**Immunology in the News**

**HIV Vaccine Feat Leaves More Questions Than Answers**

A COMBINATION OF VACCINES IS FOUND TO PROVIDE MODEST PROTECTION AGAINST INFECTION. NOW SCIENTISTS HAVE TO FIND OUT HOW THAT HAPPENED.

By Karen Kaplan and Thomas H. Maugh II

Los Angeles Times
September 25, 2009

Only hours after HIV vaccine researchers announced the achievement of a milestone that has eluded them for a quarter of a century, they began plotting their next steps—and coming to grips with a sobering reality. Their ultimate goal, halting the spread of AIDS, remains far in the future.

A Thai and American team had announced early Thursday in Bangkok that they had found a combination of vaccines that provided modest protection against infection with HIV, offering the first proof of principle that the deadly disease could be tamed by teaching the immune system to recognize the virus and defeat it.

Scientists around the world hailed the achievement. But by Thursday afternoon, the initial wave of euphoria and new threats like superbugs MRSA and C. difficile, rising worldwide emphasis on government support has been drawing in new companies, from nascent biotechs to Johnson & Johnson. That means recent remarkable strides in overcoming dreaded diseases and annoying afflictions likely will continue.

“Even if a small portion of everything that’s going on now is successful in the next 10 years, you put that together with the last 10 years (and) it’s going to be characterized as a golden era,” says Emilio Emini, Pfizer Inc’s head of vaccine research.

Vaccines now are viewed as a crucial path to growth, as drugmakers look for ways to bolster slowing prescription medicine sales amid intensifying generic competition and manufacture vaccines. Rising worldwide emphasis on prevention health care, plus the advent of the first multibillion-dollar vaccines, have further boosted their appeal.

While prescription drug sales are forecast to rise by a third in five years, vaccine sales should double, from $19 billion last year to $39 billion in 2013, according to market research firm Kalorama Information. That’s five times the $8 billion in vaccine sales in 2004.

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**Vaccines on Horizon for AIDS, Alzheimer’s, Herpes**

By Linda A. Johnson

Associated Press
November 17, 2009


Many could be on the market in five years or less.

Contrast that with five years ago, when so many companies had abandoned the vaccine business that half the U.S. supply of flu shots was lost because of contamination at one of the two manufacturers left.

Vaccines are no longer a sleepy, low-profit niche in a booming drug industry. Today, they’re starting to give Alliance for Health and American Health Partnership leaders the sorts of challenges and opportunities that top executives would have likely been anxious to avoid.

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worked, and an additional five to 10 years to produce a vaccine that was ready to test in people. Some researchers even wondered whether the approach reduced their chances of success. Nevertheless, a statistical fluke resulting from the small number of HIV cases observed in the trial. The abundance of unanswered questions hasn’t sapped the enthusiasm of many HIV researchers. After 26 years of seemingly futile research on vaccines, they have finally made some progress on developing a universal HIV vaccine, said Dr. Anthony Fauci, director of the National Institute of Allergy and Infectious Diseases, which largely funded the $120-million study. “This is the first positive signal. We’ve been passed by—where we have never gotten with any vaccine that we have ever tested in humans,” Fauci said. But it is a vaccine that is ready for prime time? No.”

The Thai trial, which began in 2003, had been disparaged by many critics as a waste of time and money because its two vaccines had produced no benefit in individual trials. But a few researchers speculated that using them together—with one vaccine priming the immune system and the second boosting that response—would be more effective. The primer in this combo is Alvac, made by Sanofi Pasteur, which uses a defanged canary-pox virus to carry three synthetic HIV genes into the body, while the boost is made from Aidenovax, originally made by VaxGen Inc. and now owned by the nonprofit group Global Solutions for Infectious Diseases. It contains a genetically engineered version of one of the proteins from the HIV surface.

The study, led by Dr. Supachai Rerks-Ngarm of the Thai Ministry of Public Health’s Department of Disease Control, involved more than 16,000 volunteers in Thailand, all from the general population, rather than from a pool of high-risk homosexuals and intravenous drug users used in past studies. Half received the primer from Alvac and two boost doses of Aidenovax over a six-month period; the other half received placebo shots. After three years of follow-up, new HIV infections were observed in 74 of the 8,198 people who received the placebo, but in only 51 of the 8,197 given the vaccine, a statistically significant 31% lower rate. To the researchers’ disappointment, however, the vaccine did not reduce levels of HIV activity in those who became infected after being vaccinated. Full details of the study will be released next month at a conference in Paris, and researchers are eagerly awaiting them.

Dr. Salim S. Abdool Karim, an epidemiologist at Columbia University in New York and director of the Centre for the AIDS Programme of Research in South Africa in Durban, said he was particularly eager to know whether people who got vaccinated and stayed healthy had a bigger response from the white blood cells known as cellular T lymphocytes. “A whole range of vaccines were developed on the hypothesis that they generated sufficient [cellular T lymphocyte] responses to either prevent infection or impact viral load,” he said. “We’ve never been able to test that hypothesis because no vaccine has worked until now.” And with it, he added, “if lymphocytes, then ‘what kind of compounds were the cells making when you inoculate them with the vaccine?” asked Dr. Spyros Kalams, an HIV immunology researcher at Vanderbilt University. Nurturing the future of the HIV Vaccine Trials Program there. “Was it a compound that could kill infected cells? Does it make proteins that stop the virus from replicating? Researchers now will begin the painstaking work of comparing the blood of those who were vaccinated and resisted infection and those who did not. Then they will look for molecules that are more abundant in the healthy people, Fauci said. “That led to the 2004 flu season when half the U.S. flu shot supply was lost overnight, plus continuing periodic shortages of some kids’ vaccines.”

Today, five companies supply flu vaccine: GlaxoSmithKline, Switzerland’s Novartis AG, Australia’s CSL Biologics, Medimmune, part of Britain’s AstraZeneca PLC, and France’s Sanofi-Aventis SA. “What kind of compounds were the cells making when you inoculate them with the vaccine?” asked Dr. Spyros Kalams, an HIV immunology researcher at Vanderbilt University. Nurturing the future of the HIV Vaccine Trials Program there. “Was it a compound that could kill infected cells? Does it make proteins that stop the virus from replicating? Researchers now will begin the painstaking work of comparing the blood of those who were vaccinated and resisted infection and those who did not. Then they will look for molecules that are more abundant in the healthy people, Fauci said. “That led to the 2004 flu season when half the U.S. flu shot supply was lost overnight, plus continuing periodic shortages of some kids’ vaccines.”

Vaccines command higher prices—roughly $375 for the three-shot Gardasil series—and so are more profitable than in the past. With only one or two manufacturers, prices are liable to change as competition increases. For flu shot makers, the risk of having to throw out millions of unused doses here come spring and fall. A government bought huge amounts of flu vaccine to stockpile in the event of a pandemic. But several scientists cautioned that there was no guarantee the Thai blood samples would reveal the biological secrets of HIV immunity. “Surely some of the people who resisted HIV infection were protected by the vaccine, but not all,” said Dr. Otto Yang, an immunologist at UCLA’s David Geffen School of Medicine.

Yang also expressed doubt that a combination of vaccines made the difference in those who benefited. He offered a positive sign that this was the first large vaccine trial to focus on a low-risk population. Perhaps transmitting the virus through heterosexual sex instead of directly into the bloodstream on an intravenous needle would help the immune system a better chance of fighting off infection.

Although it is also unclear whether these particular vaccines could be used elsewhere in the world, scientists said that if they could figure out what made this combination work, they could localize the approach to other regions. The dominant HIV strain varies from region to region. At least 33 million people worldwide are infected with HIV and 25 million have died, the World Health Organization said. An estimated 7,500 are infected each day, accentuating the need for a vaccine.

There have been three previous vaccine trials in humans. Adshek had previously failed in two large trials. But several scientists cautioned that there was no guarantee the Thai blood samples would reveal the biological secrets of HIV immunity. “Surely some of the people who resisted HIV infection were protected by the vaccine, but not all,” said Dr. Otto Yang, an immunologist at UCLA’s David Geffen School of Medicine.

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Experimental Vaccine Cures Pre-cancer Vulvar Growths

Reuters
November 5, 2009

BOSTON—An experimental vaccine cured nearly half of women with pre-cancerous growths on their genitals, producing major improvement in nearly four out of five, researchers in the Netherlands reported on Wednesday.

“We hope to get results like this in women with cancer, but those tests are in the future,” team leader Dr. Gemma Kenter of Leiden University said in a telephone interview.

The vaccine is different from the Merck’s Gardasil vaccine and GlaxoSmithKline’s rival Cervarix, which are available to prevent cervical cancer caused by common forms of the human papillomavirus. For example, there are innate sensors for many viruses that share RNA as genetic material. Once the sensor is engaged the body makes the protective antiviral substance interferon.

This subject is illustrated in the article about Andrew Meble and colleagues at Berkeley, “When Body Meets H1N1 Flu,” page 4, which describes the intricate, even amazing, innate response to several RNA viruses. The fulcrum is the rapid production of interferon, and this interferes to influenza, West Nile, dengue, yellow fever and likely several other RNA viruses.

Can we define chemical immunics to elicit these innate responses and keep people from having to experience the whole virus or bacterium? If so, this is what Bill had in mind as “universal boosters” of our defenses. Research is now proceeding very actively to identify these microbial mimics.

Innate immunity contrasts with the narrower breadth of adaptive or acquired immunity. But what adaptive immunity sacrifices in breadth it makes up in depth and longevity (years or more) of the induced resistance. This is why adaptive immunity is the basis for successful vaccines. But a vaccine is never universal. Instead the Jonas Salk and Albert Sabin vaccines gave us a durable defense specifically against the poliovirus, and we needed other vaccines to prevent infection with yellow fever, influenza, measles and other diseases.

Why do I bring up adaptive immunity and vaccine science, which seemingly go beyond Bill Safire’s interest in universal boosters of innate immunity? It turns that to bring about adaptive immunity, any individual vaccine first has to trigger an innate response. In essence, immune cells called dendritic cells first see the vaccine as a class of attacker, and this allows the cells to initiate the specific, but powerful and durable, response that will protect us for years in the future.

How can we improve things? First, we should pay more attention to the vaccine’s capacity to elicit innate immunity, which lets the body’s dendritic cells know that it is time to act. The dendritic cells must capture the vaccine and acquire many other features needed to induce protective, long-lived adaptive immunity.

A Reuters article discusses an exciting early study from Gemma Kenter and colleagues in the Netherlands (“Experimental Vaccine Cures Pre-cancer Vulvar Growths,” below). The vaccine is composed of parts of the cancer-causing human papillomavirus. In my view, the chosen stimulus for innate immunity did not seem powerful. Nevertheless, many patients in the study did show a durable therapeutic effect; the vaccine helped their immune systems attack an existing precancerous lesion. Since death rates from cancer remain stubbornly high, I wish the cancer community would overcome a huge gap and vigorously try to harness these principles of immunology against cancer.

The Associated Press article summarizes the surge in interest in vaccine science from the pharmaceutical industry (“Vaccines on Horizon for AIDS, Alzheimer’s, Herpes,” also on the front page). Vaccines have the capacity to specifically teach our immune systems to block many clinical problems—not only infections but also cancer. Vaccines are unique “drugs.” They are not taken every day. Rather, or at most a few injections endow our bodies with a lasting capacity to resist disease. New vaccines will prove to be easier and more effective to develop, I think, if we can better link the principles of innate and adaptive immunity.

Immunology was only one of Bill’s responsibilities at the Dana Foundation. Throughout his tenure he provided us a mix of creativity, candor and collegiality that was unique. We miss him enormously.

Ralph Steinman, M.D., is professor and senior physician at The Rockefeller University in New York City, and is the recipient of the 2007 Albert Lasker Award for Basic Medical Research. He serves as scientific consultant for the Dana Foundation and scientific advisor for Immunology in the News.

Two Types of Immunity; A One-of-a-Kind Person
Ralph Steinman, M.D.

This is my first commentary in which I have not been guided by Bill Safire and his wonderful talents. Bill died suddenly this past September after heading the Dana Foundation for nine years. As an informed commentator like me, it was an exceptional and lucky experience to benefit from the patience and wisdom he extended.

Bill’s zest and sharp mind made science more stimulating. He wanted the Dana Foundation to help launch the careers of young scientists, and he wisely prioritized the need to communicate science. He was deeply committed to Dana support for programs that were new and would have a multiplier effect on future benefit. It was special to work with him to pursue his brainstorm.

His scientific focus was the brain, but he was also intrigued by immunology, especially neuroimmunology. Remarkably, Bill foresaw the threat of bioterrorism before 9/11. To deal with this, he wondered if science could identify ways to boost the body’s resistance against a wide number of infectious threats, not just one. Maybe scientists could identify such “universal boosters” to be taken during a bioterrorist attack.

This idea now has a real footing in the field of innate immunity, the rapid defense mechanisms the body uses to detect and respond to infection. These mechanisms involve innate sensor molecules that individually perceive wide classes of microbial challenges. For example, there are innate sensors for many viruses that share RNA as genetic material. Once the sensor is engaged the body makes the protective antiviral substance interferon.

This subject is illustrated in the article about Andrew Meble and colleagues at Berkeley, “When Body Meets H1N1 Flu,” page 4, which describes the intricate, even amazing, innate response to several RNA viruses. The fulcrum is the rapid production of interferon, and this interferes to influenza, West Nile, dengue, yellow fever and likely several other RNA viruses.

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When Body Meets H1N1 Flu

Two separate research teams have cataloged interactions between the H1N1 influenza virus and human cells, with one group reporting that human cells already contain powerful anti-flu agents that also help defend against other viral infections, including West Nile virus and dengue.

Published online December 17 in “Cell,” both studies may help scientists build better flu-fighting therapies in the future.

One of the studies concentrated on learning how the body responds to the flu, says Stephen Elledge, a Howard Hughes Medical Institute investigator at Brigham and Women’s Hospital and Harvard Medical School in Boston. Elledge and Abraham Brass led the study, which identified more than 120 human genes required by the H1N1 virus to infect a cell. For most of the genes, their removal stopped or slowed virus growth. But for three of these genes, removal actually helped the virus grow better, indicating that those genes are normally involved in fighting the virus.

These genes encode proteins in a family called the interferon-inducible transmembrane family, or IFITM proteins. The proteins IFITM1, IFITM2 and IFITM3 are normally made at low levels in cells. Scientists knew that an immune-stimulating protein called interferon causes IFITM levels to rise, but hadn’t known what increased levels of those proteins does for the cell.

Now, Brass, Elledge and their colleagues show that IFITM proteins help kill flu viruses, and that IFITM3 may be particularly important. That protein may help block viruses from entering host cells, though the team has not pinpointed the mechanism. IFITM3 also thwarts viruses such as dengue, West Nile and yellow fever, the team found.

“This [protein] blocks them all,” Elledge says. Increasing levels of IFITM3 might boost the body’s ability to combat the flu. And the team shows that blocking the protein in chicken and dog cells used to grow vaccine strains could make the virus grow better, possibly speeding vaccine development, he says.

If people have varying levels of IFITM3 in their cells, people with low levels may be more susceptible to flu, speculates Andrew Mehle, a virologist at the University of California, Berkeley. He also wonders whether a species’ versions of the IFITM proteins may determine which viruses can infect that species.

The other “Cell” paper documents the hundreds of interactions between the H1N1 virus and host proteins that take place during an infection. Previously scientists have studied how individual virus proteins interact with human cells. The new, large-scale screen reveals that the H1N1 flu virus’ 10 proteins connect to 1,756 human proteins in some way, report researchers led by Aviv Regev and Nir Hacohen of the Broad Institute of MIT and Harvard in Cambridge, Mass. Of those relationships, 87 are direct between flu and human proteins. Indirect connections make up the remainder and include some interactions that affect levels of human proteins in a cell.

On average, one influenza protein interacts with about twice as many human proteins as does one typical human protein with other human proteins, says Regev. The flu virus “really is sending many tentacles into the cell,” giving the virus a big impact on a host cell’s behavior, she says.

Both studies raise intriguing questions, Mehle says. “They both seem to lay the foundation for several careers right now,” he says. “It will be pretty exciting for the field to chase down these leads over the next two or three years.”

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Gene Variants Behind Vulnerability to Yeast Infections

Scientists have identified two genetic mutations that help account for the presence of recurring yeast infections in certain women.

Although the researchers focused their work on small and very specific populations with extreme conditions, the findings provide new insights into one of the most common and annoying maladies to afflict women.

“This discovery is important as a starting point for further work,” said Dr. Bart Jan Kullberg, co-author of one of two papers appearing in the Oct. 29 issue of the New England Journal of Medicine.

“It is the first proof in the area of fungal infections that subtle genetic differences exist that explain why some [apparently healthy] persons do get certain ailments, and even suffer from recurrent episodes, whereas others never acquire these infections,” said Kullberg, a professor of medicine at Radboud University in Nijmegen, the Netherlands.

Although the people studied here had extreme conditions, “you could potentially move to other mutations in the [same] gene or in this pathway to give more subtle phenotypes that we might see in everyday medicine,” said Dr. Anthony Gregg, director of maternal and fetal medicine and medical director of genetics at the University of South Carolina in Columbia.

Ultimately, researchers hope to use the findings to develop better treatments for these conditions, which become serious in some people.

“One does understand the pathway, what we can potentially offer is therapies that take advantage of augmenting the normal pathways or utilizing redundant pathways that are working just fine but are not normally turned on to such a high degree,” said Gregg, who is also on the board of directors at the American College of Medical Genetics.

“At this point, however, the reports really have no relevance to patients, cautioned Dr. Steven Goldstein, a professor of obstetrics and gynecology at New York University Langone Medical Center in New York City.

Yeast infections, which are typically caused by Candida albicans, arise from imbalances in the body’s...
Missed Vaccines Weaken ‘Herd Immunity’ in Children

By Liz Szabo
USA Today
January 6, 2010

Brenda Lee Flint did everything she could to keep her baby safe. She nourished her with breast milk; she gave her all the routine vaccines. But Flint never realized that living with her daughter, Ryn, would depend on the actions of her friends, neighbors and even strangers.

By 15 months old, Flint's daughter, Julieanna Metcalf, was walking, exploring and even saying her first few words. Then one day in the bath, while fighting what seemed like an ordinary stomach bug, Julieanna became so weak and floppy that she couldn't hold up her head.

"She couldn't say 'Help me,' but her eyes were begging me to do something," says Flint, 35. Flint rushed the baby to the hospital, where she was diagnosed with meningitis, a swelling of the lining of the brain, caused by a severe case of Hib, or Haemophilus influenzae type b. Julieanna was one of five children in Minnesota hospitalized with Hib in January 2008, the state's biggest outbreak since 1992. Three of the other Minnesota children hospitalized for Hib were vaccinated, including one who died, according to the Centers for Disease Control and Prevention.

Experiments worry that such outbreaks—a long with mumps outbreaks in the East Coast and more than two dozen measles outbreaks around the country in 2008—represent cracks in the country's protection against terrifying childhood diseases that were once virtually eliminated.

Parents who have never seen their children gasp for breath no longer fear these diseases and, in some cases, are delaying or skipping immunizations, says Paul Offit, chief of infectious diseases at Children's Hospital of Philadelphia. Many parents who reject vaccines do so because of the mistaken notions that they cause autism or overwhelm the immune system, Offit says.

That worries moms such as Flint, who learned that her daughter has a rare immune deficiency only after she contracted Hib. Because Julieanna doesn't respond to vaccines, she depends on other parents to keep germs out of circulation by vaccinating their kids, a phenomenon called "herd immunity." "It's not just your kid. When you get your child vaccinated, it helps to protect the other kids who don't have the ability to protect themselves." —Brenda Lee Flint

Parents such as Rebecca Esteppe of San Diego don't want to vaccinate her younger son after his older brother was diagnosed with autism. When measles broke out in Southern California in 2008, "I had to decide, 'Would I rather have him get the measles or risk having him get autism like his brother did?'" says Esteppe, national policy manager for Talk About Caring Autism. "My husband and I decided we'd rather he get measles.

In 2005, the number of children exempted from school immunization requirements has grown by 50% since 1991, to 1.48% in 2004, according to a May article in "The New England Journal of Medicine."

Exemption rates are alarmingly high in pocketsof the country, however. In Ferry County, Wash., 27% of children have a non-medical exemption from school vaccine requirements, the article says.

These are the types of communities where imported diseases such as measles hold; Kellie Holdt, senior research associate at the Centers for Disease Control and Prevention.

Nearly 30% of patients in the current mumps outbreak—which has hit communities in New York state, Florida and other states—were fully vaccinated but failed to receive one or both recommended shots. And more than 90% of victims in the 2008 measles outbreaks, which spread out across the USA, were either unvaccinated or had used vaccination records, the CDC says.

A study published Monday in the "Archives of Pediatrics & Adolescent Medicine" found that unvaccinated children are nine times as likely as others to contract chickenpox—which killed 100 children and hospitalized 10,000 a year before a vaccine became available in 1995. The same authors found that unvaccinated kids are 23 times as likely to develop whooping cough.

Dorset didn't believe shots against hepatitis B or pneumococcus only after her daughter became ill. She didn't vaccinate her son or daughter against either disease after their pediatrician said the shots weren't needed.

In 2001, both children were hospitalized because of a bacterial illness called invasive pneumococcal disease. Her 5-year-old survived. Her daughter, Abigale, who was two weeks shy of turning 6, died.

"I can't tell parents enough the importance of vac-
cination," Peterson says in video on the PKIDS website.

"I hope that no one else has to hold their child when they die."

Lingering effects

Julieanna spent a month in the hospital, mostly in intensive care. By the time Julieanna left the hospital, she had lost the ability to walk, talk and even swallow.

"It was like having a newborn again," Flint says. "I would rub her throat for swallowing and rub her cheeks for chewing. She couldn't crawl. She could screech, and that was about it."

Two years later, Julieanna still needs weekly injec-
tions to prop up her immune system—and might for the rest of her life, Flint says.

Although Julieanna has relearned how to walk, she often falls, Flint says. She attends special-ed-
cuation for physical therapy, speech therapy and occupational therapy.

Flint says she lives with the fear that Julieanna will suffer from lingering brain damage, as well as the knowledge that she remains vulnerable to a host of germs carried by her classmates.

"I don't know if she will grow out of this," says Flint, who spoke to Congress about vaccines in May. "I just don't want to see my child fall from the top of the ladder."

Schaffner says he sees vaccination as a part of the obligation of the strong to protect the weak. "There are certain things you have to be protected, so the virus can't find these babies," Schaffner says. "We have to provide a cocoon of protection around them. We surround them with strength. I find that to be part of our responsibility."

We cannot think just about ourselves."

Vaccines have nearly eliminated some diseases

Before vaccines became available, hundreds of thousands of Americans—including thousands of children—routinely came down with dreaded infectious diseases each year. Although vaccines have not eliminated all of these diseases, doctors say outbreaks in unvaccinated communities put everyone at risk.

A couple years ago, I found out that I’m allergic to peaches. I’ve had a handful of food allergies for my entire life, but they have been mostly petty annoyances—now, I think I’ve had a severe reaction to at least two dozen things. And I had eaten peaches for my entire life with no apparent difficulty. However, one afternoon, I took a single bite of a peach. As the fruit traveled down my throat, my throat felt like it was collapsing. My voice disappeared to a raspy whisper. I was told later that I should have gone to the hospital, but I didn’t have any money for a taxi. Instead, I just took a Benadryl and went to bed.

Since then, I’ve had allergy testing, and I discovered that I have 33 other food allergies to go along with my peach allergy. I’ve heard this story hundreds of times from kids with food allergies has jumped up 18 percent in the past 10 years. The overall prevalence is still quite low (3.9 percent of kids have allergies), but that kind of a leap gives researchers pause.

“We do think this is an increasing trend” confirms Branum. “And anytime you see any health condition going up—that’s always a concern. Going up is not the right direction.”

Branum and Lukacs also found that the number of kids seeking emergency medical treatment for an adverse reaction to food has tripled in the past few years. In 2006, 317,000 kids were rushed to doctors’ offices and hospitals because of something they ate. What is particularly scary about food allergies, says Branum, is “not the food itself, but the reactions that they are having.” A minor reaction can become a life-threatening condition with no warning. Essentially a response from the immune system, allergic reactions are not proportional to the amount of food ingested: a very small amount can trigger anaphylaxis, a whole-body reaction. An allergic person may be one peanut away from a peanut butter sandwich—which has made parents and physicians more vigilant about allergies they would have otherwise ignored. This parent-fear factor is considered as a serious explanation, particularly since about 25 percent of American adults claim to have an allergy, and the real adult prevalence is probably much different from that of kids—about 2 to 4 percent.

One reason for this overreporting is that there is a lot of confusion about what an allergy is. Allergies are often confused with food intolerances—when food is difficult to digest. But a food intolerance is considered less serious than an allergy, because (unlike allergies) a person with a food intolerance generally has a predictable reaction. The food, and the symptoms are proportionate—the more food ingested, the stronger the reaction. Initially, Branum was among those who suspected that parent fear was the real explanation behind the reported allergy increases. However, she isn’t sure now. If fear was the only explanation, then she might not have seen the fear and different explanations in the same families.

But Branum found allergy increases in each demographic group—that indicates that there’s a biologic, not cultural, factor at work. Researchers abroad had already begun studying microRNAs and their involvement in cancers, Prof O’Neill said, but the food immune system hadn’t been studied before. Prof O’Neill is also the 2009 recipient of the RDS/IRish Times Boyle Medal for Scientific Excellence. Prof O’Neill and his team published in the leading journal, “Nature Immunology”.

“We have discovered a new off switch for the immune system, a discovery that could one day treat or cure certain chronic diseases such as rheumatoid arthritis,” the researchers at Trinity College Dublin said in the December 8, 2009 issue of *Nature Immunology*.

The discovery is hugely important given the number of people who are allergic to the world you live in. For example, in the U.S. and Japan, the most common food allergies include milk, eggs, wheat, soy, and peanuts. In the sample of kids with food allergies, the major food allergens were milk and egg—9 percent of the kids had IgE antibodies for peanuts; 12 percent had them for milk. Five percent had the shrimp IgE, while almost 7 percent had had reactions to fish. Many of those were the same kids who had reactions to foods. Also, children can grow out of allergies, but still get a positive antibody test. If an infant had a milk allergy that was “cured” by the time they were two, the antibodies would still be present in her system for years.

Branum’s analysis of this data ultimately confirmed that parents were being pretty accurate about their kids’ allergies. Parents weren’t just being hysterical; their kids probably really did have the allergies parents were listing.

Amazingly, just two years ago, children’s food allergies weren’t even on the CDC’s radar. The agency had some scattered data in studies, but it had never occurred to them that they should take a more thorough look at the research. It wasn’t until the staff of Sen. Christopher Dodd called, asking for a briefing on the issue (Dodd’s daughter has a severe peanut allergy) that the CDC began a more comprehensive analysis.

Branum volunteered for the task. But once she’d finished briefing Dodd’s staff, she decided that the information could be useful to other scholars, and she set about preparing the research. The Pediatrics study is actually an outgrowth of her first briefing for the congressional staff.

Now, Branum has quickly become the CDC food allergy expert. And the CDC has realized that it needs to be doing more for kids with food allergies.

Researchers at the Graduate School of Agriculture, the CDC is now regularly bringing parents, educators, school administrators, and policy experts together to figure out how to best care for kids with allergies. They are tackling how kids can bring medicines to schools with zero-tolerance policies. They are figuring out what sort of staff training should be required for emergency situations.

They’re also listening to the kids. Says Branum, “They don’t want to be treated differently. Don’t force them to sit at a lunch table by themselves. They are very aware of the food allergies—they know what to ask and what to do.”

But the kids have to know that. Their lives may depend on it.

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**Trinity College Scientific Team Discovers Immune System ‘Off Switch’**

By Dick Ahearn

*The Irish Times*

December 8, 2009

Scientists in Dublin have found a new ‘off switch’ for the immune system, a discovery that could lead to a treatment for the most common chronic diseases such as rheumatoid arthritis.

Researchers at Trinity College Dublin made the discovery after feeding mice with the RNA interferes with the immune system's response or prevents it from causing damage.

The discovery is huge, given the number of people who are allergic to the world you live in. For example, in the U.S. and Japan, the most common food allergies include milk, eggs, wheat, soy, and peanuts. In the sample of kids with food allergies, the major food allergens were milk and egg.

The team published in the leading journal, “Nature Immunology”.

“We have discovered a new off switch for the immune system,” lead researcher and professor of biochemistry Prof Luke O’Neill said yesterday. Prof O’Neill is also the 2009 recipient of the RDS/Irish Times Boyle Medal for Scientific Excellence.

Graduate student Fred Sheedy was the lead author on the study and, as part of his postgraduate studies, Prof O’Neill said.

The switch, “microRNA-21”, is released by the body to reduce inflammation caused by the immune system, Prof O’Neill said. “It is all about turning on or off the chemical reactions in the immune system and reducing the body's reaction.”

Researchers abroad had already begun studying microRNAs and their involvement in cancers, Prof O’Neill said. MicroRNA involvement in the immune system diseases had not yet been examined, however.

The discovery of microRNA-21 may provide new kinds of treatments to slow down the immune response or prevent it from causing damage.

“There are whole companies built around these microRNAs,” he said. “We are trying to study more about what microRNAs are and how to manipulate this.”

It will take much more research before treatments emerge from the discovery, but it was significant, Prof O’Neill added. “We are still trying to prove that we understand all of the biology.”

The work is likely to have implications in a wide range of diseases linked to inflammation.

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Prenatal Programming against Allergy is Induced via the Maternal Immune System

Summary by Melanie Conrad
Full text: Journal of Experimental Medicine
December 2009

Allergy is the result of an inappropriate immune response to harmless environmental substances, and the number of people affected by allergies has been rising over the past few decades. Though possible explanations for this phenomenon include increased diagnosis or exposure to more pollutants, the hygiene hypothesis, proposed by David Strachan in 1989, has gained much support. Stated simply, the hygiene hypothesis attributes the rise in allergy incidence to a decreased exposure to microbes in the environment. In the original research that led to the hypothesis, Strachan compared families of different sizes and discovered that allergies were less common in children from larger families, presumably due to a higher exposure to bacteria and viruses from their siblings.

Further research has identified that growing up in a farming environment also protects against allergies; children from such environments have fewer allergies than children who grow up in the city. Other studies have shown that prenatal exposure to farming can have the same effect: Pregnant women who inhale microbes when they are working on a farm have children that are protected against allergy. In the context of the hygiene hypothesis, the high level of exposure to microbes on the farm, especially either prenatally or early in life, may influence the developing immune system and make it better able to tolerate exposure to allergens later in life.

In an effort to investigate how this protection works, my colleagues and I demonstrated the hygiene hypothesis experimentally using a mouse model. Pregnant mice exposed to farm-derived bacteria showed a decreased exposure to that of the lung. The expression of TLRs and cytokines decreased.

A previous study, which showed that the mild inflammatory response did not occur in offspring that carried functional TLRs. When exposure, we created a mouse that could no longer translate into allergy protection in the offspring.

TLR generates signals in the mother that translate into allergy protection in the offspring.

Since TLRs appeared to be strongly involved in the mother mouse’s response to farm bacteria exposure, we created a mouse that could no longer express TLRs and therefore was largely impaired in recognizing bacteria. These mother mice were mated to male mice with functional TLRs, resulting in offspring that carried functional TLRs. When these mothers were exposed to bacteria during pregnancy, their offspring were not protected against asthma. Additional observations revealed that the mothers had impaired inflammatory responses that did not occur in these mothers. This strongly indicates that TLRs generate signals in the mother that translate into allergy protection for the offspring.

These data provide strong evidence in support of the hygiene hypothesis and suggest that TLR signaling plays an essential role in the transfer of allergy-protective factors from mother to fetus. Whether this protection comes by way of a soluble molecule that traverses the placenta or by alterations in the immune composition of the placenta remains a topic of intense interest.

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“Maternal TLR signaling is required for prenatal asthma protection by the nonpathogenic microbe Acinetobacter lwoffii B78.”

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UAB Researchers Discover Antibody Receptor Identity, Propose Renaming Immune-system Gene

UAB Reporter Online
December 11, 2009

Researchers at the University of Alabama at Birmingham (UAB) have uncovered the genetic identity of a cell receptor for the immune system’s first-response antibody, a discovery that sheds new light on infection control and immune disorders. The discovery is such a crucial part of immunology that UAB researchers, in conjunction with Japanese researchers, are asking that the gene linked to this antibody receptor be renamed to better describe its role in early immune responses.

“The new study shows, and DNA analysis helped us to confirm, that the Fc mu receptor is made from the gene we describe,” Kubagawa says. “This is a fundamental discovery that science has been waiting to answer for nearly 30 years.”

To identify the true FCMR gene, the UAB researchers used chronic lymphocytic leukemia cells as a source of this gene, since such leukemia cells are known to over-express the Fc mu receptor. This enabled researchers to identify the FCMR gene more efficiently.

The potential novel agents that target and regulate FCMR function hold promise in fighting cancer, AIDS and autoimmune disorders, says Kubagawa. The generic description and request for renaming the gene does not prove it has a direct role in any particular disease; however, it fills a crucial gap in understanding the science behind immune deficiencies and allergy diseases.

The study is a partnership between UAB, Brookwood Medical Center in Birmingham, RIKEN Research Center for Allergy and Immunology in Yokohoma, Japan, and the University of Tokyo.