Gene therapy for a severe inherited blindness, which produced dramatic improvements last year in 12 children and young adults who received the treatment in a clinical trial, has cleared another hurdle. The same research team that conducted the human trial now reports that a study in animals has shown that a second injection of genes into the opposite, previously untreated eye is safe and effective, with no signs of interference from unwanted immune reactions following the earlier injection.

These new findings suggest that patients who benefit from gene therapy in one eye may experience similar benefits from treatment in the other eye for Leber’s congenital amaurosis (LCA), a retinal disease that progresses to total blindness by adulthood. Researchers had exercised caution by treating only one eye in the human trial.

In the current study, the study team found no evidence of toxic side effects in the blood or the eyes of the 10 animals — six dogs and four monkeys — that received the gene therapy. Each animal received an injection first in the right eye, then in the left eye 14 days later. All six dogs, which had been specially bred to have congenital blindness, had improved vision, in addition to showing no toxic effects from the gene therapy.

Investigators from The Children’s Hospital of Philadelphia and from the University of Pennsylvania School of Medicine, and colleagues from two other institutions published their study in the journal Science Translational Medicine. The first authors are Defne Amado, of the F.M. Kirby Center for Molecular Ophthalmology at Penn, and Federico Mingozzi, Ph.D., of the Center for Cellular and Molecular Therapeutics (CCMT) at Children’s Hospital.

As in the human trials of this gene therapy, the investigators packaged a normal version of the gene that is missing in LCA inside a genetically engineered vector, adeno-associated virus (AAV). The vector delivers the gene to cells in the retina, where the gene produces an enzyme that restores light receptors. Although the virus used does not cause human disease, it previously set off an immune response that cut short the initial benefits of gene therapy, notably in a 2002 human trial of gene therapy for the bleeding disorder hemophilia.

“Our current study in large animals provides encouraging indications that immune responses will not interfere with human gene therapy in both eyes,” says co-author Katherine A. High, M.D., a pioneer in gene therapy who helped lead the hemophilia trial. “Like humans, monkeys generate neutralizing antibodies against both naturally occurring and injected AAV, but these antibodies did not prevent the injected gene from producing the desired enzyme.” Dr. High is director of CCMT, which manufactured the vector used in the current study and the previous human trial for LCA.

In the human trial for LCA reported last year, the Children’s Hospital and Penn researchers, led by Drs. Bennett, High and retina specialist Albert M. Maguire, M.D., injected the vector into only one eye in each of their 12 patients. Because the treatment was experimental, researchers left one eye untreated in the event of unexpected complications. After the subjects experienced partially restored eyesight in their treated eyes, many were eager to receive the same treatment in the other eye. The current study advances that possibility, and the research team is planning another clinical trial of LCA gene therapy, which may include some of the subjects from the first group.

Additionally, the results may set the stage for gene therapy in LCA patients who were excluded from the previous trial. Adopting a conservative approach, the researchers did not treat patients who already had neutralizing antibodies against AAV in their blood. As many as a quarter of all people may carry these antibodies by their teenage and young adult years. Fortunately, unlike other organs, both human and animal eyes are insulated from these circulating antibodies. The authors conclude that the presence of those antibodies in the blood will most likely not prevent effective gene transfer in human eyes.

Funding support came from the CCMT, the Foundation Fighting Blindness sponsored CHOP-PENN Pediatric Center for Retinal Degenerations, the National Institutes of Health, Research to Prevent Blindness, Hope for Vision, the Paul and Evanina Mackall Foundation Trust at the Scheie Eye Institute, and the F.M. Kirby Foundation. Dr. High is an Investigator of the Howard Hughes Medical Institute, which also provided support.
According to recent Children's Hospital study, one month after their child was injured, 27 percent of parents experienced acute stress disorder (ASD) or significant traumatic stress symptoms, including re-experiencing the incident, avoiding reminders of the incident, and increased general anxiety or jumpiness.

Of those parents 15 percent displayed longer-term symptoms of post-traumatic stress disorder (PTSD) more than six months after the initial injury, according to the study published recently in the *Journal of Traumatic Stress*.

“Research consistently shows the important role that parents play in a child’s recovery. So, in addition to all the things parents do to help their child recover, it’s very important that they also take good care of themselves,” says Nancy Kassam-Adams, Ph.D., the study’s lead author and director of the behavioral science core at CHOP’s Center for Injury Research and Prevention. “To help families understand and deal with their reactions to a child’s injury, we created a Web site, www.AfterTheInjury.org.”

“It is natural for parents to feel very upset or anxious in the first days and weeks following a child’s injury,” explains Flaura Koplin Winston, M.D., Ph.D., a co-author of the study and co-scientific director of the Center for Injury Research and Prevention. “But, when traumatic stress reactions go on for longer than a month, worsen, or get in the way of normal life, it is important for parents to seek support for themselves.”

“It’s harder to help your child if you — the parent — are feeling nervous, worried, upset, or overwhelmed,” says Dr. Kassam-Adams. “Parents need to take time to talk about their concerns or feelings with loved ones, take a break, and recognize when outside help might be needed.”

In this study, the investigators worked with 334 parents of children who had suffered road traffic injuries requiring hospital care. The researchers identified factors that predicted the severity of ASD (acute trauma symptoms rated in the first month) and PTSD (longer-lasting trauma symptoms rated about six months later) in parents of the injured children. Highlights from these findings include:

- The severity of parents’ PTSD six months after the injury was strongly associated with the severity of their traumatic symptoms within one month after the injury.
- Parents who had experienced a previous trauma had more severe traumatic stress symptoms immediately after their child’s injury and six months later.
- Parents’ traumatic stress symptoms were linked to their experience of the injury. Those that experienced more severe and persistent symptoms were present when their child was injured, perceived their child to be in pain, or thought that their child’s life was in danger.
- Parents’ traumatic stress symptoms were linked to their child’s symptoms. They were more likely to experience PTSD if their child was in poorer physical health six months after the injury than they were before the injury, or when their child reported more severe acute traumatic stress symptoms.

“The focus after an injury is on the child’s physical recovery. Our previous research demonstrated that a child’s full recovery plan needs to address physical and emotional needs. This study points to the needs of parents of injured children, which might be overlooked,” says Dr. Winston. “Parents need to know how to find the help and support they need so that they can give help and support to their injured child.”

AfterTheInjury.org is a parent-friendly Web site designed by CHOP experts to help parents ensure they — and their kids — achieve a full physical and emotional recovery. The site includes expert tips and help for parents on managing hospital visits, making the transition to home, helping children with fears and worries, and returning to life as usual.

For more information on research about parents’ and children’s emotional reactions to injury or to find resources for families and physicians, visit www.AfterTheInjury.org.
Bystander CPR Can Improve Survival of Children Who Have Cardiac Arrests Outside of a Hospital

Bystanders who perform cardiopulmonary resuscitation (CPR) on a child with cardiac arrest increase the child’s likelihood of survival, according to the largest pediatric study to date. The outcomes are similar for both chest compression alone (hands-only) CPR and CPR with chest compression and rescue breathing.

CPR was more effective when rescue breathing was combined with chest compressions for children with cardiac arrest from non-cardiac causes, such as trauma, near drowning, or respiratory problems. Nevertheless, say the authors, because most children suffering cardiac arrest outside a hospital receive no bystander CPR, even compression-only CPR is preferable to no CPR.

The study was published online in The Lancet. Two prominent pediatric CPR investigators from Children’s Hospital, Robert Berg, M.D., and Vinay Nadkarni, M.D., collaborated on the study, analyzing and interpreting data and co-authoring the final report.

This is the largest study of children to identify the important beneficial impact of bystander CPR on pediatric cardiac arrest survival outcomes. Importantly, the relative value of rescue breathing during bystander-initiated CPR depends on the cause of the arrest, whether from an underlying heart condition, or a non-cardiac cause such as sudden trauma, near drowning, or respiratory illness.

“This study is the first large study to specifically confirm that CPR with rescue breathing is the best approach for a cardiac arrest from respiratory problems in children,” says Dr. Berg, chief of Critical Care Medicine at Children’s Hospital. “Our study is also sufficiently large to identify the important beneficial effect of any bystander CPR on survival outcomes after pediatric cardiac arrest.”

The American Heart Association recommends bystanders who are not trained or willing to provide rescue breathing with CPR to provide “hands-only” chest compressions for adults who have cardiac arrests outside of a hospital. However, previous studies have not included enough pediatric patients to evaluate this strategy for children.

The current study’s investigators enrolled 5,170 children ages 1 through 17 who had an out-of-hospital cardiac arrest in Japan. They compared whether the children had been given CPR, and if so, whether CPR was compression-only or CPR with rescue breathing.

Children receiving any CPR were three times more likely to have better survival outcomes; 4.5 percent of patients receiving CPR had a favorable outcome compared with 1.9 percent who received no CPR. In children whose cardiac arrests had a non-cardiac cause, conventional CPR with rescue breathing was more likely to improve survival than compression-only CPR (7.2 percent compared with 1.6 percent). For children whose arrests were cardiac in cause, both types of CPR had the same effect.

“CPR with rescue breathing should continue to be taught as the gold standard for those who care for children and who have a duty to respond,” says Dr. Nadkarni, medical director of the Center for Simulation, Advanced Education, and Innovation at Children’s Hospital. “Most importantly, if you witness a child suddenly collapse, such as an athlete on the field, and suspect cardiac arrest, perform at least chest compressions until medical help and a defibrillator arrives.”

The study authors encourage a two-pronged CPR training strategy: hands-only CPR training for everyone, to increase CPR by bystanders, and conventional CPR (chest-compression plus rescue breathing) training for individuals who are most likely to witness children who have cardiac arrests with non-cardiac causes, such as medical professionals, lifeguards, school teachers, families with children, and families with swimming pools.

Awards for Outstanding Presentations Announced at 2010 CHOP Research Poster Day

At the 20th annual CHOP Research Poster Day, a celebration of innovative research and scientific discovery, more than 120 researchers in training displayed poster presentations representing the groundbreaking research undertaken throughout Children’s Hospital. Held in Abramson Research Center on Feb. 24, the event demonstrated CHOP Research’s unique position to celebrate the past and build the future of research.

This event was made possible by the generous support of Mrs. Klaus Hummeler, wife of the late Dr. Klaus Hummeler, who served as the first director of the Research Institute at Children’s Hospital; CHOP Research Institute administration; and corporate sponsors.

CHOP Research awarded prizes to the following investigators for their outstanding presentations in laboratory-based and patient-oriented research.

**Patient-Oriented Research Track**
- Robert Avery, Division of Neurology
- Upal Bhalala, Division of Critical Care Medicine
- Christopher Bonafide, Division of General Pediatrics
- Ronnie Collins, Division of Cardiology
- Donna Goff, Division of Cardiology
- Soma Jyonouchi, Division of Allergy and Immunology
- Javier Lasa, Division of Cardiology
- Andrew McInnes, Division of Critical Care Medicine
- Matthew O’Connor, Division of Cardiology
- Swaroop Pinto, Division of Pulmonary Medicine
- Homaira Rahimi, Division of Rheumatology
- Eric Shelov, Division of General Pediatrics
- Lakshimi Srinivasan, Division of Neonatology
- Deepika Thacker, Division of Cardiology
- Jason Williams, Division of Clinical Pharmacology

**Laboratory-Based Research Track**
- Hamid Bassiri, Division of Infectious Disease
- Xin Cheng, Division of Hematology
- Shuang Cui, Division of Gastroenterology, Hepatology, and Nutrition
- Davide Elletto, Division of Cell Pathology
- Nick Hand, Division of Gastroenterology, Hepatology, and Nutrition
- Li Changhong, Division of Endocrinology
- Patrick Mayes, Division of Oncology
- Ashley Mentlik, Division of Allergy and Immunology
- John Meshki, Division of Allergy and Immunology
- Marta Rowh, Division of Cancer Pathobiology
- Jessica Roybal, Division of General, Thoracic, and Fetal Surgery
- Jianguang Wang, Division of Rheumatology
- Susan Wood, Division of Stress Neurobiology
- Jingxuan Liu, Division of Developmental Biology
- Joseph Briggs, Division of Cancer Pathobiology

For questions about CHOP Research Poster Day, please contact the Office of Responsible Research Training at researchtraining@email.chop.edu.
CHOP Research Named One of the Best Places to Work for Postdocs

CHOP Research was included in the 8th annual “Best Places to Work for Postdocs” survey from The Scientist, a magazine for life science professionals.

CHOP Research was ranked among the top 15 U.S. institutions that support the values and needs of their postdoctoral fellows, frequently referred to as postdocs. Institutions were evaluated according to 11 categories: quality of training and mentoring, career development opportunities, quality of communication, networking opportunities, value of the postdoc experience, quality of facilities and infrastructure, funding, equity, remuneration and compensation, benefits, and family and personal life. Institutions that topped the 2010 list were noted for encouraging rich personal lives outside the lab, as well as offering comprehensive benefits packages.

Postdocs are an essential part of a research community; they make indispensable contributions in almost every lab, including the labs of the most high-achieving scientists. By listening to the intellectual and personal needs of the postdoc community, CHOP Research has strengthened its overall research program.

Investigators Show Children Can Have Recurrent Strokes

Children can have strokes, and the strokes can recur, usually within a month, according to pediatric researchers. Unfortunately, the strokes often go unrecognized the first time, and the child does not receive treatment before the recurrence.

Pediatric neurologist Rebecca Ichord, M.D., director of the Pediatric Stroke Program at Children’s Hospital, reported on a study of arterial ischemic stroke in children at the International Stroke Conference 2010 in San Antonio, Texas. The conference was sponsored by the American Stroke Association.

Dr. Ichord and colleagues at Children's Hospital followed 90 children with a median age of about 6 years old, treated for stroke between 2003 and 2009. Twelve patients (13 percent) had a recurrent stroke during the study period, most recurrent strokes occurred within a month of the first stroke. In six of the 12 children with recurrent strokes, no one diagnosed the initial stroke until a recurrent stroke occurred.

“Strokes don’t occur only in the elderly,” says Dr. Ichord. “They can also affect children as young as infants. Our findings reinforce how important it is to diagnose stroke in children as quickly as possible so that medical caregivers can provide emergency treatment and take measures to prevent recurrence.”

An arterial ischemic stroke results from a blockage or constriction in an artery in or leading to the brain. Strokes can arise in children as a complication of other illnesses, such as sickle cell disease, which obstructs blood circulation, or from an undetected heart condition. A whiplash injury to a child’s neck may damage an artery and leave it vulnerable to a blood clot that causes a stroke. Signs of a stroke are the same as in adults — a sudden loss of neurologic functions such as vision or speech, unsteadiness, or weakness on one side of the face or in limbs. What is different in children, says Dr. Ichord, is that symptoms may be subtle, examination is difficult, and children are less able to describe their symptoms than adults are.

Emergency treatment for a stroke typically involves assuring adequate breathing and circulation, supplying intravenous fluids, and improving blood supply to the brain. Medications such as aspirin or blood thinners are given to lower the risk of a recurrent stroke. In the aftermath of a stroke, rehabilitation is critical to promote recovery.

“Because a stroke can recur, we need improved awareness of pediatric stroke among primary health care providers, and more research on the best ways to prevent a recurrence after a child suffers a first stroke,” adds Dr. Ichord.

Hospital Investigator Receives Neurological Scholar Award

Carsten Bonnemann, M.D., received this year’s Derek Denny-Brown Neurological Scholar Award from the American Neurological Association, a professional society of pediatric and adult academic neurologists. The Derek Denny-Brown Award is a prestigious honor given to newly elected members in recognition for creating a body of work in the neurological sciences that shows particular significance and promise.

Dr. Bonnemann was honored with this award for his research into the clinical, molecular, and translational aspects of congenital disorders of muscle, in particular those associated with a form of collagen in skeletal muscle, known as collagen VI. Mutations in the genes coding for collagen VI cause a spectrum of congenital muscular dystrophy. Dr. Bonnemann’s current investigations are exploring the use of short interfering RNA segments as a therapeutic tool to silence these mutations, and determining the genetic cause in patients for whom no mutations in the known genes are found.

“This is a tremendous honor,” says Dr. Bonnemann. “The recognition of my work in childhood onset muscle disease is a great source of encouragement as I continue my clinical and laboratory investigations, with the ultimate goal of finding treatments that will make a difference in the life of children and adults affected by these conditions.”

The award was presented to Dr. Bonnemann during the American Neurological Association’s annual meeting in Baltimore, Md. on October 13, 2009. This is only the fourth time in the 19-year history of the award that it has been presented to a child neurologist.
Experts Describe Current State of Fetal Surgery Advancements

Repairing birth defects in the womb, inserting a tiny laser into a mother’s uterus to seal off an abnormal blood flow and save fetal twins, and advancing the science that may allow doctors to deliver cells or DNA to treat sickle cell anemia and other genetic diseases before birth are all examples of the still-emerging field of fetal surgery. Pediatric surgeon N. Scott Adzick, M.D., medical director of the Center for Fetal Diagnosis and Treatment (CFDT) at Children’s Hospital edited the February 2010 issue of the journal Seminars in Fetal & Neonatal Medicine, entirely devoted to fetal surgery advances.

“Fetal surgery is a unique field in maternal-fetal medicine,” says Dr. Adzick. “Detecting birth defects prenatally has allowed physicians to provide better perinatal care, but many of these babies were already too sick for us to treat them successfully after they were born. This dilemma led to the development of fetal surgery.”

“Some of the fetal anomalies we treat are so rare that a physician may encounter them only once or twice in a career,” continues Dr. Adzick, who is the Hospital’s surgeon-in-chief. “However, as prenatal diagnosis continues to improve, along with surgical techniques and tools of molecular biology, we have an expanded range of conditions for which we may devise ways to intervene before birth with clear benefits.”

Internationally prominent as a pioneer in fetal surgery, Dr. Adzick and other practitioners at Children’s Hospital describe innovative surgeries, high-tech procedures, and the prospect of prenatal gene therapy and stem cell treatments in a collection of articles in the February issue reviewing the current state of the science in fetal therapy.

Open fetal surgery to remove abnormal masses or patch an opening

Open fetal surgery involves cutting into the mother’s abdomen and uterus in order to operate on the fetus. In his article on open fetal surgery, Dr. Adzick gives details on the multidisciplinary team and sophisticated imaging technologies used to assess patients referred to the CFDT, the only such facility that includes a special delivery unit for mothers carrying babies with known birth defects. He then describes fetal surgeries for two life-threatening defects: lung masses, which may compress the developing heart, leading to heart failure, and sacrococcygeal teratomas, large tumors attached to the fetus’s tailbone, which can lead to heart failure or a fatal hemorrhage before birth. Fetal surgery, he adds, places special demands on caregivers to ensure safety for two patients — the mother and the fetus.

Dr. Adzick’s second article concerns fetal surgery for open spina bifida, referred to as myelomeningocele. A defect in which part of the spinal cord remains unprotected by skin and tissue, it may result in hydrocephalus, mental retardation, bowel and bladder problems, and lifelong paralysis. While usually non-lethal, it is a relatively common cause of major disability, affecting one in 2,000 live births.

To repair a myelomeningocele, fetal surgeons shield the developing spinal cord by closing the defect with the fetus’s own tissue. Definitive results of outcomes after fetal surgery are expected from a randomized clinical trial sponsored by the National Institutes of Health. The Management of Myelomeningocele Study (MOMS), which began in 2003, is expected to conclude treatments in the trial in 2011 at three fetal surgery centers, Children’s Hospital, Vanderbilt University, and the University of California-San Francisco.

Laser treatment shuts off dangerous twin-to-twin connection

Another application of fetal surgery is for twin-to-twin transfusion syndrome, occurring in 10 to 15 percent of identical twins. In this condition, one fetus grows at the expense of its twin because of abnormal blood vessel connections in their shared placenta. Michael Bebington, M.D., of the CFDT, reviews current therapies for this condition, noting that the scientific evidence favors selective laser photocoagulation. In this procedure, using a viewing instrument called a fetoscope, the fetal surgeon employs a laser to seal off the blood vessels that carry hazardous blood flow between the two fetuses.

Prenatal stem cell and gene therapy moving toward clinical use

The greatest future impact of fetal treatments probably lies in non-surgical approaches — prenatal stem cell therapy and gene therapy. In contrast to the relatively rare anatomical defects addressed in fetal surgery, cell and gene therapy offer the possibility of treating many genetic diseases before birth, including sickle cell anemia, immune deficiency disorders, and some types of muscular dystrophy.

These potential therapies are reviewed by Alan W. Flake, M.D., and his colleagues at the Center for Fetal Research at Children’s Hospital. Now in his third decade of investigating fetal surgery, Dr. Flake pioneered fetal bone marrow transplantation in 1996, successfully treating severe combined immunodeficiency disease (SCID) in utero.

In utero hematopoietic stem cell transplantation (IUHCT) focuses on stem cells that develop into all the types of cells found in the blood. The keystone of this approach is the fetal immune system’s unique tolerance of transplanted cells. Dr. Flake’s strategy involves using prenatal stem cell transplants to achieve tolerance of foreign cells, which are incorporated into the fetal circulation. This sets the stage for postnatal transplant of therapeutic blood cells from the same donor that will not be rejected by the infant’s immune system.

The specific characteristics of SCID make this disease uniquely amenable to a prenatal stem cell approach. Now, says Dr. Flake, research in animal models is progressing toward using IUHCT to treat other immune deficiency diseases; the hemoglobin disorders sickle cell anemia and thalassemia; and lysosomal storage diseases, genetic disorders in which the lack of an enzyme causes metabolic chemicals to accumulate to toxic levels in cells.

The CFDT, staffed by the fetal surgery experts who authored and edited this special issue, marks its 15th anniversary this year. It is a premier program, one of a handful worldwide to offer a full range of fetal procedures. Since the center opened in 1995, more than 10,000 parents have used its services, from all 50 U.S. states and from 46 other countries.
Research Intranet Upgrade Completed

Maintenance and an upgrade were successfully performed on the CHOP Research Institute's intranet. The upgraded CHOP Research intranet looks the same, but includes several new performance enhancements.

The modules in the left column of the intranet’s home page are now customizable widgets. You can rearrange these widgets or remove them directly from the home page. You can also manage your widgets from the new Widget Library. This area can be accessed either by clicking on the pencil icon in the upper right corner of a widget or by using the link provided on the Tools page. If you have an idea for a home page widget, please feel free to suggest one from the Widget Library page.

One new kind of widget available to all users is a Custom Quicklinks list. This widget allows you to create a set of links for your own personal use. If you think your custom list will be of use to other users, you can request that it become globally available. You can access your Custom Quicklinks from a new tab on your CHOP Research intranet profile.

Another enhancement to the intranet is the capability to create a list of your activities and interests in your intranet profile. When you are logged in, you will see an “Update Status” link in the upper right-hand corner of the screen. This currently is set up to act as a kind of “memo pad,” where you can make entries and log them to your profile. These memos will show up in search results, so if other people share your interests, they may find you through your status updates.

A “Session History” link is also newly accessible to users who are logged in to the intranet. Clicking on this link opens a pop-up box containing a list of the CHOP Research intranet pages you have viewed since logging in.

Two additional enhancements are available for individuals who manage intranet content. An expanded number of page layout templates have been added so content editors can have better control over the layout of the information they provide. Also, the Research intranet now includes the ability to display Microsoft Office documents directly within intranet Web pages.

If you run into any issues or have questions about new features you may encounter, please contact David Milley at ext. 4-1197.