

Human Vaccines: News

On-time shots are safe for babies

Researchers from the University of Louisville, KY found that there is no benefit to delaying immunizations during the first year of life.

"Some parents request alternative immunization schedules as a precaution against widely publicized, but unfounded concerns about vaccines," explained lead author and pediatric infectious diseases specialist Dr. Michael J. Smith. "This study suggests that delaying vaccines does not give infants any advantage in terms of brain development."

The study, which appeared in the June issue of the journal *Pediatrics* (2010, 125: 1134-1141), evaluated the health records of 1047 children to determine the long-term neuropsychological impact of multiple vaccinations received in the first seven months of life.

Using records collected for a previous VaccineSafety Datalink study of thimerosal

exposure, researchers compared children's performance on 42 neuropsychological tests with the timeliness of vaccinations during their first year of life. The developmental tests, given when the children were between the ages of 7 and 10, included assessments of speech and language, fine motor coordination, behavior regulation, general intellectual functioning and other abilities.

Children with timely receipt of vaccination were compared to all other children in the study who had delays in receipt of one or more doses. In a second analysis, children who received the maximum number of vaccines during the first seven months of life were compared to those who received the fewest vaccines in the study group.

Researchers found that children who received each dose of each vaccine on time

performed better on two of the 42 tests, after adjustment for familial and socioeconomic factors. Those who missed or were late for one or more doses of vaccine did not perform better on any test. Thus, there was no evidence to suggest that multiple vaccines in the first year of life affect a child's cognitive abilities later.

The infant immunization schedule has changed over the past decade, so more studies are needed to confirm this study's implications for new generations of babies. For example, today's newborns receive two additional vaccines. Still, today's infants' immune systems are exposed to fewer vaccine antigens than they were during the period covered by this study, so the findings are likely to be similar.

PROVENGE shows few side effects

After approval of PROVENGE by the US Food and Drug Administration (FDA) in April (*Human Vaccines News & Policy & Profiles* 6-6) Dendreon presented additional safety data from the integrated analysis of four randomized clinical trials of the autologous cellular immunotherapy in prostate cancer at the 105th Annual Scientific Meeting of the American Urological Association (AUA) in San Francisco, CA.

The world's first approved therapeutic cancer vaccine, PROVENGE, is made from patient's own white blood cells. Once removed from the patient, the cells are treated in cell culture and placed back into the same patient. These

treated cells then cause an immune response, which in turn kills cancer cells, while leaving normal cells unharmed. According to the FDA, Provenge is given intravenously in a three-dose schedule delivered at two-week intervals.

The analysis included data from four randomized trials in patients with either metastatic castrate resistant prostate cancer or androgen-dependent prostate cancer, that were integrated to examine the safety profile of PROVENGE across the four studies.

The vast majority (83%) of the men enlisted in the Phase III trials were able to go about their lives without restrictions. The most common side effects were symptoms similar to the

flu, with 3.5% experiencing chills, fever and headache. Usually it took only a day or two for the symptoms to resolve. Another 3.5% experienced more serious infusion reactions.

Thus, the latest safety data from four Phase III trials confirm that the vaccine extends survival, improves quality of life, and has only mild side effects. However, one of product's biggest drawbacks, it appears, is cost.

"I've heard \$30,000, I've heard \$90,000 ... I have no idea what it's going to cost. And who's going to pay for it?" asks Dr. Nelson Neal Stone, a clinical professor of urology and radiation oncology at Mount Sinai School of Medicine in New York City (NY, USA).

Brain cancer vaccine looks promising in small trial

A Phase I trial of an experimental dendritic cell-based brain cancer vaccine sponsored by the Los Angeles-based biotech company ImmunoCellular Therapeutics (IMUC) has produced some unusually positive results.

Sixteen patients suffering from glioblastoma multiforme (GBM) - the most common of all brain cancers - were recruited for the Phase I study. The newly diagnosed patients who

received the vaccine ICT-107 in addition to the standard of care of surgery, radiation and chemotherapy demonstrated a one-year overall survival of 100% and a two-year survival of 80%. This compares favorably with historical 61% one-year and 27% two-year survival based on the standard of care alone.

The 18-month disease-free survival from the time of surgery was almost 50% with

ICT-107, compared with 18% historically. The median progression-free survival (PFS) of 18 months after surgery compared especially favorably with the historical median PFS of 7 months observed with the standard treatment.

Seven of the 16 patients continued to live with no disease progression with an average time of over 29 months. No serious adverse

events were reported for ICT-107, and minor side effects were limited to fatigue, skin rash and pruritis.

"These new data further establish ICT-107 as a promising potential treatment for glioblastoma, a disease for which there are currently few and limited treatment options", said Dr. Surasak Phuphanich, Director of the Neuro-Oncology

Program at Cedars-Sinai Medical Center (CA). "We are excited for what these data mean for patients, the medical community, and the field of immunotherapy as a whole. We look forward to further investigating ICT-107 in additional clinical studies."

IMUC is developing immune-based therapies for the treatment of brain and other cancers.

In the second half of 2010 the Company is planning to initiate a multicenter phase II study with its lead product candidate ICT-107, a dendritic cell-based vaccine targeting multiple tumor associated antigens as well as cancer stem cell antigens for glioblastoma.

Only one-third of girls receive HPV vaccine

According to a new report from researchers at Washington University School of Medicine in St. Louis (MO) about two-thirds of young women eligible for receiving the human papillomavirus (HPV) vaccine are not getting the shot, although the vaccine can help guard against cervical cancer.

Public health officials recommend that women and girls receive the HPV vaccine Gardasil, which prevents four strains of the sexually transmitted human papillomavirus, two of which are found in about 70 percent of all women with cervical cancer.

A recent study evaluated the influence of geographic disparity and area poverty on HPV vaccination. The authors analyzed data from 1709 girls in 274 counties of six US states (Delaware, New York, Oklahoma, Pennsylvania, Texas and West Virginia) and found that only 34% of girls ages 13-17 were vaccinated in these six states.

The information came from a national telephone survey called the Behavioral Risk Factor Surveillance System (BRFSS). "This was the first year the survey asked about HPV vaccination," explained Dr. Sandi Pruitt, one of the study authors. "That portion of the survey was optional, and only six states opted to use it. Ideally, we'd like to know what's happening in more states, but these six states represent a good cross-section of urban and rural, rich and poor, and they do include girls from racial and ethnic groups that closely mirror the rest of the country."

More than 70% of the girls in this study were white, and almost 75% had health insurance. Girls living in states with more poverty were less likely to get the HPV vaccine, but higher poverty rates in the individual counties within those states and lower family income levels actually made it more likely a girl would be vaccinated. According to Dr.

Pruitt, those seemingly contradictory findings may be explained in part by the way in which funding for vaccines is allocated.

"Individual states set different guidelines for providing vaccines to those with no insurance versus those who may be underinsured," Pruitt explains. "So girls from poorer counties may be more likely to qualify for a free vaccine, whereas those states with more poverty may not have adequate funding to provide it or may be less likely to fill in gaps for those who may not have enough private insurance coverage to pay for it."

The study was published in the May issue of the *American Journal of Preventive Medicine* (2010, 38: 525-533).

Therapeutic CMV vaccine: promising Phase II trial

The San Diego-based company Vical (CA) presented encouraging preliminary data from an ongoing Phase II clinical trial with their cytomegalovirus (CMV) vaccine TransVax™ at the recent World Vaccine Congress Washington.

CMV affects 30-60% of patients undergoing transplant procedures, causing transplant rejection, serious illness and even death if untreated. There is no approved vaccine against this virus. For transplant patients, Vical is developing TransVax, a therapeutic bivalent DNA vaccine encoding CMV glycoprotein B (gB) and phosphoprotein 65 (pp65) for the induction of both, cellular and humoral immune responses. The vaccine is formulated with a proprietary poloxamer-based

delivery system, designed to enhance primarily a cellular immune response. TransVax has orphan drug designation for transplant patients.

The current Phase II trial is evaluating the potential for TransVax to prevent CMV reactivation in immunosuppressed CMV-seropositive hematopoietic stem cell transplant (HCT) recipients, which could reduce antiviral usage and CMV-associated disease. The vaccine elicited sustained increases in both cellular and antibody immune responses compared with placebo through the final 12-month follow-up. Final results are expected in the second half of 2010.

"We were excited to see that our TransVax vaccine was able to enhance both T-cell and

antibody responses to the encoded CMV antigens through the final 12-month data point," said Dr. Richard Kenney, Vical's Vice President of Clinical Development. "And we are excited to see how these responses impact viral control. We also saw an encouraging boost in both T-cell and antibody responses after the fourth injection, which could prove important in controlling late-onset CMV reactivation. We expect to complete our analysis of the final trial data and report on our full evaluation of viral load and clinical endpoints in the third quarter."

Linking Smallpox eradication to spread of HIV

According to a new study, the eradication of smallpox might have inadvertently aided the spread of human immunodeficiency virus (HIV). In fact, the vaccine used to wipe out smallpox offered some protection against the AIDS virus and, now that it is no longer used, HIV has flourished.

The relatively sudden appearance and explosive spread of HIV throughout Africa and around

the world beginning in the 1950s has never been adequately explained. Theorizing that this phenomenon may be somehow related to the eradication of smallpox followed by the cessation of vaccinia immunization, researchers from the George Mason University in Manassas (VA) undertook a comparison of

HIV-1 susceptibility in the peripheral blood mononuclear cells from subjects immunized with the vaccinia virus to those from vaccinia naive donors.

Looking at the white blood cells taken from people recently immunized against smallpox, scientists found significantly lower replication rates of HIV, compared with those from unvaccinated controls. The study, which was recently published in the journal *BMC Immunology* (2010, 11:23) suggests that prior immunization with vaccinia virus might provide an individual with some degree of protection to subsequent HIV infection and/or progression.

“There have been several proposed explanations for the rapid spread of HIV in

Africa, including wars, the reuse of unsterilised needles and the contamination of early batches of polio vaccine,” lead researcher Dr. Raymond Weinstein told the BBC. “However, all of these have been either disproved or do not sufficiently explain the behavior of the HIV pandemic.”

Smallpox immunization was gradually withdrawn from the 1950s to the 1970s, following the worldwide eradication of the disease, and HIV has been spreading exponentially ever since. Currently, only scientists and medical professionals working with the disease are vaccinated against Smallpox. But the US investigators emphasize that it is too early to recommend smallpox vaccine for fighting HIV.

Future pandemic vaccines may face suspicion

When the next pandemic hits, a high number of people in the US are expected to steer clear of any new vaccine developed to prevent an outbreak. Doubts regarding the safety of the new vaccine combined with the belief that the pandemic does not pose a serious health threat may lead to low compliance in the population.

That is the conclusion of a new study by researchers at Boston's Harvard School of Public Health (MA, USA). Given the crucial role that the public plays in containing or spreading illness and in seeking related medical care, the researchers examined 20 national opinion polls taken as the H1N1 pandemic swiftly spread throughout the country last year.

The authors looked at the extent to which people adopted specific behaviors during

three periods: (1) the early months of the pandemic, when no vaccine was available; (2) at the time of the initial, delayed release of vaccine to high-priority groups; and (3) after the vaccine became widely available. They also examined the reasons that many Americans did not get vaccinated and reviewed the public's view of the government's response to the pandemic. The report was published online in the *New England Journal of Medicine* (2010, 362: e65).

Only one-third of all adults concluded that the new swine flu vaccine was “very safe,” with a deep undertow of doubt regarding its safety. Even ahead of the vaccine's arrival last fall, only about half of adults said they planned to get a shot. By December, as a large

quantity of flu vaccine became available, there was a growing belief that the pandemic was not as serious as originally believed.

“In the event of a future influenza pandemic, a substantial proportion of the public may not take a newly developed vaccine because they may believe that the illness does not pose a serious health threat, because they (especially parents) may be concerned about the safety of the available vaccine, or both,” the report concludes.

The take-home message is that governments will need to roll out an ambitious education program if they expect widespread use of any new pandemic vaccine made to guard against a future outbreak.

Human Vaccines: Profile

Questions for Biotechs

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Dr. Martin Bachmann is the Executive Vice President and Chief Scientific Officer of Cytos

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

The Company started 1996 as a spin-off of the ETH, the Technical University of Zürich. Cytos initially was set up as a process development company and developed processes for various biosimilars, including human growth hormone, which is now marketed by Sandoz. In 1999, Cytos started to build up the vaccines platform we are currently working on.

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

We have about 80 employees. Most of them we recruit through ads; some of them through head-hunters.

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

The core of both our technologies is virus-like particles (VLPs). We use VLPs to display antigens of choice in a highly repetitive and ordered manner, which leads to very potent antibody responses against these antigen (they obtain a "viral fingerprint"). Our vaccines against hypertension, Alzheimer's disease, smoking and type II diabetes are based on this platform. The second way we use the VLPs is as delivery systems for toll-like receptor 9 (TLR9) ligands. Specifically, we package CpGs into these nanoparticles, which leads to in vivo activation of TLR9. These immunomodulators are used to treat rhinitis and asthma. The vaccines and immunomodulators have been or are in Phase II studies.

Can you provide a short overview of your product pipeline?

Clinically, we have vaccines against smoking and Alzheimer's disease together with Novartis in development. A vaccine against type II diabetes is currently unpartnered in Phase I/II. For the smoking cessation vaccine, we immunize against nicotine, for Alzheimer's disease against a short A β -derived peptide, for type II diabetes against IL-1b. We are establishing GMP-production for three more products, a vaccine targeting TNF (for rheumatoid arthritis), IL-17 (for psoriasis) and flu. We are co-developing the latter with Singapore.

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

The competition with vaccination against self-molecules is very limited. Nabi is a competitor for the generation of a smoking cessation vaccine. Our platform has the advantage to induce (from what we can tell without formal side-by-side comparison) much stronger antibody responses. For flu, all major vaccines producer are competitors. Our approach has the advantages of generating stronger and more rapid immune responses, and very large amounts of vaccines can be

produced very quickly. Hence, our approach could satisfy the needs of seasonal as well as pandemic vaccines. This is why Singapore has great interest in the approach.

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

- A successful Phase II study for the treatment of hypertension (*Lancet* 2008 371:821-7).
- A success for Phase II study for smoking cessation (*PLoS One* 2008; 3:e2547).
- Two recent successful phase II studies for the treatment of rhinitis as well as asthma.
- Numerous preclinical studies.

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

Our approach to immunize against self-molecules is very novel and is therefore viewed critically. We can only overcome this skepticism by being successful. Nevertheless, we have ongoing clinical programs with Novartis and preclinical programs with Pfizer.

What is your company's value proposition?

Most of our vaccines target large markets classically occupied by pharma producing small molecules. If things work out, the overall market will be huge.

What business development strategy do you pursue?

Reach proof-of-concept and license the products out to large partners.

How does your company attract partners?

We have been in constant contact with big pharma over the last ten years.

Who are your most important partners?

Novartis and Pfizer.

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

We have established key animal models and GMP production of the vaccines in house. Models that we use rarely are outsourced.

What are your product development goals for the next 3 years?

To enter the clinic and reach proof-of-concept with vaccines against TNF, IL-17 and 3 more vaccines in the field of infectious diseases. To successfully finish phase II development of the vaccine against type II diabetes.

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