DECEMBER 2017

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Clinical Trial Targets Devastating Heart Failure Diagnosis

Northwestern Medicine Researcher is Principal Investigator for International Trial

CHICAGO – Lynne Austin found she was increasingly out of breath doing even the simplest of tasks as 2015 came to a close. She couldn't walk more than a few steps at a time. She couldn't breathe. Her health was rapidly deteriorating and she wasn't sure she would get relief.

She had been diagnosed with heart failure with preserved ejection fraction (HFpEF). What was previously called diastolic heart failure, HFpEF (pronounced "huff-puff") is a condition where the heart's lower left upper chamber (left ventricle) is not able to fill properly with blood, so the blood backs up in the upper chamber (left atrium) and lungs, resulting in shortness of breath.

With the encouragement of family members, Austin enrolled in the first international randomized trial designed to treat HFpEF using a medical device to relieve the pressure on her left heart, and lungs. Her participation in this trial, along with many other pioneering patients with HFpEF who participated in the trial, led to the second international randomized trial, REDUCE LAP-HF II.

The trial is co-led internationally by principal investigator Sanjiv Shah, MD, director of the T1 Center for Cardiovascular Therapeutics and director of the Heart Failure with Preserved Ejection Fraction Program at Northwestern Memorial Hospital in Chicago.

"Heart failure is one of the biggest public health issues in the United States, and nearly half of all those with heart failure have a preserved ejection fraction (HFpEF), for which there are inadequate treatment options," said Dr. Shah, who is a professor of medicine-cardiology at Northwestern University Feinberg School of Medicine. "By leading and taking part in the REDUCE LAP-HF trials, we hope to make a significant difference for patients who suffer from this devastating condition."

Mark Ricciardi, MD, director of cardiac catheterization and interventional cardiology at Northwestern Memorial Hospital, is the lead investigator for patients participating at Northwestern. Participants in the trial are randomized and may receive a dime-sized shunt device designed to lower the pressure in the left upper heart chamber. Those who do not receive the device initially will have the option to receive the device after two years.

For Dr. Ricciardi, REDUCE LAP-HF II is an important clinical trial that is putting Northwestern Medicine at the forefront of the safe and effective evaluation of transcatheter therapies; minimally

Dr. Sanjiv Shah

invasive procedures performed through a small catheter that avoid open-heart surgery and typically take less than an hour.

"Our involvement in this and similar clinical trials positions Northwestern's Bluhm Cardiovascular Institute at the forefront of medical breakthroughs," said Dr. Ricciardi, an associate professor of medicine-cardiology at Feinberg. "We are constantly looking for the best, safest and most effective treatment options for our patients. By doing this type of clinical research, we also help the cardiovascular community at large learn how to help patients with heart disease."

Austin learned in 2017 that she received the device, known as the InterAtrial Shunt Device, the world's first transcatheter device designed to treat HFpEF. Austin said her quality of life has improved dramatically more than a year after participating in the clinical trial.

Nanotechnology May Lead To Tissue Regeneration

By: Biloine W. Young

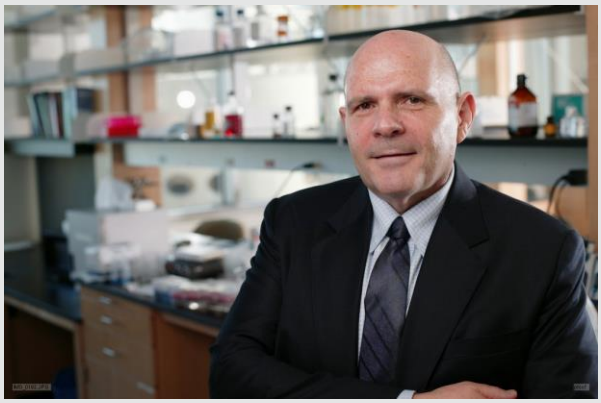
Abody having the capacity to regenerate its own parts, once the realm of medical science fiction, is now within reach, according to Samuel Stupp, Ph.D., director of Northwestern University's Louis A. Simpson and Kimberly K. Querrey Institute for BioNanotechnology.

According to a writer for *Northwestern Medicine Now*, Stupp has pioneered one of the advances in researching how organic structures at the nanometer scale (the width of a human hair if it were split 80,000 times) can be absorbed into the body without rejection.

"Stem cells are normally regarded as the therapy for regenerative medicine," Stupp says. But the problem with stem cells is "it's nearly impossible to ensure stem cells get to the right place," he explains. "Stem cells also have a hard time adapting to new environments—even if they knew where to go, approximately 90 percent don't survive the trip."

"What we're doing is jumpstarting biological regeneration using synthetic nanomaterials," Stupp says. "Molecule by molecule, this is bottom-up design using nanotechnology concepts."

This is where Stupp's research comes in: He is manufacturing self-assembling natural matrices that



Dr. Samuel Stupp

mimic those that normally surround cells to protect and direct them to a specific location in the body. Since these matrices are made of organic materials they can biodegrade without leaving unnecessary—and potentially harmful—foreign objects in the body.

Stupp is presently working with the U.S. Food and Drug Administration for approval to launch a clinical trial for spinal regeneration in humans. If approved, Stupp and his staff may soon be growing new bone between the vertebrae in the backs of patients.

Director of the Maggie Daley Center among Top 27 Breast Cancer Oncologists in the Country Picked By Big Data

William Gradishar, MD, Deputy Director for the Clinical Network in the Lurie Cancer Center, is among the top 27 academic breast oncologists in the country identified in *Forbes Magazine*, based on "big data" analysis from Grand Rounds. This company uses a machine learning algorithm to analyze publicly available and proprietary data.

Gradishar is Chief of Hematology and Oncology in the Department of Medicine, Betsy Bramsen Professor of Breast Oncology and Director of Lurie Cancer Center's Maggie Daley Center for Women's Cancer Care in Prentice Women's Hospital, where he develops and implements clinical trials of new therapeutic approaches for breast cancer.

Dr. William Gradishar

Center for Genetic Medicine's 17 Years of Growth

Founded in 2000 with just a few faculty, Northwestern's Center for Genetic Medicine (CGM) has grown in size and significance paralleling expanded comprehension of the human body's 25,000 genes. The CGM was formed at a time when exciting advances in genetics were being made: Dolly the sheep had only recently been cloned (1997) and the Human Genome Project to identify and map all of the genes in the human body was still underway (it was completed in 2003).

In October 2002, was the NUgene Project, a genomic biobank collaboration between Feinberg and its clinical affiliates. NUgene was launched to use information from the human genome sequence to unravel the genetic cause of many diseases and eventually help scientists develop new tests, determine which patients would respond best to a particular drug and develop therapies to fight specific illnesses. This would be accomplished by collecting thousands of DNA samples and related health information to search out "candidate genes" believed to play a role in disease, ascertain their role in the disease process and determine, based on an individual's genetic information and medical history, which therapies would be most effective. By January 2004, NUgene had enrolled their 1,000th patient, and today it has over 13,000 patient samples in its repository.

In the fall of 2007, Northwestern was chosen as one of five initial sites for the National Institutes of Health funded national Electronic Medical Records and Genomics (eMERGE) Network. eMERGE was created to incorporate DNA biorepository data with electronic medical record systems for large-scale, high-throughput genetic research. Currently, eMERGE has completed its first two phases examining what elements are needed to implement genome-informed personalized medicine, and it now is focused on continued development of best practices and strategies for analysis and distribution of genomic data for patients.

On September 1, 2014, Elizabeth McNally, MD, PhD, Elizabeth J Ward Professor of Genetic Medicine, became the new CGM director under current dean

Eric Neilson, MD. McNally has conducted numerous studies to identify genetic indicators of hereditary heart disease. With her expertise, a new clinical cardiac genetics program was inaugurated, based in the Bluhm Cardiovascular Institute, involving Northwestern in yet another area of genetics research.

Today, under McNally's leadership the CGM continues to grow. It currently includes more than 150 faculty members from 28 departments and three schools. In addition to NUgene, the CGM oversees two core facilities, which provide expert advice and state-of-the-art technology to scientists at Northwestern and other Chicago institutions: The NUSeq Core Facility provides full next-generation sequencing and bioinformatic analysis to Northwestern faculty, giving clinicians and investigators access to DNA and RNA sequencing, genotyping, epigenetic profiling, and the Transgenic and Targeted Mutagenesis Laboratory helps create gene-edited animal models for human disease using the newly discovered tools of CRISPR/Cas9.

As personalized medicine becomes ever more precise, the importance of genetics research in medicine cannot be understated. As the cost of whole genome sequencing decreases and accuracy improves, individual genetics is playing a larger role in the treatment and prevention of human disease. How will the next 17 years of genetic breakthroughs affect the direction of the CGM's future growth? One thing is certain: Northwestern will continue to be a leader in this innovative arena of research.

Northwestern to Advance Understanding of the Role of Environment on Genes

$10 million Gift Creates Simpson Querrey Center for Epigenetics at Northwestern University Feinberg School of Medicine

By: Marla Paul

CHICAGO - A new $10 million gift from University trustees and supporters, Louis A. Simpson ’58 and Kimberly K. Querrey will create a center at Northwestern University Feinberg School of Medicine, to study the effects of environment on the activation and expression of genes.

The new Simpson Querrey Center for Epigenetics will investigate how environmental factors such as emotional experiences, chemical exposure, obesity, exercise, and diet and drug therapies can modify genes packaged in human chromatin, causing them to become more or less receptive to new biochemical signals. Epigenetic modifications of chromatin can have a direct effect on the regulation of gene expression. Some of this regulation is good, and some of it causes disease.

The center brings together experts in biochemistry, molecular genetics, computational biology, fundamental biology, epidemiology and clinical medicine to develop foundational insights about how environmental conditions impact the human genome using sophisticated molecular, biochemical and computational methods.

“Epigenetic-driven insights are proving fundamental to a myriad of diseases including cancer, heart, immunologic and neurological conditions,” said Dr. Eric

Neilson, vice president for medical affairs and the Lewis Landsberg Dean at Feinberg. “Understanding the details of how individual genes, groups of genes and environmental factors work together to determine the human condition is at the forefront of medicine today.”

The center will be led by Ali Shilatifard, the Robert Francis Furchgott Professor of Biochemistry and Pediatrics and chair of the department of biochemistry and molecular genetics at Feinberg. Shilatifard’s work focuses on understanding the intricate chromatin mechanisms that regulate gene expression. This year, Shilatifard’s laboratory and his collaborators published several groundbreaking discoveries reporting the development of epigenetic targeted therapeutics for childhood leukemia, childhood brain cancer and adult triple negative breast cancer. One study on childhood brain tumors led to a Phase I clinical trial planned for next year at the Ann & Robert H. Lurie Children’s Hospital of Chicago.

Message from Dr. Daniel Derman

President, Northwestern International Patient Services
Sr. Vice President, Northwestern Memorial Healthcare

As we come to the close of another year, we remain honored that you entrust us with the care of your patients. In our newsletters, we have tried not only to keep you informed about the latest innovations and best treatment options at Northwestern for your patients, but also to highlight some of the most cutting edge bench-to-bedside research that will profoundly benefit your patients in the future.

Our goal is always to provide you and your patients with the highest quality and service possible. Please remember you can reach out to myself and Laura Leahy, Senior Practice Manager, if there is anything you need, or if there is any feedback to help us improve. May you have a wonderful new year!