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RESEARCH AT THE CHILDREN'S HOSPITAL OF PHILADELPHIA May 2008

Gene Therapy Improves Vision in Patients With Congenital Retinal Disease

Investigators have used gene therapy to safely restore vision in three young adults with a rare form of congenital blindness during a clinical trial at The Children's Hospital of Philadelphia.

Patients' vision improved from detecting hand movements to reading lines on an eye chart. Although the patients have not achieved normal eyesight, the preliminary results set the stage for further studies of an innovative treatment for this and possibly other retinal diseases.

An international team led by the University of Pennsylvania, Children's Hospital, the Second University of Naples and the Telethon Institute of Genetics and Medicine (both in Italy), and several other American institutions reported their findings in an online article in the *New England Journal of Medicine*.

The study — the first gene therapy trial for a nonlethal pediatric condition — centered on Leber congenital amaurosis, a group of inherited blinding diseases that damages light receptors in the retina. LCA usually begins stealing sight in early childhood and causes total blindness during a patient's twenties or thirties. Currently, there is no treatment for LCA.

The scientists used a vector, a genetically engineered adeno-associated virus, to carry a normal version of the gene *RPE65* that is mutated in one form of LCA. Three patients, ages 19, 26 and 26, received the gene therapy between October 2007 and January 2008 via a surgical procedure performed at Children's Hospital, where the gene vector was manufactured at the Hospital's Center for Cellular and Molecular Therapeutics (CCMT).

Katherine A. High, M.D., a study leader and an investigator of the Howard Hughes Medical Institute, directs the CCMT and has been a pioneer in translational and clinical studies of gene therapy for genetic disease. In 2005 she began collaborating with colleagues Albert M. Maguire, M.D., and his wife Jean Bennett, M.D., Ph.D., at the University of Pennsylvania to translate their exciting animal findings into a clinical study.

In 2001, Bennett and Maguire were part of a team that reported successfully reversing blindness using gene therapy on dogs affected by the same naturally occurring form of congenital blindness.

In the present study, all three patients reported improved vision two weeks after the injections. The investigators also reported that each injected eye became approximately three times more sensitive to light, and each was improved compared to the uninjected, previously better functioning eye.

The LCA gene therapy vector showed no signs of causing inflammation in the retina or other toxic side effects, the investigators reported, although one patient experienced an adverse event that did not affect eyesight and may have been attributed to previous surgery.

The patients were tested for six months after receiving the gene therapy vector. One patient was better able to navigate an obstacle course compared to before the injection. The patients also had less nystagmus, an involuntary movement of the eyes that is common in LCA. In the patient who experienced better vision even in the uninjected eye, the researchers suggest that the reduced nystagmus benefited both eyes.

The current clinical trial will continue with more patients and with ongoing follow-up to monitor results. The investigators expect improvements to be more pronounced if treatment occurs in childhood, before the disease progresses.

"This result is important for the entire field of gene therapy," notes High, a past president of the American Society of Gene Therapy. "Gene transfer has been in clinical trials for over 15 years now, and although it has an excellent safety record, examples of therapeutic effect are still relatively few. The results in this study provide objective evidence of improvement in the ability to perceive light, and thus lay the groundwork for future studies in this and other retinal disorders," says High.

The clinical trial was sponsored and primarily funded by CCMT at Children's Hospital. Research support was received from The Department of Ophthalmology at the University of Pennsylvania, the F.M. Kirby Foundation, the Foundation Fighting Blindness, Research to Prevent Blindness, the Macula Vision Foundation, the Paul and Evanina Mackall Foundation Trust at the Scheie Eye Institute, the Rosanne H. Silbermann Foundation, the Italian Telethon Foundation, the Associazione Italiana Amaurosi Congenita di Leber, the National Center for Research Resources, the Howard Hughes Medical Institute, the National Eye Institute of the National Institutes of Health, private philanthropy, and an anonymous donor who is committed to advancing pediatric medicine through maximizing the potential of gene therapy.

New Research Employees (April 2008)

We welcome the following new research employees:

Clinical Research Associate
Claudia Garcia-Leeds

Counselor
Diana Constantinides

Sponsored Projects Analyst
Barbara Boddie

Research Assistants
Barbara Bungy
Erin Cummings
Stephanie Hullmann
Sarah Khan
Betty Kim
Anuli Njoku
Janaki Patel
Michael Rey

Research Charge Analyst
Sonia Woods

Research Technicians
Susannah Elwyn
Michelle Joshi
Kristin Lewis
Christopher Riling

Resource Coordinator
Joshua Taton

Innovative Blood Vessel Stent Materials Allow Better Gene Therapy Control, Delivery

In an attempt to make gene therapy a safe and effective treatment for human diseases, cardiology researchers at Children's Hospital have advanced delivery techniques by creating a versatile synthetic material that can bind to a variety of gene therapy vectors and be custom-designed for controlled local release of therapeutic genes at a disease site.

Robert J. Levy, M.D., William J. Rashkind Chair in Pediatric Cardiology, led the study, published in the May 2008 online version of the journal *Circulation*.

Dr. Levy's research group used their new synthetic formulation to bind adenoviruses to bare metal stents — tiny metal scaffolds — placed inside the carotid arteries of rats. The adenovirus served as a gene therapy vector to carry genes for an enzyme that significantly reduced restenosis, the hazardous narrowing of a blood vessel that often occurs despite the presence of a stent designed to hold it open.

Although the materials are in an early stage, the hope is that this method may help to treat arterial disease in people. "We developed a synthetic gene delivery system that can be used for any gene therapy vector, not just adenoviruses," says Dr. Levy. "This new formulation allows us to increase the dosage of gene therapy vectors delivered, and we can tune the materials for sustained release over a longer time period."

Over the past decade, stents have become increasingly useful in treating constricted blood vessels in heart disease and in peripheral artery disease. Stents, which expand partially blocked blood vessels to improve circulation, may be made of bare metal or may have a coating of polymers that release drugs.

Neither type is ideal. Polymer coatings cause inflammation in vessels, which may lead to new bottlenecks at the same time the coating releases drugs meant to reduce vessel injury. Bare metal stents produce less inflammation, but don't have the benefit of drug delivery. In a previous proof-of-principle study in animals, Dr. Levy's group attached to stents an extremely thin layer of protein, one molecule thick, containing adenovirus vectors. That method delivered genes that successfully inhibited restenosis; however, it had serious limitations. It operated only within a narrow range of temperatures and acidity levels and was useable only with adenovirus vectors.

The new formulation, says Dr. Levy, is robust, controllable and adaptable to any virus used as a gene therapy vector, not just adenoviruses. His team synthesized three components into a complex that tethers viral vectors to stent surfaces. One of the three components is an amplifier that increases the dose of gene vector more than fourfold over the previous formulation.

In addition, by varying another component, the stent can be tuned to release vector at a controlled rate that can theoretically be tailored to a schedule appropriate for the particular treatment. "Prior studies have shown that 90 percent of the gene vector is released within 12 to 24 hours, after which vessel blockages re-grow," says Dr. Levy. "In this study, the stents had significant coverage of the vector seven days later — and less restenosis. Our goal is to customize the materials to allow peak release of the vector when it can have the maximum benefit."

The adenovirus vector carries genes that code for inducible nitric oxide synthase (iNOS), a protein that controls cell damage in blood vessels. In the current study, the iNOS reduced restenosis by 56 percent in the carotid arteries of treated rats, as compared with control animals.

Although this particular study used adenovirus vectors, says Dr. Levy, the synthetic formulation could tether any other type of viral gene therapy vector to the metal stents. It might also carry other therapeutic agents in addition to gene vectors. Further studies, he adds, will refine these methods and investigate them in larger animal models that more closely simulate human vascular disease.

The National Institutes of Health and the American Heart Association supported the study. Dr. Levy's co-authors from Children's Hospital were Ilia Fishbein, M.D., Ph.D.; Ivan Alferiev, Ph.D.; Marina Bakay, Ph.D.; Stanley J. Stachelek, Ph.D.; Peter Sobelewski, Ph.D.; Meizan Lai, M.D.; and from the University of Pennsylvania School of Engineering and Applied Sciences, Hoon Choi, Ph.D.; and I-W Chen, Ph.D.

Investigators Find Gene Location That Gives Rise to Neuroblastoma

Using advanced gene-hunting technology, an international team of investigators has identified a chromosome region that is the source of genetic events that give rise to neuroblastoma, an often fatal childhood cancer.

The investigators found that the presence of common DNA variations in a region of chromosome 6 raises the risk that a child will develop a particularly aggressive form of neuroblastoma.

"Until now we had very few clues as to what causes neuroblastoma," says John Maris, M.D., who led the study at Children's Hospital, where he is the director of the Center for Childhood Cancer Research. "Although there is much work to be done," adds Maris, "understanding this cancer's origin provides a starting point for developing novel treatments."

Neuroblastoma, the most common solid cancer of early childhood, usually appears as a solid tumor in the chest or abdomen. The disease accounts for 7 percent of all childhood cancers but, due to its aggressive nature, causes 15 percent of all childhood cancer deaths. Neuroblastoma has long been known to include subtypes that behave very differently. Some cases strike infants but spontaneously disappear with minimal treatment, while other cases in older children may be relentlessly aggressive from the start.

Investigators at Children's Hospital and colleagues in the multicenter Children's Oncology Group have for decades analyzed tumors for characteristics such as amplified levels of a cancer-causing gene and deletions of chromosome material. They used those tumor peculiarities to classify neuroblastoma into risk levels that guide oncologists toward the most appropriate treatments.

Properly defining risk level helps us to avoid the twin pitfalls of undertreating or overtreating any given child with neuroblastoma, according to Dr. Maris.

However, little was known about genetic events that predispose a child to developing a neuroblastoma tumor. In roughly half of neuroblastoma cases, the cancer is not discovered until it has spread widely in a patient's body, so understanding how a tumor originates may allow oncologists to design earlier and more successful interventions.

In the current study, Maris's team collaborated with Hakon Hakonarson, M.D., Ph.D., director of the Hospital's Center for Applied Genomics, to analyze blood samples from approximately 1,000 neuroblastoma patients, as well as samples from some 2,000 healthy children recruited through the Children's Hospital network. A DNA chip analysis performed at the genome center identified three single nucleotide polymorphisms (SNPs) — changes in single bases on the DNA helix. Out of more than 550,000 SNPs studied, those SNPs were much more common in patients with neuroblastoma, compared to the controls. The three SNPs occurred together on a band of chromosome 6 designated 6p22.

The researchers repeated the analysis in blood samples from additional groups of patients and control subjects from the United States. and the United Kingdom, and confirmed their finding that variants in the 6p22 region were implicated in neuroblastoma. There are two genes in the 6p22 region, but their functions are largely unknown.

The researchers found that patients with these at-risk SNPs on chromosome 6 were more likely to develop aggressive neuroblastoma. The initial changes on chromosome 6 in all their body cells eventually led to the genetic abnormalities seen in tumor cells in high-risk forms of the disease.

Because their finding reveals only the first step in a series of molecular events, Dr. Maris cautioned it would be premature to do prenatal genetic testing for the SNPs on chromosome 6. His research team will continue to perform genetic analyses, in search of other gene changes that interact with those SNPs. One data source will be 5,000 tissue samples in Dr. Maris's lab — the world's largest collection of neuroblastoma samples, drawing on decades of research into the disease by Dr. Maris, his colleagues and predecessors at Children's Hospital.

"This discovery lays the foundation for learning how these initial changes influence biological pathways that lead to neuroblastoma," says Dr. Maris. "Understanding those pathways may guide us to new and better therapies that precisely target this cancer."

The study team reported its findings in the May 7 Online First version of the *New England Journal of Medicine*. The National Institutes of Health supported the study, along with grants from the Alex's Lemonade Stand Foundation, the Center for Applied Genomics, the Abramson Family Cancer Research Institute and the Institute of Cancer Research, located in the U.K.

Among Drs. Maris's and Hakonarson's co-authors were several collaborators from The Children's Hospital of Philadelphia and the University of Pennsylvania School of Medicine; the Institute of Cancer Research in Surrey, U.K.; the University of Birmingham, U.K.; the University Federico II, Naples, Italy; the University of Rome; the Children's Hospital of Los Angeles; and the University of Florida.

Stokes Becomes Institutional Member of the Federal Demonstration Project

The Federal Demonstration Partnership (FDP) is a cooperative initiative among nine federal agencies and more than 100 institutional recipients of federal funds. The partnership aims to reduce the administrative burdens associated with research grants and contracts.

FDP members cooperate in identifying, testing and implementing new, more effective ways of managing the more than $15 billion in federal research grants. The goal of improving the productivity of research without compromising its stewardship has benefits for the entire nation.

The interaction between FDP's 300 or so university and federal members takes place during three annual meetings and, more extensively, in the many collaborative working groups and task forces that meet often by conference calls in order to develop specific work products.

At its regular meetings, FDP members hold spirited, frank discussions, identify problems, and develop action plans for change. Then these new ways of doing business are tested in the real world before putting them into effect.

More information on the partnership is available on the FDP Web site at http://www.thefdp.org/index.html.

Steroids Provide No Survival Benefit for Children With Bacterial Meningitis

Corticosteroids given to children who are hospitalized for bacterial meningitis do not provide a benefit in survival or in reduced hospital stays, according to a large multicenter study by pediatric researchers.

The finding by lead investigator Samir S. Shah, M.D., Division of Infectious Diseases, and colleagues stands in contrast to previous studies in hospitalized adults, for whom corticosteroids dramatically reduced mortality.

"Because of the demonstrated benefits of these drugs in adults, physicians have increasingly been using corticosteroids in children with bacterial meningitis," says Dr. Shah. "This study reminds us again that children are not just small adults. We need to consider whether the problems associated with corticosteroid use, such as gastrointestinal bleeding, outweigh any potential benefits."

Dr. Shah's team analyzed medical records of 2,780 children with bacterial meningitis at 27 U.S. pediatric hospitals from 2001 to 2006. The median age of the children was nine months. Approximately 9 percent, or 248, of the children studied received corticosteroids, with steroid use doubling during the study period, from under 6 percent of children in 2001 to 12 percent in 2006.

There was no significant difference in mortality or in time to hospital discharge between children who received corticosteroids and those who did not. Overall, unadjusted mortality rates were 6 percent among children receiving corticosteroids, versus 4 percent among those not receiving them. There also was no significant difference in those outcomes between those receiving and not receiving corticosteroids in the subsets of children with meningitis caused by pneumococcal bacteria or by meningococcal bacteria.

Previous studies had shown that corticosteroids had a clear benefit in preventing hearing loss in children whose meningitis was caused by *Hemophilus influenzae* type b (Hib) bacteria. However, since the Hib vaccine was approved for routine use in childhood immunizations in 1985, cases of Hib meningitis have dropped sharply in the United States. Now bacterial meningitis in children is more commonly caused by pneumococcal or meningococcal bacteria.

Further studies may reveal that corticosteroids may also reduce hearing loss or other neurologic injuries in children with bacterial meningitis not caused by Hib, says Dr. Shah, but there is currently no such evidence.

"Our study shows the need for a further study in children — a large randomized clinical trial to examine all outcomes of steroid use, before the use of these medicines becomes routine in children with bacterial meningitis," he says.

The study appeared in the May 7 issue of the *Journal of the American Medical Association*.

The National Center for Research Resources, part of the National Institutes of Health, supported the study, along with the Agency for Healthcare Research and Quality. One co-author received support from the Doris Duke Medical Student Clinical Research Fellowship. Shah's Children's Hospital co-author was Zeinab Mohamad, M.S.

Receptor Deformation Model May Solve T-cell Triggering Puzzle

T-cells, an essential component of the immune system, are activated after the T-cell's antigen receptor (TCR) binds to an antigen presenting cell's peptide-loaded major histocompatibility complex (pMHC). How this activation occurs has puzzled immunologists for more than two decades. However, it is considered critical to understanding how the immune system works.

Terri Finkel, M.D., Ph.D., and Zhengyu (Mark) Ma, M.D., Ph.D., Division of Rheumatology, have developed a model that shows how an activating signal from the TCR is initiated, or triggered, by the engagement of pMHC. This model, the "receptor deformation model," is an entirely new explanation for how TCR triggering occurs. After being published in *PLoS Biology*, it was featured in *Science* and a "Hypothesis" paper in *The FASEB Journal*.

Dr. Finkel and colleagues looked at an aspect of the triggering process that had been previously overlooked — the mechanical stress exerted on pMHC-TCR interaction by cytoskeletal forces where the dynamic T cell and the antigen-presenting cell meet.

Building on the knowledge that T cells respond well to antigens on antigen presenting cells but do not respond to the same antigens in solution, the team used an artificial system comprised of a lipid bilayer or plastic surface to present defined foreign pMHCs to the TCR. They found that T cells are triggered by very low numbers (less than 10) of pMHCs, even in the absence of endogenous (self) pMHCs or the surface molecules of antigen presenting cells.

TCR triggering critically depended on the T-cell adhesion to a surface and a functioning cytoskeleton that gives T cells the ability to move. These findings led to the receptor deformation model, in which the TCR signal is initiated by conformational changes of the TCR complex, induced by a pulling force. This is the first model to take into consideration the role of external mechanical forces in pMHC-TCR binding in a dynamic 2D environment.

This new model addresses all three aspects — mechanism, sensitivity and specificity — of the TCR triggering puzzle. "By introducing mechanical force into the equation, the receptor deformation model offers a straightforward mechanism for T-cell antigen receptor signal initiation, and explains the extraordinary sensitivity and specificity of the T-cell immune response" says Dr. Ma.

This finding may lead to further understanding of a key step in the recognition of foreign antigens by the immune system, as well as the identification of potential targets for the manipulation of T-cell activation and self-tolerance by drugs.

The study was supported by the NIH, Children's Hospital, the Joseph L. Hollander Chair and the Stokes Institute.

Future studies, funded by a new 2-year NIH grant, will study single molecules of TCR and pMHC to focus on the external force required to detach interacting T-cells and antigen presenting cells and the components of the cytoskeleton critically involved in the process.

Unique Approach Leads to Identifying Gene for Rare Disorder

A Children's Hospital investigator has led a study that used a novel laser microdissection and proteomics approach to identify the gene behind a rare condition that leads to progressive muscular weakness.

Identifying the genes responsible for reducing body myopathy (RBM) through traditional genetic techniques has posed a challenge for investigators because of the rarity of the condition. Although this condition was described more than 30 years ago, the gene that causes RBM had remained elusive because most of the patients found subsequently were "sporadic" — there were no larger families to use for more conventional linkage analysis to identify the responsible gene.

As a new patient with RBM was diagnosed in the Neuromuscular Program at Children's Hospital by Carsten Bönnemann, M.D., Division of Neurology, Dr. Bönnemann and his colleagues began to consider alternative ways to identify the genes responsible for the debilitating and often fatal condition.

Reducing bodies are aggregates of proteins that progressively form inclusions in the muscle cells, at times leading to rapidly advancing loss of muscle strength. Figuring that knowledge about the major component stored in the inclusions could yield crucial information about the gene underlying RBM, Dr. Bönnemann and his team used an unusual approach to get at this information — laser microdissection of the reducing bodies out of biopsy material followed by proteomic analysis.

Using this approach the research team found that a protein referred to as Four-and-a-Half-LIM-Domain-1 (FHL1) was the predominant component in the aggregates in the patient as well as in another patient recently diagnosed at the Unversity of Utah. They went on to show mutations in the *FHL1* gene itself lead to RBM in sporadic as well as in additional familial cases. The FHL1 protein is expressed predominantly in skeletal muscle but can also be found in cardiac muscle. The group showed in cell culture that the mutated FHL1 protein is prone to aggregate into conspicuous inclusions, recapitulating what is seen in the muscle from patients.

"We believe this is the first example in which this type of analysis has directly led to the identification of a disease gene," says Dr. Bönnemann, who took full advantage of the advanced technologies offered through the Hospital's core facilities to pursue identification of the gene.

Dr. Bönnemann believes the same approach could also prove to be useful in other conditions with prominent intracellular inclusions that are seen in many neurodegenerative disorders.

Joachim Schessl, M.D.; Yaqun Zou, M.D.; Ying Hu; Michael Rosenblatt, Ph.D.; Lynn Spruce; Alexander Judkins, M.D.; Jeffrey Golden, M.D.; and Daniel Martinez were Children's Hospital co-authors on the study, which was published in a recent issue of *The Journal of Clinical Investigation*.

Hospital Contributes Genotype Data to Enhance Autism Research Worldwide

Children's Hospital has contributed a large genotype dataset to the Autism Genetic Resource Exchange (AGRE), a scientific program of the organization Autism Speaks, dedicated to advancing genetic research in autism. This large genetic dataset will now be broadly accessible to autism researchers worldwide.

The Hospital's Center for Applied Genomics (CAG) uses highly automated microarray technology to perform high-speed genome analysis. The center's HumanHap550 system, manufactured by Illumina Inc., analyzed 4,500 DNA blood samples gathered by AGRE and generated genotypes — a compilation of 550,000 genetic markers for each person. Children's Hospital then contributed the genotyped data to AGRE.

By studying patterns of variation in those genotypes, researchers using the AGRE resources will be able to discover and investigate multiple genes that may contribute to autism. Previous family studies have strongly suggested a genetic contribution to autistic spectrum disorders (ASDs). The 4,500 individuals who provided blood samples for the genomic analysis represent approximately 900 families, including 1,250 children with ASDs, their parents and their unaffected siblings.

"Scientific work using AGRE's data repository will complement our own comprehensive research and clinical programs in autism at Children's Hospital, aimed at finding the causes and cure for this devastating disease," says CAG Director Hakon Hakonarson, M.D., Ph.D.

The high-density genotype data on the AGRE families is expected to provide novel insight into a genomic landscape of autism and other neurodevelopmental disorders.

Drawing on data from AGRE's open-access database, researchers from multiple institutions have previously published more than 120 scientific papers on the genetics of autism. These new genotypes greatly enhance the resources offered to investigators worldwide by complementing and extending the genotype data made available by other research teams.

CHOP Mentor Awards Announced

The Office of Faculty Development recently announced the recipients of the 2008 CHOP Mentor Award.

The award recognizes these mentors' extraordinary dedication to fostering the professional development of faculty members at Children's Hospital over the past three years.

This year's award went to:

- Steven D. Douglas, M.D., Department of Pediatrics, Division of Allergy and Immunology
- Catherine S. Manno, M.D., Department of Pediatrics, Division of Hematology
- Michael B. Robinson, Ph.D., Department of Pediatrics, Division of Child Development, Rehabilitation and Metabolic Disorders

Parents Follow Pediatrician's Advice on MMR Vaccinations

News stories about an allegedly harmful link between the mumps, measles and rubella (MMR) vaccine and the onset of autism had little effect on whether U.S. parents immunized their children, according to a review of immunization records and news stories done by Children's Hospital investigators.

The study, led by Michael Smith, M.D., formerly of Children's Hospital, says that parents' decisions were more likely influenced by recommendations from their child's pediatrician.

The study appears in the April issue of the journal *Pediatrics*. The data was collected from public-use files of the National Immunization Survey from 1995 to 2004. It compared immunization records of 215,643 children ages 19 months to 35 months with spikes in news stories about the MMR vaccine and autism. The news accounts were gathered from a database known as LexisNexis, which tracks newspaper, television and radio news.

The number of children not receiving the MMR vaccine increased after February 1998, when a study proposing a link between the MMR vaccine and autism appeared in the British journal *The Lancet*. After two years, the U.S. numbers of unvaccinated children declined and did not rebound when the MMR vaccine-autism link started to receive widespread coverage in the mainstream press, suggesting a limited influence of news media on MMR immunization rates in the United States.

These findings suggest that physicians may have been an important buffer against the potential negative impact of media coverage of immunization controversies.

The study published in *The Lancet*, led by Andrew Wakefield, was flawed and later discredited, although widely publicized in the United Kingdom. National rates of MMR immunization in Britain fell from 92 percent to 73 percent following publication, resulting in measles outbreaks and the first measles death in the United Kingdom in more than a decade.

The Children's Hospital study set out to provide the first population estimates of MMR vaccination rates in the United States following publication of *The Lancet* study and its subsequent media coverage. According to the data, nearly 1 in 50 U.S. children missed the opportunity for MMR immunization in the two years following publication of *The Lancet* study. In private physician practices, non-immunization rose as high as 1 in 40 children.

Significant mainstream media coverage of the MMR vacccine-autism controversy did not begin in the United States until almost two years after *The Lancet* published the study. By that time, the number of children not receiving their MMR vaccinations was returning to the pre-Wakefield study level. Children were identified as intentionally missing MMR vaccinations if they were up to date for other childhood immunizations, but not MMR.

The decision to immunize children is influenced by three things: the parents' willingness, the healthcare provider's attitude and input toward guiding the decision, and the vaccine's availability. Since there was no supply shortage during the study period, the decline can only be attributed to either the parents' or the healthcare provider's reluctance to vaccinate. According to Dr. Smith's team, some medical providers, made aware of *The Lancet* study, may initially have become hesitant to administer the MMR vaccine.

"The lesson for the public health community may be that the willingness to immunize a child is a story played out in the examination room during private conversation between the doctor and family," says Dr. Smith. "Updating the doctor with the most credible information and with strategies for discussing vaccine safety with parents may be the most efficient way to guarantee successful immunization practices in the face of increasing amounts of often unreliable and misleading information."

Dr. Smith's co-authors were Louis Bell, M.D., and David Rubin, M.D., M.S.C.E., Division of General Pediatrics, and Susan S. Ellenberg, Ph.D., University of Pennsylvania School of Medicine.

HAVE NEWS? Contact Jennifer Long at ext. 4-2105 or by e-mail at longj@email.chop.edu.

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