Study Shows Gene Therapy Reverses Nerve Damage in an Inherited Disease

A recent study has shown that a naturally occurring genetic disease may be treated by injecting a therapeutic gene directly into the brain.

If human trials are ultimately successful, according to the study investigators from The Children’s Hospital of Philadelphia, the University of Pennsylvania School of Veterinary Medicine and the U.S. Naval Academy, the approach may one day be used to treat an entire class of diseases called lysosomal storage disorders.

The investigators caution, however, that human trials of the gene therapy approach for lysosomal disorders may be several years away.

Affecting one in 5,000 births, the approximately 50 various lysosomal disorders can cause severe, sometimes fatal, disabilities. The research team studied animals with the lysosomal disorder called alpha-mannosidosis (AMD), an inherited disease in humans that causes severe mental retardation and skeletal abnormalities. Animals with AMD do not live more than six months. Children born with the worst form of the disease rarely survive into their teens.

“Through gene therapy, we replaced a ‘broken’ gene responsible for alpha-mannosidase with the correct, functioning copy, to dramatic results,” said John H. Wolfe, V.M.D., Ph.D., a professor of pathology and medical genetics at the Penn School of Veterinary Medicine and a neurology researcher at Children’s Hospital. Dr. Wolfe added that brain tissue is still physically maturing shortly after birth, creating a potentially important window of opportunity for future gene therapy in infants.

According to Charles H. Vite, D.V.M., Ph.D., the lead author of the paper and an assistant professor of veterinary neurology at Penn, the treated animals not only demonstrated dramatic clinical improvement, but MRI also revealed that white-matter tracks (myelin) in the brain had been largely restored.

The study also demonstrated that only a limited number of injections are necessary to introduce the working gene, one of the first steps that will prepare this particular gene therapy for practical use in humans.

The gene is transported through a neutralized virus that “infects” cells with the functioning gene. Since the blood-brain barrier would block the virus carrying the gene if it were circulating in the bloodstream, the researchers injected the virus directly into the brain.

“As we move forward toward the clinical use of this therapy in humans, we must develop and utilize non-invasive methods to monitor the regression of the disease following treatment,” Dr. Vite said. “The ability to monitor the improvement in brain myelination in alpha-mannosidosis using imaging allows the clinician to see improvement in brain pathology without the need for brain biopsy.”

The study, funded by the National Institutes of Health, was published in the March issue of the journal *Annals of Neurology*.

Stokes Scientific Symposium Set for April 29

The annual Stokes Scientific Symposium will be held on April 29, 2005, at the Gregg Conference Center of the American College in Bryn Mawr, Pa. The symposium aims to highlight the breadth of the research programs at the Stokes Institute and to build on the Institute’s intellectual community.

The event will begin with registration and a breakfast buffet at 8 a.m. The first of the four scientific sessions will begin at 8:45 a.m. Michael Brown, M.D., will deliver the keynote address during the daylong event. Dr. Brown and his long-time colleague, Joseph L. Goldstein, M.D., discovered the low-density lipoprotein (LDL) receptor, which controls the level of cholesterol in the blood and in cells. They have received numerous awards for this work, including the U.S. National Medal of Science and the Nobel Prize for Medicine or Physiology.

Additionally, the event will feature displays and poster presentations by the Stokes Core Facilities, which will have staff on hand to answer questions.

Stokes encourages all investigators to submit abstracts for the symposium. Those received by March 31 will be used to select speakers for the symposium agenda, and all abstracts will be printed in the symposium program.

Investigators interested in the symposium may contact the event’s organizers, Vivian Cheung, M.D., (ext. 44950, vcheung@mail.med.upenn.edu), or Harry Ischiropoulos, Ph.D. (ext. 45320, ischirop@mail.med.upenn.edu), for more information. Investigators should contact Kelli Dolison (ext. 43954 or dolison@email.chop.edu) to register.
New Research Employees (February 2005)

We welcome the following new research employees:

Administrative Assistant
Taren Morris

Adolescent Case Manager
Maya Blanc

Animal Caretaker
Kathleen Fitzgerald

Infant/Toddler Specialist
Shari Roulac

Research Assistants
Debra Abrams
Pan Chen
Alexia Clarke
Megan Fox

Research Technicians
Joshua Courtright
Denise Gibbs
Kevin Richberg
Qi Wan

Scientist
Engin Ozkaynak

Secretary to the Chief
Maria Whitty

Staff Accountant
Maria Prado

Correction
A story in the January issue of Bench to Bedside (“Researchers Find Newborns with Heart Defects Have Low Cerebral Blood Flow Before Surgery”) erroneously stated that Daniel Licht, M.D., is in the Division of Neonatology. He is in the Division of Neurology. We regret the error.

Hospital Holds Fellow’s Research Poster Day

Children’s Hospital has long supported and valued the training of young scientists – the next generation of investigators whose research may advance children’s healthcare. Graduate students, postdoctoral fellows and clinical fellows showcased their basic, translational and clinical research at the 15th annual Children’s Hospital/Stokes Institute Fellow’s Research Poster Day on Feb. 14.

More than 130 abstracts were presented during the poster day, an event organized by William Fox, M.D., Division of Neonatology; Helen Korcak, Ph.D., Division of Allergy and Immunology; and Roger Wood, director of Research Operations.

Mrs. Mary Hummeler – wife of the late Dr. Klaus Hummeler, the first director of the Stokes Institute – provided generous support for the event. With Mrs. Hummeler’s support, Stokes developed a proceedings book and awarded prizes for outstanding presentations in clinical, translational and basic research by clinical and postdoctoral fellows and pre-doctoral candidates.

The awardees and their poster topics were:

Obinna Adbie, M.D., Department of Surgery, “Retrospective comparison of outcomes following open versus laparoscopic pyloromyotomy.”

Majed Aljamali, Division of Hematology, “Hemostatic effects of long-term expression of activated murine FVII in normal and hemophiliac mice.”

Pinaki Banerjee, Ph.D., Division of Allergy and Immunology, “Cdc42 interacting protein 4 is a potential link between actin and microtubules at the natural killer cell immunological synapse.”

Elsa Bianchini, Division of Hematology, “Ratcheting between two distinct conformations of substrate drives the sequential cleavage of prothrombin by prothrombinase.”

Angela Breidenstine, Department of Psychology, “Protective factors in the lives of children experiencing the risks of poverty and maternal depression.”

Jin-Wen Chen, Ph.D., Division of Infectious Diseases, “Normal heart development requires cardiomyocyte-specific expression of coxsackievirus and adenovirus receptor.”

Michael Chorny, Ph.D., Division of Cardiology, “Injectable adenovirus-poly lactide nano-particle composites for efficient gene transfer to smooth muscle cells (A10) and cardiomyocytes (HL-1).”

Julie Davis, M.D., Division of Cardiology, “Longitudinal assessment of cardiovascular exercise performance after pediatric heart transplantation.”

Daniel Delaney, Division of Urology, “Molecular analysis of the HOX9 gene in cryptorchidism.”

Marco Gonzalez, Division of Child Development and Rehabilitative Medicine, “Regulation of the neuronal glutamate transporter, Eaac1/Eaat3, by caveolae/lipid rafts.”

Lisa Meltzer, Ph.D., Department of Psychology, “Sleep and functioning in caregivers of ventilator-dependent children.”

Karna Murthy, M.D., Division of Neonatology, “Cathepsin H (CTSH) and Napsin A (NapA) expression during human lung development.”

Emily Rowell, B.A., Department of Pathology, “Opposing roles for the cyclin-dependent kinase inhibitors p18ink4c and p27kip1 in allograft tolerance induced by costimulatory blockade.”

Diana Sheffler, Department of Psychology, “Pediatric HIV: effects of adjustment, social support, and disclosure on cognitive and psychosocial functioning.”

Amanda Shillingford, M.D., Division of Cardiology, “Inattention and hyperactivity are common 6-11 years after neonatal cardiac surgery.”

Jason Stoller, Division of Neonatology, “Mechanisms of DiGeorge syndrome: characterization of human TBX1 mutations.”

David Teachey, M.D., Division of Hematology-Oncology, “Unmasking Evans syndrome: T cell phenotype and apoptotic response reveal autoimmune lymphoproliferative syndrome (ALPS).”

Zhi Wang, Division of Neonatology, “Zinc protoporphyrin IX inhibits cell proliferation via suppression of cyclin D1 protein synthesis in hepatoma cells.”

Mingee Zhang, Ph.D., Division of Rheumatology, “C-maf cooperates with NFAT1 to augment HIV-1 transcription in T-helper-2 CD4 T cells.”
Stokes Launches Clinical Research Coordinator Education Program

Those working as clinical research coordinators often have a wide range of responsibilities, yet their formal training is largely limited to that received on the job or through one-on-one mentorship.

Children's Hospital has more than 200 employees either with the job title of research coordinator or who function as clinical research coordinators. About half these coordinators are nurses; others have bachelor's or master's degrees in other fields. Most have no formal training or certification through professional organizations.

The national trend in clinical research is leaning toward more formal training and certification, especially for those involved in research involving human subjects. Although the federal government doesn't yet require training and certification, many institutions are implementing formal training programs for employees working in clinical research.

In September 2002, the Hospital’s Research Compliance Oversight Committee approved a policy mandating training for all clinical research staff. As a result, the Hospital developed a training and certification program through the Department of Research Education.

Introduced in March, the Web-based, interactive program contains seven core modules and advanced training modules. The six- to eight-hour program covers institutional policies and procedures, federal regulations and study implementation. More specifically, the modules – developed by a team of leading study coordinators in conjunction with Research Education, faculty and other staff – address topics such as project initiation, pre-study activities, clinical and administrative responsibilities, study termination and the Hospital’s Institutional Review Board.

Advanced training modules address Investigational New Drugs (INDs) and Investigational Device Exemptions (IDEs). Future training-module topics will include research ethics and budget development.

Study coordinators must complete the seven core modules within 90 days to serve as a primary or sole coordinator on a project. Research Education anticipates the program will be adapted in the near future to train investigators as well.

For more information, contact Jodi Leckrone at ext. 67360 or leckrone@email.chop.edu.

Faculty Honors

Steven Douglas, M.D., chief of the Section of Immunology and director of Clinical Immunology Laboratories, will serve as chair of the AIDS Immunology and Pathogenesis Study Section at the National Institutes of Health (NIH). The study section reviews grant applications for research into cell- and tissue-level events involved in the development and progression of HIV infection. Dr. Douglas will chair the study section for a two-year period beginning July 1, 2005.

The Education and Research Trust (ERT) of the American Academy of Allergy, Asthma and Immunology recently chose Jordan Orange, M.D., Ph.D., Division of Immunology, as the recipient of the 2005 ERT Faculty Development Award. The award supports one faculty member each year who represents the specialty of Allergy and Immunology and shows promise in research that will promote the specialty. Dr. Orange received the award March 21 in San Antonio during the academy's annual meeting.

The Pennsylvania Chapter of the American Academy of Pediatrics recently named Physician-in-Chief Alan Cohen, M.D., Pediatrician of the Year.

In addition, two Children's Hospital investigators received teaching awards from the University of Pennsylvania School of Medicine. Mary Cay Harris, M.D., Division of Neonatology, received the university’s Blockley-Osler Award, while Ian Krantz, M.D., Division of Human Genetics, received the Dean's Award for Excellence in Basic Science Teaching.

FYI

Celebrating HIPS Week: Children's Hospital is participating in the national Health Information Privacy and Security (HIPS) week, April 10 through 16, 2005, sponsored by the American Health Information Management Association. During HIPS week, the Hospital will highlight easy ways that each of us can better respect patient privacy and protect confidential information in our everyday routines. Visit the Hospital's intranet at http://intranet.chop.edu/employee/jsp/home.jsp for more information on privacy, information security and HIPS activities beginning April 10.

GCRC Awards for Junior Clinical Investigators: The General Clinical Research Center (GCRC) recently announced the availability of support for junior clinical investigators through the NIH Clinical Research Feasibility Funds (CReFF) program. The CReFF program aims to encourage junior investigators to develop clinical research projects that ultimately will lead to extramural NIH funding.

The guidelines for submitting applications, due May 13, 2005, are at http://stokes.chop.edu/forms/CReFF.doc. Questions about the program should be directed to Veronica Mazzaccaro (ext. 4-2215 or mazzaccaro@email.chop.edu).

Bioinformatics Core Tools: The Bioinformatics Core has made some of its tools and its new computer system available for general user testing. The resources can be accessed through the core’s Web site on the Stokes Institute intranet (stokes.chop.edu). Contact Ge Zhang at ext. 67172 or zhangg@email.chop.edu for more information.

AAALAC Accreditation: On Feb. 23 the Association for Assessment and Accreditation of Laboratory Animal Care International (AAALAC) fully accredited the Laboratory Animal Facility (LAF) without any recommendations for improvement

During its evaluation, the AAALAC council noted the high level of support provided by Hospital administration, the engagement and quality of oversight provided by the Hospital Institutional Animal Care and Use Committee, the excellent animal care staff, the high quality training programs, the teamwork and communication among members of the animal care and research staff, the well-maintained and operated facilities, and the LAF’s biological security programs.

AAALAC accreditation occurs every three years. The Hospital’s LAF has been fully accredited since June 1977.
Clinical Process Improvement Initiative Moves Beyond Pilot

Part of the Hospital's strategic plan conducted by the Stokes Institute revolves around the Clinical Research Process and Systems Improvement Project. The project is designed to ensure all clinical research business processes are consistent with best practices, improve principal investigators' and other stakeholders' experiences related to clinical research, and improve the quality of service to research subjects and families to make participation in research studies easier and more convenient.

The initiative will soon be ready for a Hospital-wide roll-out, which will affect all existing and new clinical research protocols.

The team's efforts have centered on several clinical trial elements, including correct budget preparation; proper registration of subjects in Hospital systems; appropriate identification of procedures as research or standard of care; centralized subject scheduling; and appropriate billing of procedures and account reconciliation. In addition, the team created multiple policies on topics such as budgeting standards and clinical research in the operating room.

Based on the results of an ongoing pilot program launched in May 2004, the clinical research business project team addressed compliance issues to improve patient registration and facilitate proper routing of research-related billing. The team is currently piloting several projects using the Hospital's Access Center, a centralized subject/patient scheduling resource. The team has also worked closely with the Patient Access Revenue Cycle (PARC) group, Information Services, Finance, the Process Innovation Center, investigators and many others to develop the new clinical research business processes.

To further assess the Hospital's clinical research business needs and plan to implement the necessary changes, the team recently sent a Web-based questionnaire to all investigators, requesting certain study demographics and information on research projects. This information helps determine study location and type, and helps set priorities for areas in which the new business processes should be instituted first.

As the Hospital implements the new procedures throughout the fiscal year, investigators and study coordinators will be freed from some of the administrative issues surrounding clinical trials, allowing more time to focus on research.

Specifically, investigators and study teams will no longer have to handle issues related to improper billing or worry about whether study costs are reimbursed appropriately. The ultimate benefit, however, will be to research subjects, whose experience in clinical research will be enhanced by the streamlined procedures.

A planned roll out date for all ongoing and new studies will be released in the coming month. Investigators and coordinators of active clinical research projects are therefore encouraged to respond to requests for process input and information to help meet the overall goal of enhancing the clinical research business support process.

Study Concludes Child Occupants at Risk from Teen Drivers

A national study of children in car crashes led by Children's Hospital investigators found that children driven by teenagers were three times as likely to have a serious injury as those driven by adults. The investigators determined the risk of injury was highest for young teenage passengers, ages 13 to 15.

According to researchers from Partners for Child Passenger Safety (PCPS), a research partnership of Children's Hospital and State Farm Mutual Automobile Insurance Company, teen drivers were also more likely to sit in the front seat as compared to those driven by adults. Also, children under age 13 years riding with novice teen drivers were three times as likely to have no restraint at all as those with adult drivers. Children riding by 15- to 17-year-olds had a higher likelihood of being seated in the front seat and not using restraints, the investigators found. Children riding with these novice teen drivers were more than likely to have no restraint at all as those with adult drivers. Also, children under age 13 years riding with novice teen drivers were more likely to sit in the front seat as compared to those driven by adults.

A planned roll out date for all ongoing and new studies will be released in the coming month. Investigators and coordinators of active clinical research projects are therefore encouraged to respond to requests for process input and information to help meet the overall goal of enhancing the clinical research business support process.

Contact Jennifer Long at ext. 4-2105 or by e-mail at longj@email.chop.edu.
Read this and previous versions of Bench to Bedside online at http://stokes.chop.edu/intranet/pubs/