cancers including breast, bowel and cervical tumors has been developed by Celldex Therapeutics (Needham, MA) and scientists at Middlesex University (London, UK).

After animal tests had already demonstrated good results and preliminary trials on people showed it to be safe, the vaccine is now being advanced into a Phase 2 trial with 60 newly diagnosed bladder cancer patients selected for human chorionic gonadotropin (hCG)-expressing cancers.

The vaccine CDX-1307 directs the immune system to eliminate the hormone hCG, which is normally present only during pregnancy, but also is made by about half of patients who have bladder and pancreatic cancer, as well as some people who have breast, bowel, ovarian and cervical tumors. Eliminating hCG shrinks tumors and stops their metastasis. Cancer is obviously much easier to treat, and even cure, with chemotherapy and other drugs when it is confined to one part of the body. The destruction of hCG would also mean the jab acted as

a contraceptive. However, women's fertility should return to normal within a year after completing treatment.

Dr. Ray Iles, Professor at Middlesex University and creator of the vaccine said: "Not only are you causing the cancer to shrink, but it is not metastasizing. If you come in with chemotherapy and surgery, you've got a cure."

Pertussis outbreak in California

The current whooping cough outbreak in California may become the worst in 50 years. The two main factors contributing to the rise of pertussis cases are: (1) some parents refusing vaccines for their children due to safety fears, and (2) a number of doctors not offering all the recommended immunizations because of payment issues.

Experts say that the financial challenges of vaccinating patients may be one factor in the rising pertussis incidence. A December 2008 *Pediatrics* study (2008, 122:1319–24) that surveyed 597 US pediatricians and family physicians found that 49 % of the doctors practiced

in an office that had delayed purchasing a new vaccine due to financial concerns.

Immunization efforts are further complicated by parents who are hesitant to have their children vaccinated. Dr. Sumana Reddy, a California physician, told *American Medical News*: "We encounter lots of patients' families who are pretty clear that they're suspicious of vaccines. It's a frustrating issue, because these are often people ... who don't understand the possible effects of going without the pertussis or mumps vaccines."

According to a statement from California's Department of Health, 1496 cases of pertussis

were reported in the first half of 2010, a five-fold increase from the same period last year when 304 cases were reported. Rising cases of the disease have also been reported in Idaho, Texas, Michigan and South Carolina.

To combat the outbreak, the California Health Department is recommending an adolescent-adult pertussis booster vaccine for anyone seven years and older who is not fully immunized—especially women of child-bearing age, before, during, or immediately after pregnancy as well as other people who have contact with pregnant women or infants should get the pertussis vaccine.

Vaccine to combat chronic stress

Scientists from Stanford University (CA) may be on the verge of a vaccine to combat chronic stress. The team headed by Dr. Robert Sapolsky, a neuroscience professor at Stanford, has successfully tested a genetic therapy that can prevent stress from destroying brain and body.

Dr. Sapolsky has been studying stress and the involved hormones called glucocorticoids for 30 years. He first noted the damage caused by stress, when studying animals in Kenya in the late 1970s. When a person experiences stress, a tiny circuit in the base of their brain triggers the release of glucocorticoids, thus putting the body in a heightened state of alert. But glucocorticoids can linger in the bloodstream, leading to damage. This also can

prove toxic to the brain, slowing the production of new neurons. Chronic stress is linked to a range of diseases, including diabetes and heart attacks.

Sapolsky's team has adapted a herpes simplex virus—a good candidate because it is able to slip easily into brain cells—to carry engineered neuroprotective genes into the brain and neutralize the hormones. The selected neuroprotective genes could increase the production of growth factors, various antioxidants and substances that mimic estrogen. As a result brain cells infected by Sapolsky's version of herpes would be protected in case they were subjected to stress.

This approach showed promising results in rats. Modified herpes virus was introduced

into rodent brains prior to a series of tragedies (such as a massive stroke or an extended seizure) which would trigger the release of glucocorticoids. Within minutes, the modified herpes virus began pumping out neuroprotective proteins, thereby limiting the extent of cell death. Rats given the herpes treatment were able to stave off practically all cell loss, while control rats lost nearly 40% of neurons in a given region. Data were published last year in the *Journal of Cerebral Blood Flow & Metabolism* (2009, 29:130–136).

"To be honest, I'm still amazed that it works", Dr. Sapolsky told *Wired*. "It's not going to help anybody soon—human trials are years away—but we've proved that it's possible. We can reduce the neural damage caused by stress."

Seasonal flu vaccines on the way

The flu season generally does not start until October, but vaccine manufacturers have already begun to deliver huge shipments of the new seasonal flu vaccine ahead of schedule.

Already in July, MedImmune, Novartis, Sanofi-Aventis and GlaxoSmithKline started shipping their vaccines to distributors. Different brands and types of vaccines are approved for different age groups.

Every year manufacturers engage in a game of chance to design a vaccine that can

guard against the flu strains that raise the greatest fears. This year's batch of vaccines protect against the 2009 H1N1 pandemic virus and two other strains of flu, as recommended by the CDC. That means just one vaccination for most people, compared to two last year.

Health officials are urging for the first time that everyone from the age of 6 months and up—including the usually low-risk 19 to 49 year olds—get a shot ahead of any outbreak. Recommendations by the CDC's Advisory

Committee on Immunization Practices say there is "evidence that annual influenza vaccination is a safe and effective preventive health action with potential benefit in all age groups."

But the public attitudes about flu vaccines could be a challenge for this year's vaccination campaign. The swine flu ended in a whimper, and the seasonal flu had only a mild impact in the US. The resulting public resistance to the flu shot may prevent the US from achieving the herd immunity needed to stop an epidemic before it starts.

Computer-aided design of live viral vaccine

A rapid and effective approach to produce vaccines for new strains of influenza viruses has been developed by a computer scientist at the University of Miami (FL, USA) in collaboration with scientists at Stony Brook University (NY, USA).

Up to now, the development of live vaccines has relied on a simple approach: Weaken a virus to the point where it is no longer a threat but spurs the immune system to guard against any future infections with the wild-type (WT) virus. Although such weakened viruses often make very effective vaccines, their application has been limited by fears that the attenuated virus can regain virulence.

Now, computer scientist Dimitris Papamichail developed a new method called Synthetic Attenuated Virus Engineering (SAVE), which uses computer algorithms to design viruses that serve as live vaccines, which are then synthesized to specification. The approach was recently published in *Nature Biotechnology* (2010, 28:723–726).

The researchers made a synthetic genome of the virus containing hundreds of changes to its genetic code. The computer algorithms indicate the best places in the genome to make the changes, such that the new synthetic genome encodes exactly the same proteins as WT genome, but in lesser quantities. Although the new sequence and the original

sequence both direct the synthesis of exactly the same proteins, the new sequence gives a weakened version of the virus, which is capable of eliciting an immune reaction against the WT virus, but is not strong enough to cause disease symptoms. Immunization of mice by a single intranasal exposure to the new-sequence virus conferred protection against subsequent challenge with WT influenza virus. This method used to weaken the influenza virus is a general one, and may allow the creation of safe, effective vaccines against many different types of viruses.

"We have been able to produce an entirely novel method to systematically design vaccines using computer algorithms," said

Papamichail, assistant professor at University of Miami and co-author of the study. "Our approach is not only useful for influenza; it is also applicable to a wide range of viruses."

This process allows a wide margin of safety, explains Papamichail. "The probability of all

the changes reverting themselves to produce a virulent strain is extremely unlikely," he says.

In the future, the researchers would like to explore the applicability of their techniques, with the ultimate goal of methodically and computationally design from

scratch synthetic organisms with predetermined functions and controlled properties, with broad applications in medicine.

HIV vaccine research: Hope for renaissance

After the recent AIDS 2010 conference in Vienna (Austria), experts are enthusiastic and hopeful for the beginning of the "renaissance" of HIV vaccines. Recent studies showing first evidence of vaccine-induced protection in humans are positive signs.

Recent encouraging advances include last year's prime-boost HIV vaccine trial RV-144 (see *Human Vaccines* N&P&P 2010; 6:157–63) with an experimental vaccine that showed a modest effect and appeared to slow the rate of infection by about 30% in Thai volunteers, which nonetheless is the only clinical trial for any HIV vaccine to ever show a benefit.

Last month, US researchers identified two new antibodies that can protect against a wide range of AIDS viruses. They said they may be able to use them to design a vaccine (*Science* 2010, 329: 811–817).

And scientists from two major Indian institutes, the *Tuberculosis Research Centre* (TRC) in Chennai and the *National AIDS Research*

Institute (NARI) in Pune, are monitoring the successful progress of an indigenous HIV vaccine trial. With no adverse reactions reported so far, the first phase of the trial is set for completion this year before the second phase rolls out early 2011, the *Times of India* reports.

"This is a pivotal moment in HIV vaccine research", said Dr. Alan Bernstein, executive director of the Global HIV Vaccine Enterprise, to *Reuters*. "The last five years have been the richest period in HIV vaccine research since the epidemic began. The question... now is how do we build on these scientific advances?"

Dr. Bernstein, whose group published a report on the "road to prevention" ahead of the international AIDS conference, said cross-border and cross-discipline collaboration among scientists was crucial. And at a time when a global economic recession is squeezing funding for the AIDS battle, trying to attract new minds and ideas would be as

important as trying to bring in new money. He pointed to several ways to strengthen HIV vaccine research and development, including getting more clinical trials up and running to test new ideas in humans, and expanding trials to those countries where people are most at risk of HIV.

Microsoft founder and philanthropist Bill Gates, whose Gates Foundation spends a large portion of its \$34 billion fund on fighting AIDS, expressed his optimism at the conference in Vienna and said: "The scientific results we've seen with the antibodies...and the Thai trial...really point us toward what we need to do".

Currently, there are around 20 drugs on the market to help treat HIV, but there is no vaccine as of yet. Since the AIDS pandemic started in the early 1980s, almost 60 million people have been infected with HIV, many of them in Africa, and it has killed 25 million.

2010 Albert B. Sabin Gold Medal Award

Dr. John D. Clemens received the 2010 Albert B. Sabin Gold Medal Award in recognition of his numerous contributions to reducing suffering and promoting peace through the development, evaluation, and distribution of vaccines.

Dr. Clemens led the first efficacy trial of an oral vaccine against cholera, and conducted additional research on a measles vaccine as a research scientist at the International Center for Diarrheal Disease Research (Bangladesh) during the 1980s. Scientists at the International Vaccine Institute (IVI) transferred the technology for the cholera vaccine to Shantha Biotechnics of (Hyderabad, India) and in 2009, Shanchol was licensed for development.

Since 1999 he has served as Director-General for IVI (Seoul, Korea) and has advanced vaccine diplomacy in many areas, including the Democratic People's Republic of Korea Program, which aims to reduce the disease burden of Hib and Japanese encephalitis in North Korean children.

The Gold Medal Award has been awarded annually since 1994 and is given to a distinguished member of the research community who has made extraordinary contributions in the field of vaccinology or a complementary field. Each recipient is a role model for young researchers, someone whose career has saved lives through the development and use of vaccines. The Medal is the highest scientific honor

given by the Sabin Vaccine Institute and commemorates the legacy of the late Dr. Albert B. Sabin. Past recipients of the Sabin Gold Medal are Rino Rappuoli (2009), Ruth Nussenzweig (2008), Hilary Koprowski (2007) and Stanley Plotkin (who is a member of Human Vaccine's Editorial Board).

Dr. Clemens' acceptance speech is published in this issue of *Human Vaccines* (see page 763–6). Photos and a video of his speech are available on the homepage of the Sabin Vaccine Institute <http://www.sabin.org/updates-events/events/gold-medal-awards>

Human Vaccines: Profile

Questions for Biotechs

Genocea Biosciences

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Jessica Flechtner is the Vice President of Research of Genocea

How and when did your company start, and where are you located?

Genocea is headquartered in Cambridge, Massachusetts, and was founded in 2006, with functional laboratories in the spring of 2007. The foundation of the company is a technology that was optimized over more than 10 years in the academic setting by scientific co-founder Darren Higgins, Ph.D., Professor of Microbiology and Molecular Genetics at Harvard Medical School. The objective of our technology is the rapid identification of protective T-cell antigens for use in human vaccines.

How many employees do you have, and how do you find/attract them?

We have 35 employees. We believe that our unique story within the vaccine space, the potential to make significant advances in global health and the culture we've developed at the company focused on innovation, teamwork and the pursuit of excellence in all areas, have made Genocea a highly desirable place to work.

What are the main focus and platform technology(ies) of your company?

Genocea is focused on developing safe and effective therapeutic and prophylactic vaccines incorporating cell-mediated immunity and offering a comprehensive approach that we believe will result in accelerated vaccine discovery. Unlike today's "trial and error" approach to vaccine development, Genocea employs a proprietary process of antigen expression, high-throughput human T-cell screening, and correlation with natural immunity and clinical protection that has resulted in preclinical validation of three vaccine candidates in approximately one year.

Can you provide a short overview of your product pipeline?

Genocea has demonstrated preclinical proof-of-concept with vaccine candidates for herpes simplex virus type 2 (HSV-2), *Streptococcus pneumoniae* and *Chlamydia trachomatis*, infections that affect hundreds of millions of people worldwide. Our lead candidate is a HSV-2 therapeutic vaccine, potentially targeting more than 500 million patients worldwide, and for which we expect to begin clinical development in early 2011. Following that, we expect to launch clinical trials on vaccine candidates for the prevention of *Streptococcus pneumoniae*, *Chlamydia trachomatis*, and HSV-2 infection in late 2012. We have also begun work in partnership with the US Military on a vaccine to combat malaria.

Who is your competition and what advantage(s) do your products/technology offer?

Major players in the global vaccine market such as GSK, Novartis and Sanofi-Pasteur have traditionally focused vaccine development on diseases involving B-cell immunity. Our unique technology enables the development of vaccines targeting T-cell responses, opening up a

relatively untapped cadre of diseases for which T cells are thought to play a role in protection. In addition, we believe that our approach enables more rapid and lower-risk development of these vaccines through comprehensive antigen expression, human screening, correlation with natural immunity and early evidence of human clinical protection.

What were the "highlights" in your recent development of vaccines/immunotherapeutics?

Over the past year, we:

- Achieved preclinical proof-of-concept with all three of our vaccine candidates,
- Filed multiple patent applications to protect our intellectual property,
- In-licensed additional intellectual property further protecting our product pipeline,
- In-licensed an adjuvant with demonstrated human safety and T-cell responses, and
- Added critical expertise and leadership to our senior management team and scientific advisory board.

What have been the most critical problems in developing products in your field, and how can your company's technology help overcome these problems?

As mentioned, traditional vaccine development has been focused on diseases with which protection is associated with B cell responses. We believe our unique and comprehensive approach enables Genocea to speed the discovery of protective T-cell antigens that can be successfully incorporated into vaccines, ultimately expanding the scope of targeted diseases while reducing the time and cost associated with vaccine discovery and potentially increasing the likelihood of success in humans.

What is your company's value proposition?

Our technology can be of significant value to major pharmaceutical companies and ultimately to patients because we can unlock heretofore intractable diseases, and we can do so rapidly.

What business development strategy do you pursue?

Genocea is the first and only company to offer a comprehensive, lower-risk approach to vaccine antigen discovery based on natural, protective T-cell responses made by humans. Through in-house and licensing efforts, we have assembled a broad patent portfolio that protects our unique discovery process. As a result of this, we have successfully raised \$26 million from the investment community and secured more than \$5 million in grant funding. We have already partnered several of our programs and are continuing partnering efforts where appropriate.

How does your company attract partners?

We believe the power and uniqueness of our platform is attractive to

global vaccine developers looking for (A) accelerated vaccine discovery, (B) the ability to target previously untapped markets, and/or (C) those seeking a higher likelihood of vaccine development success compared to traditional methodologies. In addition, our technology also enables the discovery of antigens that induce T-cell responses for the treatment or prevention of diseases such as cancer and autoimmune conditions. The technology also has application in general and/or prognostic markets for these conditions. For all of these reasons, we believe Genocea to be an extremely attractive potential partner.

Who are your most important partners?

Since 2008, we have been developing our pneumococcal vaccine candidate in collaboration with PATH and Richard Malley, M.D., from Children's Hospital Boston. In December 2009, we also received a grant from the University of Pittsburgh Medical Center's (UPMC) Sexually Transmitted Infections (STI) Cooperative Research Center for the development of vaccines for *Chlamydia trachomatis*, following a \$12.5 million grant to UPMC from the National Institutes of Health. In April 2010, we entered into a Cooperative Research and Development Agreement (CRADA) with the Naval Medical Research Center (NMRC) for the development of a vaccine against *Plasmodium falciparum* for the prevention of malaria

and were awarded \$2.7 million from the US Army Medical Research and Materiel Command (USAMRMC). There continues to be significant interest in our vaccine programs, and we intend to maintain efforts to attract additional partners for the development of our vaccine candidates.

How do you balance performing work in-house vs out-sourcing?

With funding from our investors and our partners, we continue to successfully pursue significant discovery and development efforts in house. Where appropriate and most cost effective, we are outsourcing to qualified vendors; thus far, our outsourcing has primarily involved our clinical and manufacturing activities.

What are your product development goals for the next three years?

Over the next three years, we expect to have Phase 2 data from our HSV-2 therapeutic vaccine program, and clinical trial work begun on our prophylactic pneumococcal, chlamydia, and herpes vaccines. In addition, we hope to have achieved animal proof-of-concept with our malaria program and initiated antigen discovery and preclinical proof of concept on additional disease targets.

For more information, please visit: www.genocea.com

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