Investigations led by Robert Levy, M.D., The William J. Rashkind Endowed Chair in Pediatric Cardiology at The Children's Hospital of Philadelphia, have introduced a new delivery system to magnetically target therapeutic agents to catheter-deployed stents. This novel idea has the potential to become a major platform technology for delivering drugs, cells, and other agents to specific sites in diseased or injured blood vessels.

Dr. Levy recently received an award from the University City Science Center’s QED Proof-of-Concept Program to support his efforts toward developing and commercializing this technology as a therapy called vascular magnetic intervention (VMI).

The QED-Award facilitates interactions designed to accelerate the development of technologies and rapidly translate them into products available to advance patient treatments. Award winners are supported by the QED Program’s business development components including business advice from an advisor with a background in project development and implementation; a 12-month, $200,000 grant for early-stage research and development that includes matching funds from the investigator’s research institution; and guidance from industry and investment experts who periodically review the project and guide the technology from the QED program into the private sector.

Dr. Levy and his team in the Division of Cardiology at CHOP were selected to receive the QED Award for their VMI research proposal following a rigorous, two-stage competitive review process that included an evaluation of the scientific merit of the technology and its potential for commercialization. The project was matched with business advisor Richard Woodward, Ph.D., a molecular biologist who spent much of his career helping biopharmaceutical companies develop their products.

Dr. Levy’s VMI delivery system is a combination therapy that builds upon existing stent technology by directing biodegradable nanoparticles loaded with an antiproliferative drug, paclitaxel, to stents using uniform field magnetization. Dr. Levy’s team first presented the VMI mechanism in the January 2008 issue of Proceedings of the National Academy of Sciences. A feasibility study conducted by Dr. Levy’s team, presented in the May 2010 issue of the same journal, demonstrated that VMI effectively prevented restenosis in the stented carotid arteries of rats and matched with business advisor Richard Woodward, Ph.D., a molecular biologist who spent much of his career helping biopharmaceutical companies develop their products.

One of VMI’s potential applications is treating peripheral arterial disease (PAD), a buildup of plaque that can harden and narrow the arteries. The condition affects more than 27 million individuals in North America and the European Union. The 9 million PAD patients who suffer from symptoms experience pain and numbness in their legs, which often becomes so severe they can no longer walk. Surgery and the use of stents, small mesh tubes that hold the artery open, have had limited success in treating PAD. While stents that elute an antiproliferative drug that prevents blockages from forming have been helpful in treating coronary artery disease, they have been not shown in long-term controlled studies to be of significant benefit for treating PAD.

Unlike drug-eluting stents that contain one fixed dose, VMI offers the possibility of providing a variable initial dose based upon the extent of disease and can be readministered for either redosing or treatment with a different agent. Additionally, because the magnetic effect concentrates its delivered agent at the specific site of a stent, VMI could be used to achieve stronger effects with lower overall doses of a given agent than is possible with existing routes of administration. In children, who do not commonly suffer from PAD, VMI could eventually be used to deliver drugs to improve outcomes in a number of stent-based interventions in pediatric cardiology for conditions such as peripheral pulmonary artery stenosis, coarctation of the aorta, and atrial septal defects.

Drs. Levy and Woodward are working together to identify a strategy for quickly translating this technology from an academic pursuit to a treatment reality. To keep development on track, Drs. Levy and Woodward meet weekly along with staff from the Office of Technology Transfer to monitor the progress of Dr. Levy’s research and to discuss market analysis results, sources of venture capital, and the status of their funding applications to resources such as the Small Business Innovation Research, BioAdvance, and Ben Franklin Technology Partners programs.

Current investigations at CHOP Research supported by Dr. Levy’s QED Award include a preclinical proof-of-concept study that evaluates the distribution of paclitaxel when administered using VMI and that compares restenosis in animals treated with stents and VMI to deliver paclitaxel and those treated with bare metal stents and no paclitaxel. The investigations, conducted in rabbits that have had stents implanted in their femoral arteries, will use paclitaxel doses well below the doses loaded onto current drug-eluting stents. The model for this study has previously been used in other preclinical studies submitted to the Food and Drug Administration for Investigational New Drug Applications.

“It is exciting to see something go from the design phase to a new instrument,” says Dr. Levy. “The group working on this project is very energized. We’ve proposed to do a lot during the year and have hit all of our targets so far.”

VMI has the potential to be a highly successful commercial product that could improve the health of a large number of patients. In addition to the likely need for both primary and repeated VMI treatments for PAD, the technique is versatile and could possibly be used to deliver a broad range of effective therapeutic agents. The potential of this technology has been noted as interesting and promising by many academic journals, including Science Translational Medicine and the Journal of the American Medical Association, and the popular press, such as Forbes, which named it one of five promising new technologies.

The QED award ends in May 2011, at which point Drs. Levy and Woodward will continue their translational efforts with external sources of funding. Drs. Levy and Woodward are working closely with the Office of Technology Transfer to form preliminary plans for technology licensing.
According to new research, a pneumococcal conjugate vaccine introduced in the United States 10 years ago appears to reduce pneumonia and serious associated complications, such as blood infections, in the vaccine's target range, children less than a year old.

However, the study found that pneumonia and associated complications, including a lung infection called empyema, increased in older children. The results also show a narrowing of racial disparities in the rates of pneumonia and associated severe complications.

This investigation at CHOP Research is the first national study to comprehensively examine rates of pneumonia-related complications before and after the introduction of the vaccine, known as PCV7.

The study, titled “National Hospitalization Trends for Pediatric Pneumonia and Associated Complications,” appeared in the August issue of the journal Pediatrics. It looked at data recorded in the national Kids’ Inpatient Database from 619,102 patients younger than 18 years old who were hospitalized for “community-acquired pneumonia” in the years 1997, 2000, 2003, and 2006.

“The rate of hospitalizations for pneumonia declined among infants less than one year of age. This is the primary target population for pneumococcal vaccination, suggesting that the vaccine may contribute to reductions in infant pneumonia,” says Samir Shah, M.D., M.S.C.E., senior author of the study and a pediatric infectious diseases physician at Children's Hospital. “While we aren’t sure why we are seeing higher rates of pneumonia hospitalizations in older children, we think the decrease in infection rates in younger children is due to the vaccine.”

PCV7 is administered to infants to prevent infection with Streptococcus pneumoniae, the leading bacterial cause of pneumonia. S. pneumoniae, or pneumococcus, also causes ear infections, sinusitis, blood infections, and meningitis. PCV7 protects against seven of the most common strains among the more than 90 types of pneumococcal bacteria. A recently licensed pneumococcal vaccine now protects against the 13 most common strains.

Before routine use of pneumococcal conjugate vaccine, infections caused roughly 700 cases of meningitis, 13,000 blood infections, and 5 million ear infections each year in the United States. The infection also contributed to about 200 deaths each year, according to the Centers for Disease Control and Prevention (CDC). After PCV7 was licensed, the rate of invasive pneumococcal disease such as meningitis and blood infections decreased by 76 percent among children 5 years of age and younger, according to the CDC.

“The impact of PCV7 on pneumonia has been more difficult to evaluate,” says Dr. Shah, “because the specific cause of pneumonia is sometimes difficult to determine.”

This study has shown that from 1997 to 2006 the rate of hospitalizations for community-acquired pneumonia in the first year of life declined by 22 percent. Conversely, the rate of hospitalizations for pneumonia in children ages 6 to 12 years increased 22 percent, and for children older than 13 the rate increased by more than 40 percent. Lung complications related to pneumonia, such as empyema, were highest in children 1 to 5 years of age, the study found.

“Rates of systemic complications such as sepsis and respiratory failure decreased by 9 percent overall and approximately 35 percent for infants less than 1 year of age,” says Grace E. Lee, M.D., a lead researcher in the study and pediatric infectious diseases fellow at Children's Hospital. “The overall 9 percent decrease in systemic complication rates for the entire population in the study was largely attributable to the decrease in rates for infants and might be explained in part by the fact that infants have been the primary recipient of the vaccine.”

“In contrast, rates of hospitalization for lung complications such as empyema increased by more than 70 percent for children between 1 and 18 years of age,” says Dr. Lee. The reasons for such increases are not yet known.

The vaccine may also disproportionately benefit black children, shown in past studies to have a higher frequency of pneumococcal infections, including pneumonia. While rates of pneumonia were higher for black children compared to white children in all years of this study, the difference narrowed from a ratio of 1.98 in 1997 to a ratio of 1.59 in 2006.

Additional studies are needed to determine the underlying factors associated with these changes, the study authors note.

Other authors include Scott A. Lorch, M.D., M.S.C.E.; Seth Sheffler-Collins, M.P.H., and Matthew P. Kronman, M.D., of Children's Hospital. The study was funded with support from the Academic Pediatric Association Young Investigator Award, National Institute of Allergy and Infectious Diseases, and the Robert Wood Johnson Foundation.
A physician or nurse making rounds can locate and page through a 200-page reference book that lists the possible adverse events that may occur to patients in a clinical trial, or can instead keep all the same information in their pocket, in a 4-ounce iPhone®. For many in healthcare, that’s an easy choice.

The classifications of adverse events originated in the National Cancer Institute as a way to help standardize record-keeping of side effects occurring in patients enrolled in clinical trials. Printed out, the Institute’s Common Terminology Criteria for Adverse Events (CTCAE) is a 200-page handbook in its most recent edition, version 4.0.

The Center for Biomedical Informatics (CBMi) converted all the reference information into a software application, or “app” that anyone with an iPhone® or iPod touch® can download for free from the App StoreSM on the Internet. People with iPhones can already find apps for locating restaurants, planning travel routes, or translating phrases into foreign languages. Now healthcare providers are using apps in the interests of patient care.

From an alphabetized list of symptoms, tap in “ear pain” or “tremor,” and the touch screen will display a definition, and then list grades of the problem — mild, moderate, or severe. Using these categories, a care provider or clinical trial researcher can log data into the trial’s records, so it can be shared with other hospitals and physicians whose patients are participating in the same trial. A user can bookmark adverse events and categories that require more frequent access.

Monitoring the safety of treatments used in clinical trials is crucial to providing the best results for current and future patients. “Researchers can use this app to quickly access information at the point of care, and improve the efficiency of our research,” says Peter C. Adamson, M.D., director of the Office of Clinical Translational Research at Children’s Hospital, and chair-elect of the Children’s Oncology Group.

Although the classifications used in CTCAE originated in oncology research, they have broader application in clinical trials for other conditions, says Peter White, Ph.D., director of CBMi at Children’s Hospital, and a leader of the team that created the app. “When researchers write the protocol for a clinical trial, they know that one element of patient protection is standardized record-keeping, so they may incorporate the CTCAE rubric in their protocol.”

Dr. White adds that in addition to researchers, other caregivers such as attending physicians and medical students have been using the CTCAE app as an information resource, independent of clinical trials. “This app is one example of mobile health development, in which we are assisting healthcare staff in accessing the next generation of information technologies,” he says. “Besides the immediate benefits for efficiency, we feel that using this type of technology has significant potential for standardizing care delivery, reducing error, and improving both quality of care and patient safety.”

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**Children’s Hospital Creates Free App for iPhone® and iPod touch® to Help Doctors Record Side Effects in Clinical Trials**

Children’s Hospital was awarded two training grants to support fellowship programs that recruit and train physicians in areas requiring an increased pool of qualified researchers who can continue and improve the current level of excellence provided in pediatric care.

The Pediatric Hospital Epidemiology and Outcomes Research Training (PHEOT) Program is a two-year research fellowship designed to train the next generation of clinical scientists who will enhance the understanding of how to best measure and improve outcomes, assure patient safety, and manage costs for hospitalized children. Rapidly changing trends in inpatient pediatrics present logistical, financial, and ethical challenges to healthcare providers and the healthcare system. Through PHEOT’s combination of formal coursework and mentored research projects, trainees will develop expertise in comparative effectiveness research, quality measurement, severity adjustment, and economic evaluation as they relate to pediatric hospital care.

The PHEOT, a combined effort between Children’s Hospital’s Center for Outcomes Research (COR) and Center for Pediatric Clinical Effectiveness (CPCE), is co-directed by principal investigators, Jeffrey Silber, M.D., Ph.D., and Ron Keren, M.D., M.P.H. The program provides funding for three trainees the first year and six trainees in subsequent years. During their time in PHEOT, trainees will complete and publish at least one research project under the mentorship of an advisory team and will benefit from a host of professional development activities. All PHEOT trainees will complete coursework required for either the University of Pennsylvania’s Master of Science in Clinical Epidemiology degree or the Master of Science degree in health policy research in addition to specialized coursework in pediatric hospital epidemiology and outcomes research.

The Pediatric Pharmacoepidemiology Training Program (PPTP) will use an innovative program to train pediatricians to be rigorous, independent academic investigators able to use the range of approaches available in epidemiology to study the use and effects of medications in pediatric patients. There have been few advances in research on the use and effects of prescription drugs in children, and despite federal calls for greater attention to the study of drugs in pediatric patients, no training programs with this focus have existed. The PPTP will serve this need by providing highly motivated, clinically trained individuals with intensive instruction in the methods of clinical epidemiology in pediatric populations, including biostatistics, pharmacokinetics, and pharmacogenetics.

Trainees in the PPTP will complete core courses in epidemiology, clinical research methodology, and biostatistics in addition to courses required to complete a Master of Science in Clinical Epidemiology degree from the University of Pennsylvania’s Center for Clinical Epidemiology and Biostatistics, which supports the program in combination with Children’s Hospital’s Division of Clinical Pharmacology and Therapeutics and CPCE.

The two- to three-year PPTP fellowship also requires trainees to complete a clinical experience in pediatric pharmacoepidemiology, and conduct applied research in pediatric pharmacoepidemiology under the close supervision of a senior mentor. The program, which is co-directed by principal investigators Peter Adamson, M.D., and Brian Strom, M.D., M.P.H., provides funding for two new trainees in each of the first two years of the grant, and five trainees each subsequent year.

Both grants have initial funding for five years and are eligible for continued funding. For more information about either of these programs, please contact Debbie Hillman at hillman@email.chop.edu.

New Grants Provide Outcomes and Epidemiology, Pharmacoepidemiology Training
CPCE Announces Pilot Grant Award Recipients

The Center for Pediatric Clinical Effectiveness (CPCE) recently announced the recipients of the spring 2010 Pilot Grant Awards, designed to promote and support fellows, junior faculty, and other CHOP Research investigators in clinical effectiveness pilot research studies that will attract external support for large-scale studies.

Peter de Blank, M.D., a fellow in the Division of Oncology, and Michelle Denburg, M.D., a fellow in the Division of Nephrology received the awards, which provide one year of support up to a maximum of $10,000.

Dr. de Blank studies ways of improving survival and quality of life in children with cancer by improving cancer supportive care. The CPCE Pilot Grant Award supports his current investigation into the risk factors for *Clostridium difficile* infection in hospitalized children with cancer, under the mentorship of Richard Aplenc, M.D., M.S.C.E., and Theoklis Zouritis, M.D., M.S.C.E.

*Clostridium difficile* infection, known as *C. difficile*-associated disease, or CDAD, is the most common cause of diarrhea associated with hospital treatment and can lead to a range of secondary problems. Although it is rare in children, a quarter of all cases occur in children with cancer and can impact quality of life, affect nutrition, cause therapy delays, and result in costly outbreaks in other immunosuppressed patients. The risk factors for CDAD are well known in adults; however, preliminary evidence suggests that very different factors may predispose children to the disease.

In the largest cohort study of CDAD in children with malignancy to date, Dr. de Blank is working in collaboration with Brian Fisher, M.D., Jason Kim, M.D., and Sanjeev Swami, M.D., to evaluate data from hospitalized children with cancer in more than 42 tertiary care pediatric hospitals that participate in the Pediatric Health Information System. The team will characterize the incidence and severity of CDAD and determine the risk factors associated with CDAD, an approach that has the potential to identify targets for more effective prophylactic treatments and strategies for preventing and decreasing the impact of this disease.

Dr. Denburg studies disordered mineral metabolism and cardiovascular disease in children and adolescents with chronic kidney disease (CKD), with the mentorship of Mary Leonard, M.D., M.S.C.E. Dr. Denburg received the CPCE Pilot Grant Award to support the first population-based study ever conducted to assess fracture risk in children and young adults with CKD.

End-stage renal disease (ESRD) typically occurs in patients with CKD who have had a gradual worsening of kidney function over many years. Numerous studies have shown that the majority of young adults with a history of childhood-onset ESRD have an increased risk of a number of secondary health problems, including an increased risk of hip fracture. Additional studies have shown that this risk is even seen in adults with moderate CKD. Despite the importance of recognizing and preventing this and other CKD-related complications during childhood, studies of fracture risk in children with CKD have been limited because of the lack of population-based data from these patients that includes repeated measures of renal function, medications, and clinical outcomes.

Using the U.K. Health Improvement Network (THIN) database, a previously unidentified resource for studies of clinical effectiveness in pediatric CKD, Dr. Denburg is conducting a retrospective cohort study of the rate of hip fracture in children with CKD. In previous research, Dr. Denburg performed a cross-sectional validation study to determine the diagnostic codes within THIN that best define CKD stages 3 to 5, which represent moderate decrease in kidney function to kidney failure. In the current study she will use this resource to compare the fracture rate among patients with CKD to healthy children and determine whether CKD is associated with increased risk of fracture in children and young adults and identify risk factors for fracture in children with CKD, information that may lead to new approaches for prevention and treatment.

Dr. de Blank and Dr. Denburg, who are both completing a master's degree in clinical epidemiology, plan to use the data sources employed in the current studies for future investigations that will improve clinical outcomes for children.

The next CPCE Pilot Grant Submission deadline is October 1, 2010. CHOP investigators from all Hospital departments and divisions, including fellows in their final year of fellowship transitioning to Hospital-affiliated faculty, are encouraged to apply. Details on the application and submission process, review and selection criteria are available on CPCE's Web site at http://www.research.chop.edu/programs/cpce/research.php.

If you have questions, please contact CPCE Center Manager, Debbie Hillman at hillman@email.chop.edu.

New Module Added to the Animal Care and Use Training Requirement

In addition to the existing Animal Care and Use Training curriculum, members of the CHOP Research community actively participating in research involving animals are now required to complete the American Association for Laboratory Animal Science (AALAS) Learning Library module, “Working With Controlled Substances.”

All new personnel will need to complete this module as part of their initial training requirement. Existing researchers are required to complete the module when their AALAS refresher training is due or at the time of new protocol or three-year renewal Institutional Animal Care and Use Committee submissions.

Additional information concerning the “Working With Controlled Substances” module can be found on the CHOP Research intranet at https://intranet.research.chop.edu/display/deptrtr/Animal-Care+and+Use+Training.

Please direct questions to researchtraining@email.chop.edu.