Therapeutic HIV vaccine promising in the clinic

A therapeutic human immunodeficiency virus (HIV) vaccine, developed by a team of Spanish researchers, has shown promising results in an early clinical trial. The dendritic cell (DC)-based vaccine tested in HIV-positive subjects led to a dramatic drop in the levels of HIV detected in some trial participants. The study results were recently published in the journal Science Translational Medicine.¹

“What we did was give instructions to the immune system so it could learn to destroy the virus, which it does not do naturally,” explained study lead author Dr Felipe Garcia from Barcelona University’s Hospital Clinic. Combination antiretroviral therapy (cART) greatly improves survival and quality of life of HIV-1-infected patients; however, cART must be continued indefinitely to prevent viral rebound and associated disease progression. Taking multiple medicines on a daily basis creates hardship for patients, sometimes has toxic side effects over the long term and is expensive. Therapeutic immunization as a matter to control viral replication after discontinuation of cART has been proposed as an alternative to “cART for life.”

The vaccine tested in the current clinical trial is based on autologous monocyte-derived dendritic cells (MD-DCs) pulsed with autologous heat-inactivated whole HIV. The trial included HIV-positive subjects on cART, who were randomized to receive three immunizations with MD-DCs or with nonplused MD-DCs (placebo). Vaccination was feasible, safe and well tolerated, and shifted the virus/host balance. At week 12 after cART interruption, the HIV viral load dropped by more than 90% in 12 of 22 patients (55%) who received the vaccine. Only one of 11 patients (9%) in the control group experienced a similar reduction. After 24 weeks, 35% of patients in the vaccinated group and 0% in the control group showed a 90% decrease in viral load. This significant decrease in plasma viral load observed in recipients of the specific immunotherapy was associated with a consistent increase in HIV-1-specific T-cell responses. The vaccine lost its effectiveness after a year, when the patients had to return to their cART. The study results suggest that HIV-1-specific immune responses elicited by therapeutic DC vaccines could significantly change plasma viral load setpoint after cART interruption in chronic HIV-1-infected subjects treated in early stages.

The pediatric PCV Synflorix aims to protect against IPDs, such as meningitis, bacteraemic pneumonia and sepsis. Synflorix also provides protection against pneumococcal middle ear infection, otherwise known as acute otitis media (AOM). The vaccine is available in over 90 countries. Synflorix was the first PCV eligible under the Advanced Market Commitment (AMC) to receive WHO prequalification.

It took the research team seven years to get to this point, and they plan to continue to improve the vaccine and combine it with other therapeutic vaccines. They said: “It is the most solid demonstration in the scientific literature that a therapeutic vaccine is possible. This investigation opens the path to additional studies with the final goal of achieving a functional cure—the control of HIV replication for long periods or an entire life without antiretroviral treatment.”

Reference
¹ Garcia F, et al. Sci Transl Med 2013; 5:166ra2

GAVI aims to immunize 30 million against HPV by 2020

The GAVI Alliance plans to work with developing countries to prepare them for nationwide rollouts of the vaccine against the human papillomavirus (HPV), the leading cause of cervical cancer. Pilot projects are expected to start this year in several developing countries, many of them in sub-Saharan Africa. By 2020, more than 30 million girls should be immunized against HPV with GAVI support.

“The demand for HPV vaccines has exceeded expectations, and we are looking forward to supporting developing countries in introducing these vaccines to protect adolescent girls against cervical cancer,” said Dr Seth Berkley, GAVI CEO. “HPV vaccines are our best hope to protect millions of girls against this deadly disease.”

Every year, an estimated 275,000 women die from cervical cancer, the great majority of them (85%) in developing countries where cervical cancer screening and treatment are often not available. In GAVI-supported countries, cervical cancer is the leading cause of cancer deaths among women. Without changes in prevention and control, cervical cancer deaths are expected to increase to 430,000 each year by 2030, virtually all in developing countries.

HPV vaccines can protect against ~70% of cervical cancer, and together with efficient screening and treatment could prevent even more cervical cancer. Vaccines are especially critical for prevention in developing countries, because women often lack access to screening and treatment.

For efficient prevention of cervical cancer, it is important to immunize girls before they become sexually active and exposed to HPV infection. Thus, the vaccine is given to girls aged 9-13. Reaching these girls will be one of the challenges to effectively delivering HPV vaccines because many developing countries do not offer routine preventative health service to girls in the 9–13 age group. Other challenges include identifying the appropriate target group and ensuring that the right infrastructure is in place to reach adolescent girls. The introduction of HPV vaccines could also provide many opportunities to strengthen adolescent health services, and exploit synergies with nutrition, HIV education and sexual and reproductive health.

“I am very happy to see that GAVI is investing in HPV vaccines and offering our African girls the same access to life-saving vaccines as girls in developed countries,” said Her Excellency Christine Kaseba, First Lady of Zambia and a leading advocate for women’s health. “Too many girls are robbed of their future by this cancer. I am personally committed to do what it takes to ensure that girls have access to HPV vaccines.”
Self-destructing Salmonella to deliver oral DNA vaccines

Researchers at Arizona State University’s Biodesign Institute have successfully engineered salmonella, a potentially deadly bacterium, so that it can safely be used for efficient oral delivery of DNA vaccines. An added advantage is very low manufacturing costs.

These live vaccines, known as RASVs (recombinant attenuated salmonella vaccines), can trigger a better immune response than killed vaccines. One of the major concerns is that they will cause disease or escape into the environment. However, this has been solved by engineering the bacteria to implode if they cannot find a certain type of sugar, one that does not occur naturally. The engineered Salmonella bug can quickly and efficiently enter cells, without killing them. Once inside the cell, the bacterium self-destructs and releases the DNA, which then can be transcribed and turned into antigens with the help of the cell’s manufacturing machinery. According to Dr Roy Curtiss, Director of the Center for Infectious Diseases and Vaccinology at the Biodesign Institute and senior author of the study, this approach could be used against any virus, any parasite, or any fungus. In a recent Proceedings of the National Academy of Sciences paper,1 the researchers tested a DNA vaccine encoding influenza WSN virus hemagglutinin (HA) antigen delivered by the RASV strain in mice. The vaccine induced complete protection to mice against a lethal influenza virus challenge, and was safe in newborn, pregnant and immunodeficient animals.

An important advantage of the technique is that vaccines can be manufactured quickly and cheaply, freeze-dried and stockpiled, allowing fast response to pandemics or bioterrorism.

Study lead author Dr Wei Kong explained: “By delivering the DNA vaccine using a recombinant attenuated bacterium, we can get 10-100,000 doses per liter of culture.” This is much faster than existing techniques such as isolating DNA from bacteria before injection.

One of the team’s vaccines is in phase 1 clinical trial against infant pneumonia.

Reference
1. Kong W, et al. Proc Natl Acad Sci U S A 2012; 109:19414-9.

Novel strategy for vaccine design: Enzymatically modified antibodies

A recent study showed that enzymatically modified antibodies can be used to generate highly targeted, potent immune responses. The approach, referred to as “sortagging” could be useful for developing therapeutic vaccines.

Sortagging relies on the bacterial enzyme sortase A to modify antibodies to carry various cargos such as peptides, lipids, fluorophores and proteins. In a new study, published in the journal Proceedings of the National Academy of Sciences,1 researchers from the Whitehead Institute and the Massachusetts Institute of Technology (MA, USA) used sortase A to attach a variety of small antigens to an antibody directed at the surface of key immune cells. Sortagging allowed the scientists to quickly prepare various antibody-antigen fusions and to deliver the antigens to their intended targets and track them as the immune cells mounted their intricate response.

“Sortagging is remarkably specific and efficient,” said study lead author Dr Lee Kim Swee. “We were able to create 50 different constructs (antibody-protein attachments), which would not have been feasible if we had relied on the more traditional approach of genetic fusion.”

In the Proceedings of the National Academy of Sciences study, the researchers tested the approach in a mouse model of herpesvirus. Nineteen known viral epitopes were sortagged to a cell-specific antibody, and a cocktail of these modified antibodies was used to immunize a group of mice. Upon subsequent re-exposure to the virus, vaccinated mice showed a 10-fold reduction in the amount of circulating virus.

“This is proof of principle that one could in fact use sortagging on antibodies to easily attach a tailored set of antigens, toward which the immune system can be educated,” Swee said. “This technique also helps us understand how to design better antibody-based vaccines.”

Dr Carla Guimaraes, co-author of the study, highlights the flexibility of sortagging. She compares it to “playing with Legos,” because it allows to mix and match proteins of diverse sizes, shapes and functions. “You could, for example, use sortase to attach a toxin to an antibody and use that antibody to deliver the toxin to specific cells,” said Guimaraes. Such an approach, she notes, would be an appealing strategy for developing better-tolerated cancer therapies.

Reference
1. Swee LK, et al. Proc Natl Acad Sci U S A 2013; 110:1428-33.

GSK’s four-strain seasonal influenza vaccine approved in the US

At the end of last year, the US Food and Drug Administration (FDA) approved the quadrivalent influenza vaccine (Fluarix Quadrivalent) for the immunization of children aged three years and older, and adults to help prevent disease caused by seasonal influenza virus strains A and B. The vaccine, developed by GlaxoSmithKline (GSK), is the first intramuscular vaccine to cover against four influenza strains.

Seasonal influenza strains are classified as A or B strains. Most currently available vaccines are trivalent vaccines, protecting against the two A strains most common in humans and the B strain expected to be predominant in a given year. But since the year 2000, two B virus strains (Victoria and Yamagata) have co-circulated to varying degrees each season, and frequent mismatch has occurred between the B strain included in trivalent vaccines and the B strain that actually circulated. The newly licensed vaccine Fluarix Quadrivalent offers protection against the two A strains and adds coverage against a second B strain, and thus has the potential to decrease the burden of influenza-related disease.

“Trivalent influenza vaccines have helped protect millions of people against flu, but in

www.landesbioscience.com Human Vaccines & Immunotherapeutics 229
Currently available vaccines do not offer broad protection against MenB, which accounts for up to 90% of all meningococcal disease in European countries. MenB has been a particularly challenging target because the outer coating of the bacteria is not well recognized as an antigen by the immune system. Novartis was able to overcome this difficulty by using a pioneering approach known as “reverse vaccinology”. This approach involved decoding of the genetic makeup (genome sequence) of MenB and selection of those proteins that are most likely to be broadly-effective vaccine candidates. The resulting vaccine Bexsero (also known as 4CMenB) contains multiple components, which independently are highly immunogenic and, taken together have the potential to protect against a broad range of disease-causing strains. To date, more than 8,000 infants, toddlers, and adults have been enrolled in studies of Bexsero.

With the anticipated approval of the MenB vaccine Bexsero and the 2010 approval of Menevo (protecting against meningococcal bacteria serogroups A, C, W-135 and Y), Novartis strengthens its leadership position in the global fight against meningococcal disease.

To date, Fluarix Quadrivalent is approved only in the United States. GSK will make Fluarix Quadrivalent available in time for the 2013–14 flu season.

**MVA85A TB vaccine tested in newborns of HIV-positive mothers**

The tuberculosis (TB) candidate vaccine MVA85A, developed by Oxford University (UK), will be tested in newborns of HIV-positive mothers in South Africa. The vaccine has already been successfully tested for safety in healthy adults, children and in HIV-positive adults.

The currently used TB vaccine (BCG) protects children against the most severe forms of TB, such as meningitis. However, it does not protect against lung TB, which is the most common form of the disease, and — in adults — is mainly responsible for the spread of TB infection to other people. South Africa, where BCG is given routinely at birth, has the highest rate of new TB cases worldwide, according to estimates of the World Health Organization (WHO).

The new study will be performed by University of Capetown’s (UCT) South African Tuberculosis Vaccine Initiative (SATVI) and Stellenbosch’s Desmond Tutu TB Centre. They have started to recruit newborn infants of HIV-positive moms at antenatal clinics in Worcester (SA) and Cape Town. The study will include 340 babies; half of them will be given the MVA85A vaccine at birth, and the other half a placebo. HIV-negative infants will also be given BCG two months later. All babies in the study will be monitored closely over a period of one year, to test whether the MVA85A vaccine is safe and whether it improves immune responses to TB.

“If this MVA85A vaccine study is successful, it will benefit in particular those babies at risk of HIV infection, who are also at high risk of getting TB,” said UCT’s Associate Professor Mark Hatherill, who is leading the study.

BCG has been used for more than 90 years and has proven to be safe for almost all children, but vaccination with BCG can lead to complications in HIV-infected babies. Thus, researchers are trying to develop better TB vaccines that are more effective than BCG and safe for all newborn babies, including those with HIV.

**Use of oral cholera vaccines promoted**

Cholera is an acute intestinal infection caused by drinking water or eating food contaminated with the bacterium *Vibrio cholera*. The disease affects as many as 2.5 million people annually, with 1-200,000 deaths worldwide. In addition to providing clean water and sanitation, cholera vaccines can help to control the disease. Two whole-cell killed oral vaccines, Crucell’s Dukoral and Shantha Biotechnics’ Shanchol, are on the market. They are more than 70% effective and very affordable at $1.85 per dose, but still not yet widely used to prevent outbreaks. The World Health Organization (WHO) prequalified the vaccines, and 60 countries licensed them.

The Bill & Melinda Gates Foundation recently gave a four-year, $5 million grant to the Johns Hopkins Bloomberg School of Public Health to promote the effective use of oral cholera vaccine around the world. The Delivering Oral Vaccine Effectively (DOVE) program will be part of a network of vaccine projects funded by the Gates foundation to prevent outbreaks of cholera worldwide.

DOVE will provide relief agencies and governments with technical assistance on how to use oral cholera vaccine, evaluate current vaccine-use practices and develop new field surveillance methods for monitoring and controlling outbreaks of the disease. In addition, DOVE will establish cholera surveillance in the northern region of Cameroon near Lake Chad, a hotspot for the disease. This will help researchers to develop and study methods for detecting outbreaks in hard-to-reach remote areas and potentially for using oral vaccine to contain the disease.

“We believe this grant will greatly facilitate the appropriate use of the new cholera vaccine. In partnership with the World Health Organization, UNICEF and other national and international agencies, we believe the DOVE project will provide the knowledge, technical assistance and encouragement to bring this life-saving vaccine to those who need it most,” said Dr David Sack, director of DOVE and Professor in the Department of International Health at the Bloomberg School.
GSK partners with Vodafone to increase childhood vaccination in Mozambique

GSK and Vodafone have formed a partnership to use innovative mobile technology to help vaccinate more children against common infectious diseases in Africa. It is estimated that up to one-fifth of children worldwide still do not receive basic vaccines. In recent years, there have been major advances in the funding and availability of vaccines, and the proliferation of mobile phones in Africa offers another opportunity to create cost-effective ways to address barriers to universal vaccination.

The new partnership will initially focus on a one-year pilot vaccination project in Mozambique, supported by Save the Children and run in collaboration with the Mozambique Ministry of Health. The aim of the project is to establish whether mobile technology solutions could increase the proportion of children covered by vaccination in Mozambique by encouraging mothers to take up vaccination services, supporting health workers, improving record keeping and enabling better management of vaccine stock. If successful, the project can be replicated throughout Mozambique and scaled across Africa.

Sir Andrew Witty, CEO of GSK, said: “Innovative technologies—whether mobile devices, medicines or vaccines—are helping to transform global health. Organizations such as UNICEF and GAVI have played a key role in making vaccines much more accessible in Africa, but barriers still exist which stop children from benefitting from basic immunization. This new partnership combines GSK's expertise, knowledge and resources with those of Vodafone with the potential to deliver life-saving vaccines to tens of thousands more children in Mozambique. Our hope is that together we will create a sustainable and scalable model which could ultimately be replicated to help more children live healthy lives across developing countries.”

The pilot project in Mozambique will include up to 100 clinics. In order to ensure open access, the platform will be available across any mobile network and can be used to increase take-up of any selected vaccine. Mobile technologies will be used in three ways: (1) Mothers and caregivers will be registered on a Mozambique Ministry of Health database and alerted by SMS to the availability and importance of lifesaving vaccinations against common childhood diseases. Mothers will be able to schedule vaccination appointments by SMS and receive notifications of past and future vaccinations to ensure children complete the full schedule and become fully immunized. (2) Health care workers will be provided with smartphones having software allowing them to contact mothers, view and record vaccination histories, schedule vaccinations and report on follow-up visits. (3) Healthcare facilities will be prompted to regularly report on crucial vaccination stock levels by SMS. This will enable critical supply chain management and the availability of vaccines when and where they are needed, particularly in rural areas.

Vodafone has experience with developing commercial mobile health solutions in other African countries. Five thousand clinics across Tanzania currently use Vodafone’s mobile stock management service to track malaria treatments, and more than 1800 remote community healthcare workers in South Africa are using a mobile solution to access and update patient records.