Anyone who has known a child born with a congenital disorder, paralyzed in an accident or challenged by a complex medical condition knows that hope and healing are inseparable. The dream that scientific breakthroughs will give doctors the tools and medicines needed to cure disease is a real one. At Shriners Hospitals for Children – Northern California, doctors and scientists work collaboratively to find new ways to heal children with complex medical needs.

Research studies are headquartered in the Institute of Pediatric Regenerative Medicine (IPRM), a joint project of Shriners Hospitals for Children and the University of California, Davis School of Medicine. Located inside the Northern California Shriners Hospital, the IPRM is home to an international team of scientists devoted to bringing discoveries from the research laboratory to the bedside. Their questions are many and include:

Is the ability to fight disease linked to genetic makeup?

How does folate, a B vitamin, help prevent spina bifida?

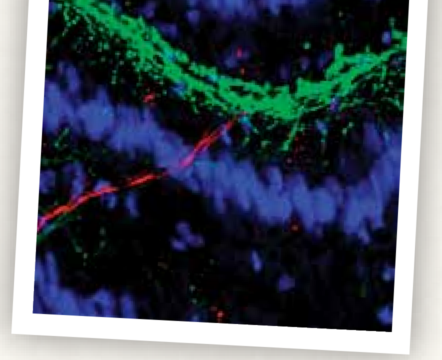
Can prescription drugs one day be used to prevent the development or the effects of cerebral palsy?

Can genetic testing be used to determine the most effective drug therapies?

We do not know precisely when the answers to these and other questions will come, but we can rest assured that the research taking place today will positively impact the lives of children for generations to come.

David Pleasure, M.D.
Director of Research
Shriners Hospitals for Children – Northern California

The Research Investigators



Scientific investigators at Shriners Hospitals for Children -- Northern California are engaged in a multitude of research studies to improve the health of children. Their work is funded by grants from Shriners Hospitals for Children, the National Institutes of Health, the National Science Foundation, the National Multiple Sclerosis Society, the Department of Defense, and the California Institute for Regenerative Medicine.

Iannis Adamopoulos, Ph.D., uses human bone cells to determine how abnormalities in immune regulation cause bone loss in childhood arthritis, and recurrent bone overgrowth after limb amputation in children.

Anita Bagley, Ph.D., M.P.H. & Jon Davids, M.D., use motion analysis to test the effectiveness of various therapies to improve neurological/orthopaedic function of children with cerebral palsy. They collaborate with Shriners burn surgeons to optimize methods for counteracting the ill effects of burn scar on limb mobility.

Andrea Bauer, M.D., is organizing a multicenter trial to compare the effectiveness of alternate methods for repairing nerves in the arms of infants injured during difficult births.

Peter Bannerman, Ph.D., develops grafts that contain engineered human bone marrow stem cells designed to improve surgical outcomes in infants who suffer nerve damage in their arms due to difficult deliveries.

Jennette (Jenny) Boakes, M.D., is an orthopaedic surgeon who devises improved methods to repair bone malformations in children.

Laura Borodinsky, Ph.D., has obtained novel evidence that folate increases the ability of cells on the two sides of the spinal cord to fuse together and prevent spina bifida. It is known that adding folic acid (a vitamin) to the maternal diet diminishes the frequency of spina bifida, but how folate does this remains mysterious. Dr. Borodinsky's findings are based on microscopic observations of the developing frog spinal cord.

Kiho Cho, D.V.M., Ph.D., works in conjunction with Dr. David Greenhalgh, Chief of Burns, to study how retroviruses impact internal organ failure in burn victims. His studies may justify the use of anti-retroviral drugs to improve survival of some children with severe burns.

Wenbin Deng, M.D., Ph.D., uses a mouse model of cerebral palsy to test whether transplantation into the brain of human skin-derived neural stem cells or treatment with erythropoietin (a drug commonly used to treat anemia) will prevent neurological deficits.

Diana Farmer, M.D., is a pediatric surgeon focused on improving surgical methods and employing cell grafts during pre-birth surgery to repair spina bifida and other fetal malformations.

David Greenhalgh, M.D., investigates the widespread variations in how children respond to Prednisone and other anti-inflammatory drugs administered in the treatment of burns, asthma and other life-threatening disorders. Dr. Greenhalgh and his team use human blood specimens to determine the genetic basis of these variable drug responses and develop genetic tests that will predict the safest and most effective therapies for individual children.

Fuzheng Guo, Ph.D., is testing to see if the administration of cobalt ions (commonly used for treatment of anemia) will mitigate brain damage caused by insufficient oxygen delivery to the brain of prematurely born infants - a major cause for cerebral palsy. Using newborn mice, Dr. Guo investigates the biochemical basis for susceptibility to this damage.

Makoto Horiuchi, Ph.D., investigates the effectiveness of grafting immature neural cells as therapy for injuries and diseases of the nervous system. Sometimes these neural cells can be obtained from autopsied brains, but this source is limited and the health of these cells varies. New techniques permit the generation of immature neural cells from skin-derived stem cells. Dr. Horiuchi compares the effectiveness of these two cell sources in repairing the spinal cords and brains of genetically-altered mice.

Takayuki Ito, M.D., Ph.D. & Aki Ito Ph.D., are investigating ways to prevent motor neuron death that may occur when nerves to the limbs are severed in infants and children. They discovered a protein responsible for this nerve damage and are investigating the mechanisms by which it operates. Based on their findings, they will design treatments to preserve these neurons.

Michelle James, M.D., is developing new tests and new procedures to enhance functional recovery from hand malformations and injuries.

Paul Knoepfler, Ph.D., studies how induced pluripotent stem cells (iPSCs), stem cells prepared from the skin, can be used to enhance the repair of many organs with minimal risk. A potential hazard in using these cells is that they might give rise to tumors, and Dr. Knoepfler designs methods to minimize this risk.

Veronica Martinez-Cerdeno, Ph.D., is developing methods that may someday improve spinal cord regeneration in humans. Her studies involve grafting specially engineered stem cells derived from human bone marrow into injured mouse spinal cords.

David Pleasure, M.D., a neurologist, is developing novel therapies to prevent damage to neurons caused by inflammation of the spinal cord. This inflammation may occur in children after immunizations and viral infections or as a component of diseases such as multiple sclerosis.

Soman Sen, M.D., a burn surgeon, designs new diagnostic tools that can be used at the bedside of critically burned children to evaluate their heart and kidney function. In this way, he will be able to continuously evaluate the clinical appropriateness of the fluid and drug therapies these children receive.

Jiho Sohn, Ph.D., is investigating the therapeutic benefits of pigment epithelial-derived factor (PEDF), a protein known to control blood vessel formation. Dr. Sohn discovered that PEDF therapy enhances the repair of experimental spinal cord and brain lesions. He is working out PEDF treatments for future application to children with neurological diseases.

Tina Palmieri, M.D., a burn surgeon, designs strategies to mitigate environmental factors that slow the recovery of children after severe burns.

Athena Soulika, Ph.D., an immunologist, focuses on the role of inflammatory cells in spinal cord and skin burn repair.

Konstantinos Zarbalis, Ph.D., investigates the genetic causes of cleft lip/cleft palate and brain malformations. His work may lead to improved methods for genetic testing of families at risk of having children with these disorders.

Chengji Zhou, Ph.D., conducts studies involving Wnt, a protein that controls development of limbs, the face, and the brain. He focuses on Wnt signaling mutations that cause spina bifida and malformations in facial and brain development. He also investigates ways in which Wnt-stimulated spinal cord scar formation can be inhibited to enhance spinal cord regeneration.

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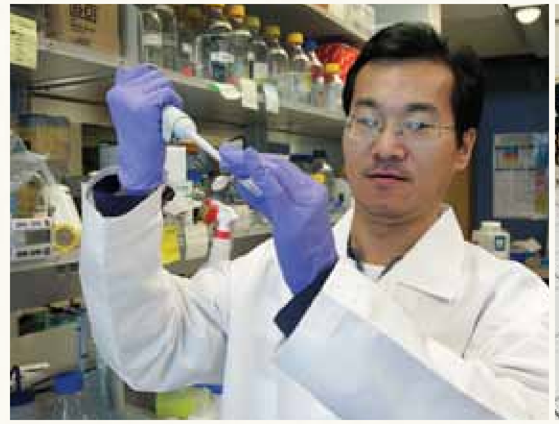

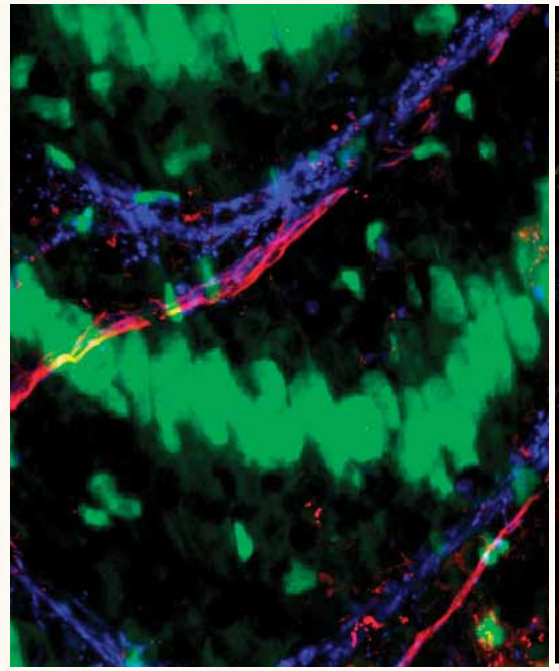

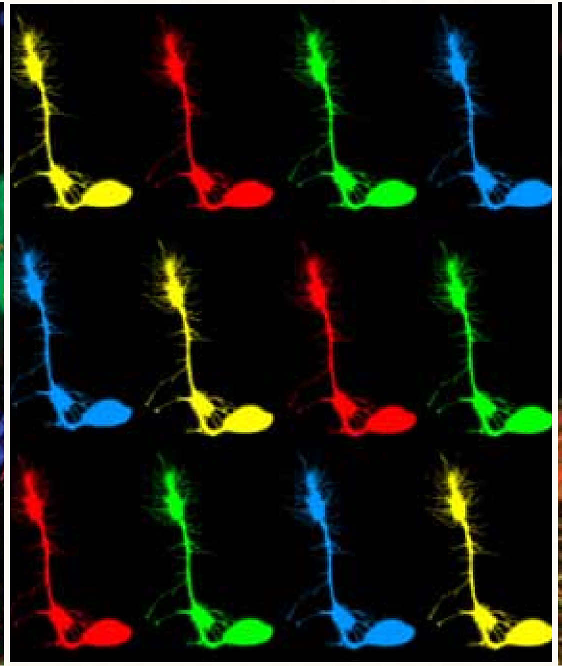

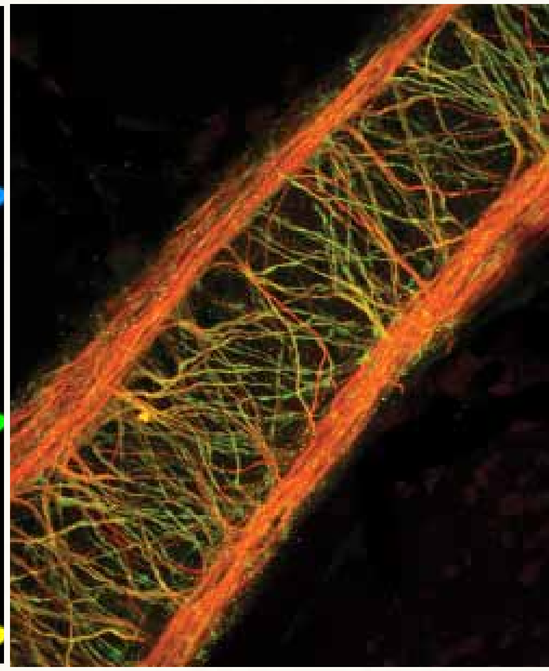

Shriners Hospitals for Children – Northern California is home to the Institute of Pediatric Regenerative Medicine (IPRM), a collaborative initiative of Shriners Hospitals for Children and the University of California, Davis School of Medicine.

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Research Provides New Hope For Children

Scientific and clinical research studies provide new hope for children with cerebral palsy, spina bifida, brachial plexus birth palsy, cleft lip and palate, burns, spinal cord injuries and other pediatric conditions. David Pleasure, M.D., a neurologist and Director of Research at Shriners Hospitals for Children – Northern California, leads teams of researchers in their quest for cures.

Bone Abnormalities

Scientists know that bone development and turnover are regulated by the immune system. While orthopaedic surgeon, Jenny Boakes, M.D., constructs improved methods to repair bone malformations in children, Iannis Adamopoulos, Ph.D., examines immune regulation abnormalities that cause bone loss in children and recurrent bone overgrowth after limb amputation.

Brachial Plexus Birth Palsy

Nerves to the arms and neck are sometimes ripped apart in newborns too large to permit easy delivery through the birth canal. The resulting diagnosis is Brachial Plexus Birth Palsy, an injury that occurs in roughly 2.5 out of every 1,000 births. Surgery is often required to restore a child's ability to reach an object or throw a ball. Pediatric hand surgeon, Andrea Bauer, M.D., is organizing a multi-center trial to compare the effectiveness of different methods for repairing nerves in the arms of injured infants. Peter Bannerman Ph.D., develops grafts that contain engineered human bone marrow stem cells that are designed to improve the outcome of surgery in these infants.

Cerebral Palsy

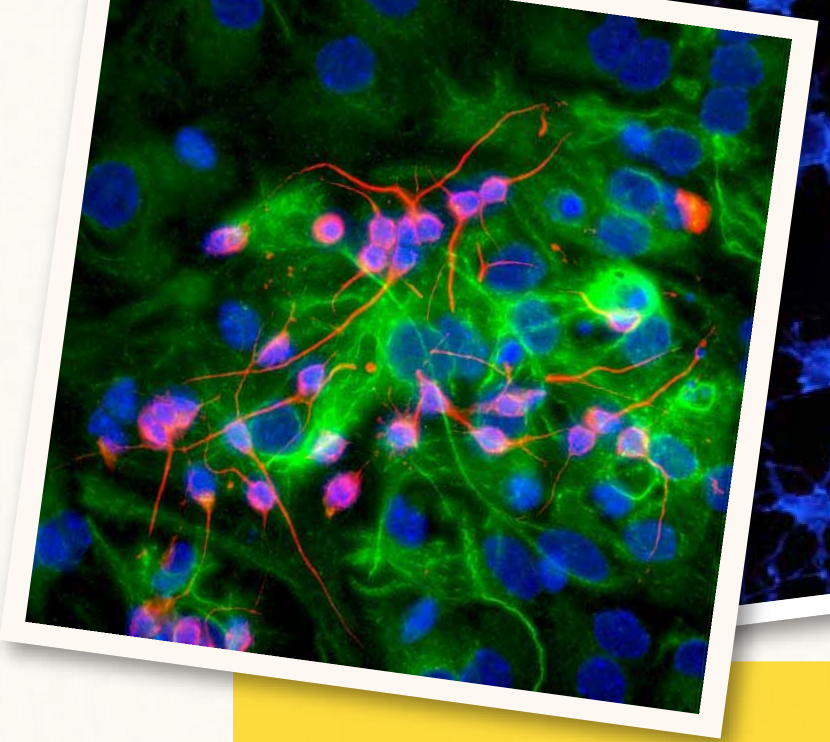
Cerebral palsy occurs in approximately 1 in every 300 children born in the United States. While symptoms vary, cerebral palsy often affects a child's ability to walk normally and other motor skills. In the Shriners Hospital high-tech Motion Analysis Lab, Anita Bagley, Ph.D., M.P.H., a biomedical engineer, and Jon Davids, M.D., an orthopaedic surgeon, use motion sensors and three-dimensional images to test the effectiveness of various therapies for improved function in children with cerebral palsy. The clinical research is complemented by scientific studies into the possible use of drugs that may prevent the development or the effects of cerebral palsy.

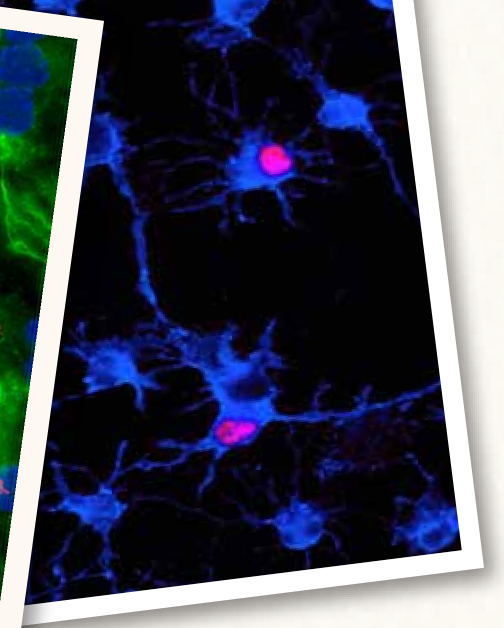
Cleft Lip & Palate

Approximately 1 out of every 700 children is born with cleft lip and/or cleft palate. Konstantinos Zarbalis, Ph.D. investigates the genetic causes of cleft lip, cleft palate and brain malformations. His investigations have uncovered a genetic link to cleft lip and cleft palate in mice, and his work may lead to improved genetic testing of families at risk of having children with these disorders.

◄ *Hand Function*

Michelle James M.D., Chief of Orthopaedics, develops new tests and new procedures to enhance functional recovery from hand malformations and injuries. If successful, the studies will help restore the gift of grip. Dr. James has directed the development of a model that uses motion analysis to evaluate the activity of the thumb in children who have congenital thumb problems. The techniques provide precise measurements that make it possible to measure the effects of different treatment strategies and, in turn, identify surgical techniques and physical therapy that can improve the grip and dexterity in children with thumb deficiency.





▲ *Neural Development*

When nerves to the limbs are severed in infants and children, the neurons that give rise to these nerves die. Drs. Takayuki and Aki Ito discovered a protein responsible for this neuronal death and are investigating the mechanisms by which it operates. Based on their findings, they will design treatments to preserve these neurons. This knowledge may suggest effective therapies to prevent mutation-induced motor neuron death in infancy.

Spina Bifida

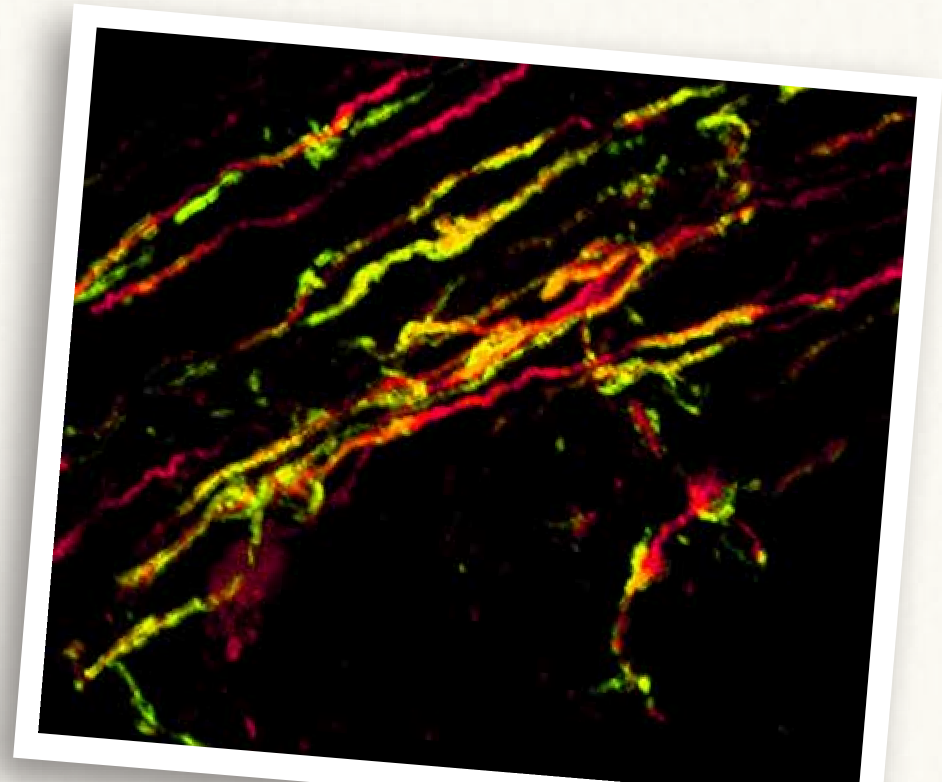
Spina bifida is a common and disabling disorder in which the embryonic neural tube does not fully close. Diana Farmer, M.D., a pediatric surgeon, works to repair spina bifida and other fetal malformations through the use of cell grafts during in-utero surgery. Meanwhile, scientific researchers search for cures. Adding folic acid, a vitamin, to the maternal diet diminishes the frequency of spina bifida, but how folate does this remains a mystery. Through microscopic observations of the developing frog spinal cord, Laura Borodinsky, Ph.D., has obtained novel evidence that folate increases the ability of cells on the two sides of the spinal cord to fuse together and prevent spina bifida. Chengji Zhou, Ph.D. investigates how mutations to Wnt, a protein that controls the development of arms, legs, the face and brain, may cause spina bifida.

Spinal Cord Injury

Approximately 12,000 cases of spinal cord injury are reported in the United States each year. Researchers at Shriners Hospitals for Children hope to find a way to heal spinal cord injury, so children paralyzed by injury can walk again. Studies by Makoto Horiuchi, Ph.D. and Veronica Martinez-Cerdeno, Ph.D. focus on spinal cord repair. Dr. David Pleasure develops novel therapies to prevent damage to spinal cord function caused by inflammation that may occur after immunizations and viral infections or as a component of diseases such as multiple sclerosis.

Tumor Formation

Stem cells prepared from skin -- known as induced pluripotent stem cells (iPSCs) -- can be used to enhance repair of many organs. A potential hazard of using these cells is that they might give rise to tumors. Paul Knoepfler, Ph.D. analyzes the risk of tumor formation from human iPSC grafts to the nervous system and designs methods to minimize this risk.

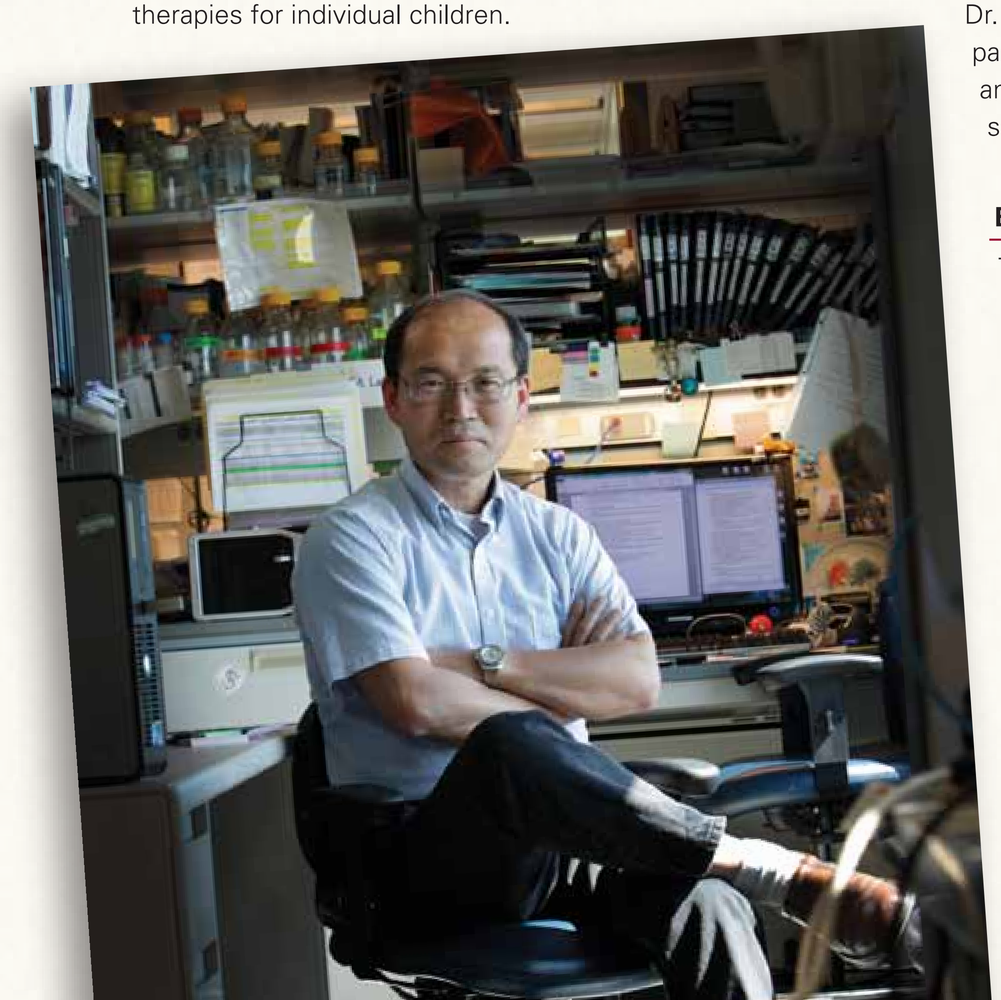


Burn Team Addresses Critical Needs Of Children

Survival rates for burn victims have improved dramatically over the past 40 years. Doctors and scientists at Shriners Hospitals for Children – Northern California are responsible for many of the advances in pediatric burn care. Studies encompass everything from how the body reacts to severe stress to diagnostic tools that can be used at the bedside when treating critically injured children.

Response to Drugs

Prednisone and related anti-inflammatory drugs are commonly administered to children with burns, asthma, and other life-threatening disorders, but there are widespread variations in how children respond to these drugs. David Greenhalgh, M.D., Chief of Burns, and his team use human blood specimens to determine the genetic basis of these variable drug responses. Their work on genetic tests may predict the safest and most effective anti-inflammatory therapies for individual children.



Organ Failure

One of the most pressing questions in burn care is why an injury to the skin, an external organ, causes internal organ failure? Kiho Cho, D.V.M., Ph.D., thinks the answer may lie within the dormant viruses – or retroviruses – all humans carry in their genome. Normally inactive and harmless viruses may activate in children with burns or other severe stresses, leading to impaired gene function and fatal organ failure. Working in conjunction with Dr. Greenhalgh, M.D., Dr. Cho is testing how often this occurs in burn patients. His studies may justify the use of anti-retroviral drugs to improve survival of severely burned children.

Environmental Influences

Tina Palmieri, M.D., Assistant Chief of Burns, crafts strategies to mitigate environmental factors that slow the recovery of children after severe burns.

Bedside Diagnostics

Soman Sen, M.D. is a burn surgeon who formulates diagnostic tools that can be used on critically burned children to evaluate their heart and kidney function. His research will enable continuous evaluation of the clinical appropriateness of the fluid and drug therapies.