The Treatments of Tomorrow:
Dr. George Gittes' Pioneering Research

With your support, UPMC Children's Hospital of Pittsburgh's Surgeon-in-Chief Emeritus George K. Gittes, MD, is positioned to uncover novel treatments and cures for several debilitating conditions affecting both children and adults.

The Vital Role of the Surgeon-Scientist

Surgeon-scientists like Dr. George Gittes offer a unique perspective to the field of medical research. Yet, federal funding for surgical research remains uncertain at best; unattainable at worst. According to a 2019 multi-institutional review published in the *Annals of Surgery*, National Institutes of Health (NIH) research funding has steadily decreased in recent years, with a 27% decline in NIH funding to Departments of Surgery between 2007 and 2014. With fewer NIH surgical research applications funded, and fewer still going to younger, less established surgeon-scientists, many surgeons are opting out of research altogether.

Unfortunately, these challenges are occurring during an exciting time in medical research. Now, perhaps more so than at any other time in our history, surgeon-scientists are poised to leverage a growing knowledge of genetic technology and recent advances in drug development to make groundbreaking findings that could change the medical landscape. **Given their proximity to the diagnosis and management of many diseases, surgeons provide a rich perspective in the effort to fundamentally understand and treat disease.**

Despite the reduced NIH funding available to surgeon-researchers, Dr. Gittes has chosen to pursue a dynamic career that emphasizes scientific study. And thanks in part to donor support from community members, he has made remarkable progress to date furthering research that can lead to life-changing therapies.

Destined for Research

Dr. Gittes was performing surgical research on rats when he was still just a kid. His dad was a physician, one who instilled in him a passion for scientific discovery during summers spent performing animal studies at Harvard Medical School.

Dr. Gittes went on to obtain his medical degree from Harvard before pursuing a surgical internship and residency at the University of California at San Francisco. Thereafter, he completed a fellowship at Children's Mercy Hospital in Kansas City, where he served as faculty until 2005. It was then that he joined UPMC Children's as surgeon-in-chief and chief of the Division of Pediatric General and Thoracic Surgery – one of the busiest pediatric

surgical programs in the country. In 2018, Dr. Gittes was appointed director of the Richard King Mellon Foundation Institute for Pediatric Research and co-scientific director at Children's. In addition to his executive role, surgical responsibilities, and prolific research work, Dr. Gittes helps to mentor the next generation of scientific researchers.

Spearheading Life-Altering Discovery

Perhaps because of those summers in Boston spent practicing animal surgery with his dad, or maybe due to the unique perspective he brings to the bench side given his years working in the operating room, Dr. Gittes is on the verge of multiple breakthrough medical treatments.

Pioneering Diabetes Gene Therapy

Dr. Gittes first became interested in studying diabetes when he was still a surgical trainee. At the time, he was focused on the pancreas because of its surgical relevance. But as he learned more about the far-reaching impact of diabetes, he couldn't imagine researching anything else.

George Kingsley Gittes, MD

"Diabetes is a leading health concern in the country, the number one biomedical cost, with 30 million people in the U.S. living with some form of the disease," Dr. Gittes shares. "It's a big problem."

To develop a corrective solution, Dr. Gittes and his team looked to gene therapy. In patients with type 1 diabetes (T1D), insulin-producing beta cells in the pancreas have been destroyed by the body's own immune system. Dr. Gittes is working to modify the cells using a gene editing procedure.

The procedure involves a minimally invasive surgery to inject a genetically engineered virus directly into the pancreas. Viruses are used because they are naturally occurring and quite good at delivering genes to cells. In the technique he developed, Dr. Gittes will "infect" non-insulin-producing cells in the pancreas called alpha cells with two important genes. The procedure effectively triggers the cells to become beta cells that produce insulin on their own.

In diabetic mice, Dr. Gittes' gene therapy treatment proved incredibly successful. The treatment is equally applicable, and likely most effective, in type 2 diabetes (T2D). **In mice with T1D, the team found that the treatment worked to stabilize blood glucose levels**

for four months or more without any additional therapy or immunosuppression. (As a comparison, four months for mice roughly translates to 16 years in humans.) In T2D, the effects would likely be much longer lasting, if not permanent.

With charitable gifts from several generous donors, the Gittes lab is currently testing the gene therapy treatment in monkeys, which is the last step before moving to human clinical trials. Over the course of the past two years, Dr. Gittes and his collaborators have conducted several rounds of gene therapy surgeries on primates. **Most recently, five monkeys received surgeries in October 2019 and one in January 2020. Of the six, all continue to demonstrate improvements in their disease, with one monkey from the October surgeries now only requiring a mere 1 unit of insulin/day (down from 18 units/day)!** Dr. Gittes and his team are also working to refine and improve their virus delivery system with plans to perform several more monkey procedures in the months ahead.

We are further pleased to share that in February 2020, the **University of Pittsburgh announced an exclusive agreement with Genprex, Inc. to license Dr. Gittes' diabetes gene therapy.** This is the first time Genprex will work with a therapy unrelated to cancer. The clinical-stage gene therapy company will not help to fund Dr. Gittes' basic science research leading up to clinical trials, but it will help the researchers navigate the many logistics necessary to launch their first trial in humans. Genprex's commitment to this research clearly demonstrates a collective confidence in its efficacy – an exciting development for the Gittes team. With ongoing support, we are hopeful that this innovative therapy could transform the lives of the millions of individuals across the world struggling with diabetes.

Advancing Treatment for Patients with Chronic Pancreatitis

Dr. Gittes and his team are additionally working on a promising potential therapy for the treatment of chronic pancreatitis, a challenging condition that affects over 200,000 Americans, and millions worldwide, and results in approximately 86,000 hospital stays each year in the United States alone.

The pancreas produces essential enzymes that aid in food digestion, as well as hormones that control blood sugar. In patients with chronic pancreatitis, the pancreas becomes inflamed and fails to heal over time. This inflammation leads to permanent damage that affects the ability to digest food and regulate blood sugar.

Patients diagnosed with chronic pancreatitis experience reduced quality of life with symptoms ranging from diarrhea and nausea to weight loss and jaundice. According to the NIH, as many as 85% of patients experience pain at some point in their disease, with many becoming addicted to opiates in an attempt to treat their pain. While lifestyle changes and surgery may help to halt the progression of the condition, treatment is fundamentally palliative. Up to 80% of patients battling chronic pancreatitis eventually develop diabetes,

and sadly, researchers estimate that patients with chronic pancreatitis have a thirteen-fold increased risk of pancreatic cancer, which is almost uniformly fatal.

To better study the disease, Dr. Gittes and his colleagues developed an animal model of chronic pancreatitis. They further developed a technique to infuse potentially therapeutic solutions directly into the pancreas. On a bit of a whim, the lab team infused a specific type of drug into the pancreas of the animal model. The solvent for the drug was 100% ethanol. **Rather remarkably, they accidentally discovered that the ethanol effectively corrected the pancreatitis – reducing inflammation without affecting healthy insulin cells and preventing diabetes!** The researchers are now using an acetic acid solution (similar to vinegar) instead of ethanol to further test the efficacy of this unexpected outcome in the animal models, while pursuing potential human clinical trials. This is an exciting development in the treatment of a long-term, progressive, and painful disease for which there is no known cure.

Developing A Novel Treatment for Unborn Babies with Diaphragmatic Hernia

Congenital diaphragmatic hernia (CDH) is a life-threatening birth defect that affects about one in every 2,500 newborns. The diaphragm is the large muscle that separates the chest from the abdomen. When the lungs form improperly, the diaphragm fails to close during development as it should, and the abdominal organs can move up through the opening into the baby's chest. The misplaced organs further hinder the development of the baby's lungs, resulting in severe pulmonary hypoplasia (underdeveloped lungs). Babies born with CDH experience significant breathing issues and may struggle with pulmonary hypertension (high pressure in the blood vessels leading to the lungs), feeding issues, asthma, and developmental delays. Diaphragmatic hernias are usually diagnosed in the womb by ultrasound.

Currently, treatment for CDH is limited. When a child is born with a diaphragmatic hernia, urgent surgery is required to move the abdominal organs back to the abdominal cavity and to repair the diaphragm. However, surgery does not correct the underdeveloped lungs. Many babies will have long-term lung problems, with some requiring breathing machine support for weeks, months, or even years after birth. Despite advances in treatment, overall survival for babies with CDH remains only about 60%.

Inspired to help these children, Dr. Gittes and his collaborators began investigating possible therapies. Starting with mouse models, the team wondered whether injecting a therapeutic

agent directly into the mouse mother's amniotic fluid might support the development of the fetus' lungs. To test their theory, the researchers turned to sildenafil, the drug marketed as Viagra. (You might recall that Viagra was originally developed to treat high blood pressure and angina.) **Amazingly, the Gittes team found that the CDH mice born to mothers that received the sildenafil injection were converted from 100% fatality to 90% survival from a single injection three days before birth.**

The study was so successful that Dr. Gittes and his collaborators moved on to primates and showed that the injections were safe for the mother and fetus.

In human babies, Dr. Gittes believes an injection administered to the pregnant mother shortly after a baby's diagnosis (CDH is usually discovered at about 20 weeks gestation during a routine ultrasound), followed by two additional injections administered about three and six weeks thereafter, would successfully trigger lung development in the unborn child.

While the infusion would likely not correct the hernia and the baby would still require surgery to relocate the abdominal organs and repair the diaphragm, it would correct the most devastating, lethal outcome caused by the CDH.

As there is no effective treatment for CDH and sildenafil is a widely used and overwhelmingly safe drug, Dr. Gittes believes that they could begin testing the therapy in human clinical trials in just the next few years. He is currently partnering with fetal medicine experts at UPMC Magee-Womens Hospital to further explore clinical trials. With continued support, we expect that Dr. Gittes may be able to bring this novel treatment to babies and their families relatively soon.