Expert Review of Vaccines

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New hope for prostate cancer patients

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Genetically engineered mice that would develop prostate cancer were protected from the disease after being immunized with a experimental vaccine. New findings were published in the February issue of the journal *Cancer Research*.

Currently, men with increased levels of prostate-specific antigen are advised to wait watchfully and no treatment is applied until the cancer develops. Anticancer treatments are toxic and costly while therapeutic vaccines are still under development with limited clinical benefit.

"What if instead of a watchful wait, we vaccinate? That could change the course of the disease," said said the lead investigator, W Martin Kast of the Norris Comprehensive Cancer Center (CA, USA). In this animal study, "by early vaccination, we have basically given these mice life-long protection against a disease they were destined to have. This has never been done before and, with further research, could represent a paradigm shift in the management of human prostate cancer."

> "After 1 year following immunization, all nonvaccinated control mice died while 90% of PSCA-vaccinated mice survived."

In their experimental vaccine, the research team used prostate stem cell antigen (PSCA), a protein that is overexpressed in approximately a third of early-stage prostate cancers and in all advanced-stage prostate tumors. PSCA is also expressed at baseline levels in normal prostate gland tissue and in the bladder, colon, kidney and stomach.

The animals received two different vaccines. The prime dose contained a naked DNA encoding PSCA, and the booster dose was a modified horse virus carrying that DNA. After 1 year following immunization, all nonvaccinated control mice died while 90% of PSCA-vaccinated mice survived. "There were tiny nodules of prostate cancer in the (surviving) mice that were surrounded by an army of immune system cells," said Kast. "The vaccination turned the cancer into a chronic, manageable disease."

Of note, the vaccine did not induce autoimmunity, despite PSCA being expressed as a protein in various tissues. "Theoretically, the vaccine could produce a response in any tissue that expresses the antigen, but the fact that PSCA is expressed in such low levels in normal tissue may prevent that complication," explained Kast. The authors cautioned that human studies are needed to confirm that autoimmune diseases do not develop.

"We feel this is a very promising approach," said Kast. "With just two shots, the vaccine will prime immune cells to be on the lookout for any cell that overexpresses PSCA." Using the same approach, the researchers are also working on another prostate cancer membrane target, which has shown promising results.

Sources: Garcia-Hernandez Mde L, Gray A, Hubby B, Klinger OJ, Kast WM. Prostate stem cell antigen vaccination induces a long-term protective immune response against prostate cancer in the absence of autoimmunity. *Cancer Res.* 68(3), 861–869 (2008); The American Association for Cancer Research: www.aacr.org

Adjuvant may be essential in cancer vaccine

Recent findings published in the February issue of the Proceedings of the National Academy of Sciences USA revealed that the boosting effect of an experimental vaccine against non-small cell lung cancer (NSCLC) was dependent on the formulation of the priming dose.

"We previously learned that our vaccine could stimulate an immune response recognizing a protein found in lung cancer cells but we did not know how long the response lasted," said the lead author Sacha Gnjatic of the Ludwig Institute for Cancer Research. "We now know that this vaccine induces strong and persistent immunity over several years, which can be further 'boosted' with additional vaccination."

In the previous study, patients received different formulations of this vaccine, either with the adjuvant AS02B or without, which both resulted in protection against NSCLC. To the researchers' surprise, a single booster dose of the adjuvanted vaccine 3 years after priming resulted in strong humoral and T-cell responses in patients who previously received the adjuvanted vaccine, but only induced a very limited response in those received nonadjuvanted prime vaccine.

"This is such a surprising result," said coauthor Lloyd Old, director of the Cancer Vaccine Collaborative. "In the vaccine field, boosters are given to convert negative or weak reactions to positive ones, and we really thought we would see the same thing. One intriguing possibility is that regulatory mechanisms were activated following the original weak response induced by the vaccine without adjuvant. These findings will certainly have ramifications for the whole field to determine the formulation and delivery of future cancer vaccines."

Sources: Atanackovic D, Altorki NK, Cao Y *et al.* Booster vaccination of cancer patients with MAGE-A3 protein reveals long-term immunological memory or tolerance depending on priming. *Proc. Natl Acad. Sci. USA* 105(5), 1650–1655 (2008); Ludwig Institute for Cancer Research, NY, USA: www.licr.org

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Grant funding for potential meningitis vaccine

Researchers receive funding from the charity Meningitis UK.

A new research grant of £200,000 will be funded for work on a potential vaccine against meningitis B. The funding goes to Karl Wooldridge and his team at the Centre for Biomolecular Sciences (University of Nottingham, UK), whose research focuses on developing a vaccine against group B meningococci.

Meningitis is the inflammation of the meninges, the thin membrane covering the brain and spinal cord. Although non-infectious meningitis can occur, the majority of meningitis cases are caused by bacterial or viral infections, of which three bacteria *Haemophilus influenzae* type b, *Neisseria meningitidis* and *Streptococcus pneumoniae* are responsible for 80% of bacterial meningitis. The current tetravalent meningococcal vaccine provides protection against *N. meningitidis* serogroups A, C, W-135 and Y. There is no vaccine against group B meningococci, which are the most common cause of meningitis in UK children under 5 years of age.

Group B meningococci contain many molecules that are similar to those in humans, making vaccine development against this serogroup very difficult. University of Nottingham's research team has identified several secreted proteins called autotransporter proteins, which may be used as antigens in vaccine research.

"If we identify one or more of these proteins that give a good protective response, we would ultimately move to human trials," said Wooldridge. "This would hopefully demonstrate a positive immune response to the vaccine. By identifying a range of active proteins, rather than just one, we could develop a vaccine that targeted all strains of the group B meningococci."

The current study is one of the many projects funded by Meningitis UK. Its recently launched 'Search 4 a Vaccine Campaign' aims to raise £7 million over the next few years to fund research into developing a vaccine against group B meningitis.

"We are extremely pleased to be funding Dr Karl Wooldridge and his team in their work to discover more about the proteins secreted by the meningitis B bacteria. If this research can go forward to help develop a vaccine, thousands of lives could be saved, said Meningitis UK's chief executive Steve Dayman. "Meningitis can be incredibly hard to detect as many of its symptoms are often similar to more minor ailments, such as the common cold or flu, plus there are occasions when people show no, or very few, symptoms. For these reasons, we believe the only way to eradicate meningitis completely is through the development of a preventative vaccine."

Sources: The University of Nottingham, UK: www.nottingham.ac.uk; Meningitis UK: www.meningitisuk.org

Synflorix™ is under review by the EMEA

Vaccine:	Synflorix™
Manufacturer:	GlaxoSmithKline Biologicals
Indication:	Pediatric vaccine against nontypeable *Haemophilus influenzae* and *Streptococcus pneumonia*

Synflorix™, a pneumococcal *H. influenzae* protein D conjugate vaccine, is being reviewed by the EMEA. The vaccine provides protection against both nontypeable *H. influenzae* (NTHi) and *S. pneumoniae*, which are the leading cause of acute otitis media, a very common middle ear infection in children. NTHi is also a leading cause of bacterial respiratory infections, for which no vaccines are available.

S. pneumoniae causes invasive pneumococcal disease, including meningitis, invasive pneumonia and bacteremia. The current licensed vaccine only covers three serotypes (1, 5 and 7F). The new vaccine Synflorix includes ten *S. pneumoniae* serotypes responsible for more than 80% of pediatric invasive pneumococcal disease worldwide. Pneumococcal serotypes are conjugated to protein D of NTHi to provide protection against *S. pneumoniae* and NTHi in a single vaccine.

> "Synflorix includes ten *Streptococcus pneumoniae* serotypes responsible for more than 80% of pediatric invasive pneumococcal disease..."

In an earlier trial (Pneumococcal Otitis Efficacy Trial), a prototype of this ten-valent vaccine showed protection against acute otitis media due to *S. pneumoniae* and NTHi. Currently, GlaxoSmithKline is filing for regulatory approval of Synflorix in several other countries besides the EU.

"We are very pleased with this important step towards the introduction of this vaccine, which is designed to offer a broad protection against pneumococcal disease and a dual pathogen protection against otitis media caused by *S. pneumoniae* and NTHi. This approach is a continuation of our heritage to develop vaccines which address multiple pathogens with a single vaccine," said Jean Stéphenne, president of GlaxoSmithKline Biologicals. "If approved, this vaccine could further reduce the mortality due to invasive pneumococcal disease and also the significant morbidity associated with a more frequent disease in children, namely otitis media."

Antibiotic resistance is slowly increasing among *S. pneumoniae* and NTHi in many areas of the world, and a vaccine such as Synflorix is much needed.

Source: GlaxoSmithKline Biologicals: www.gsk.com

New insight on where T cells kill viruses

Understanding the confrontation between T cells and viruses may help vaccine development.

New findings that appeared in the February issue of the journal *Nature Immunology* have shed more light into the battlefield between killer T cells and viruses. Researchers from the National Institute of Allergy and Infectious Diseases, part of the NIH, have shown that viruses are challenged by killer T cells just after they have entered the lymph nodes.

Lymph nodes occur along lymphatic vessels and filter pathogens and foreign particles out of the lymphatic system. Lymph enters the node and drains in a space called the subcapsular sinus, which subsequently drains deeper into trabecular sinuses and finally into medullary sinuses. Pathogens, such as viruses and bacteria, are presented to lymphocytes, a process conventionally thought to happen deep inside the node, resulting in adaptive immune responses. It is unclear where antiviral lymphocytes (CD8 cytotoxic T cell) are activated within the lymph nodes.

> "...when the viruses had just got inside the mouse lymph nodes' surface, a swarm of T cells were triggered..."

Jonathan Yewdell and colleagues had labeled mouse T cells with a fluorescein before injecting them back into the animals. The mice were then infected with vaccinia viruses that were also labeled with a recombinant protein. Using a multiphoton microscope, the scientists showed that when the viruses had just got inside the mouse lymph nodes' surface, a swarm of T cells were triggered that led to subsequent virus-specific T-cell responses, killing virus-infected cells. This is in contrast to current understanding that viruses need to travel deep inside lymph nodes before a virus-specific immune response can be triggered.

"A key challenge in viral vaccine research is developing strategies for immunizing against lethal viruses, such as HIV, that have eluded the standard vaccine approaches," said Yewdell. "We have contributed a page to the handbook of understanding how to rationally design vaccines to elicit a T-cell response."

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Understanding how and where viruses are challenged by the immune system is critical in antiviral vaccine development. These new findings are important as they detailed the interaction of viruses and immune cells inside a living animal.

Sources: Hickman HD, Takeda K, Skon CN *et al.* Direct priming of antiviral $CD8^+$ T cells in the peripheral interfollicular region of lymph nodes. *Nat. Immunol.* 9(2), 155–165 (2008); The US National Institute of Allergy and Infectious Diseases: www.niaid.nih.gov

Preliminary results show promise for a malaria vaccine candidate

Vaccine:	FMP2.1/AS02A
Trial registration:	ClinicalTrials.gov NCT00308061
Trial nature:	Phase I, double blind, randomized, controlled, dose escalation
Trial place:	Bandiagara, Mali
Subject:	60 adult volunteer
Result:	Safe, well tolerated, highly immunogenic

In the January issue of the journal *Public Library of Science ONE*, an international team of researchers have tested a new malaria vaccine candidate in 40 Malian adults and found that the vaccine was safe and induced a strong antibody response in the blood of the volunteers.

Malaria is a leading cause of death in Africa and several other developing countries, and is responsible for more than 1 million deaths each year, most of them children. The clinical trial was carried out in Bandiagara, a town in northwest Mali with heavy burden of the disease. A total of 60 volunteers were randomized to receive either full dose or half dose of the candidate malaria vaccine, or a control vaccine (rabies). The malaria vaccine was designed to prevent the entry of malarial parasites into human blood cells.

This clinical trial was led by Mahamadou Thera of the Malaria Research and Training Center at the University of Bamako (Mali) and Christopher Plowe of the National Institute of Allergy and Infectious Diseases, part of the NIH. Other collaborators included scientists from Walter Reed Army Institute of Research (MD, USA), the US Agency for International Development (DC, USA) and GlaxoSmithKline Biologicals (Belgium).

The study started at the end of a rainy season. As expected, all participants had an initial high level of antibodies against malarial parasites, indicating recent exposure to malaria. The 40 recipients of the malaria vaccine developed significantly higher antibody levels (up to sixfold) while the other 20 who received the control vaccine showed declining level of antibodies. The candidate malaria vaccine was also well tolerated.

Based on these promising results, new clinical trials are being carried out in 400 Malian children aged 1–6 years using this new malaria vaccine candidate.

Sources: Thera MA, Doumbo OK, Coulibaly D *et al.* Safety and immunogenicity of an AMA-1 malaria vaccine in Malian adults: results of a Phase 1 randomized controlled trial. *PLoS ONE* 3(1), e1465 (2008); The US National Institute of Allergy and Infectious Diseases: www.niaid.nih.gov

Influenza vaccination during hospital visits may be beneficial

Hospitalized children may avoid subsequent hospitalization if they are vaccinated against influenza.

In an article published in the February issue of the journal *Pediatrics*, researchers from Seattle Children's Hospital (WA, USA) have found that approximately 23% of children hospitalized with influenza and a serious related complication had a previous hospitalization during the most recent influenza season. The authors suggested that had these children been vaccinated during their previous hospitalization, they might have been protected from influenza and might not need to go to hospital again.

> "...approximately 23% of children hospitalized with influenza and a serious related complication had a previous hospitalization during the most recent influenza season."

Unlike the common cold, symptoms of influenza are much more severe with fever, headache, body aches, coughing, sore throat, runny nose and extreme fatigue. Influenza is also highly contagious and is responsible for approximately 36,000 deaths and 200,000 hospitalizations every year in the USA. Influenza season is between November and April, peaking in January and February. High-risk groups include children, people with compromised immune system and those with underlying conditions such as asthma. The most common complication is pneumonia, and complications can be serious in the high-risk groups.

Led by Danielle Zerr, the research team has studied the Pediatric Health Information System (PHIS) database from 2001 to 2006. The PHIS database includes administrative data from 42 hospitals, and the researchers have identified approximately 14,000 influenza cases and 170,000 cases of respiratory complications. Children from newborns to the age of 18 years were included in the study. Approximately 16% of those hospitalized with influenza and 23% of those hospitalized with influenza and another complication had previous hospital admissions during the most recent influenza season.

> "...a significant proportion of hospitalized children due to influenza could have avoided hospitalization if they had been vaccinated during their previous visits."

"This information will help pediatricians recognize hospitalization as an important opportunity to vaccinate the highest-risk children, and may hopefully prompt the development of hospital-based flu vaccine programs," said Zerr.

In 2007, the US CDC Advisory Committee on Immunization Practices recommended that unvaccinated patients of all ages and all individuals at high-risk of acquiring influenza (young children and the elderly), who are hospitalized during the influenza season, should be encouraged to receive influenza vaccination before being discharged. Findings from the current study indicated that a significant proportion of hospitalized children due to influenza could have avoided hospitalization if they had been vaccinated during their previous visits.

"Many of the sickest children have very fragile immune systems. At Seattle Children's we've already expanded our program beyond patients and staff to ensure we're doing everything we can to reduce the risk of exposing our high-risk patients to the flu and its complications," said Zerr. "With findings from this study, we can see that an industry-wide review of hospital-based flu vaccines for all children could take flu-prevention to the next level."

Sources: Zerr DM, Englund JA, Robertson AS, Marcuse EK, Garrison MM, Christakis DA. Hospital-based influenza vaccination of children: an opportunity to prevent subsequent hospitalization. Pediatrics 121(2), 345–348 (2008); Seattle Children's Hospital Research Institute, WA, USA: www.seattlechildrens.org

About the News in brief

The News in Brief highlights some of the most important events and launches in the vaccine field. The editorial team welcomes suggestions for timely, relevant items. If you have newsworthy information, please contact:

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