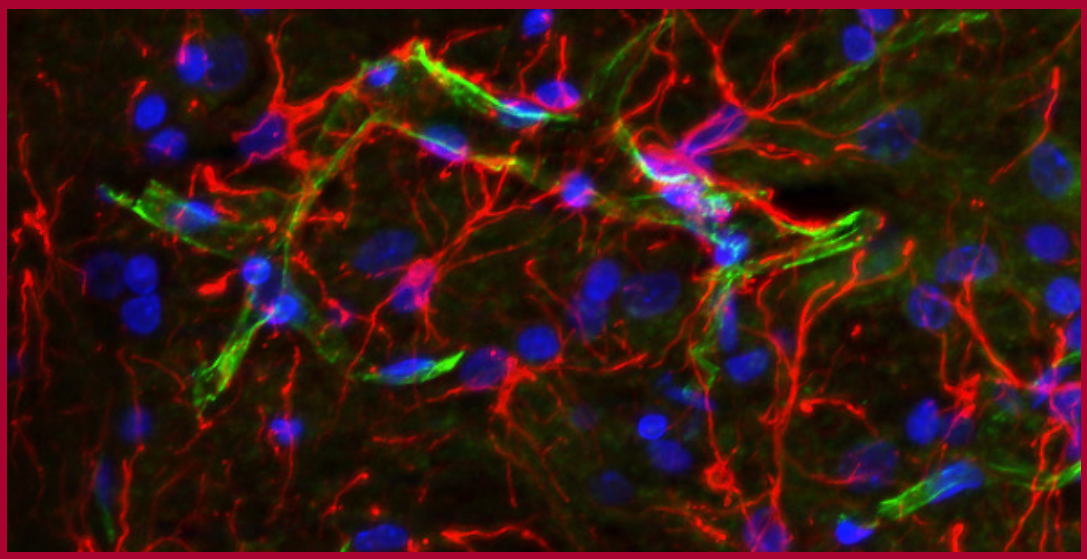
RESEARCH UPDATE



The Cryptic Masons Medical Research Foundation

and

Indiana University School of Medicine

RESEARCH UPDATE

THE CRYPTIC MASONS MEDICAL RESEARCH FOUNDATION AND INDIANA UNIVERSITY

The vascular system helps support our entire body, carrying blood, oxygen, and nutrients through a seemingly endless network of veins, arteries, and capillaries. If the vascular system of an adult human was laid out end to end it would stretch over 60,000 miles, enough to wrap around the world—twice.

Given that reach, it's no surprise that when it begins to fail, many areas of the body are affected. Research at IU School of Medicine, led by Dr. Michael Murphy, uses adult stems cells to develop new treatments for patients suffering from vascular related diseases.

Thanks to support from the Cryptic Masons, IU School of Medicine can study these incredibly useful cells, which are found throughout the body, including bone marrow, fat tissue, and the vascular system itself. They are a key part of how our bodies heal. Dr. Murphy and his team, created five clinical trials to test adult stem cell therapies in patients. Three were first-of-their-kind in the nation.

Our Vascular Research Consortium believes the next decade will bring a cure for aortic aneurysms and leg amputations in patients with diabetes. This is our "Moon Shot." And we need the continued support of the Masons.

Cryptic Masons Support:

- **Gets discoveries from the lab to patients in 12 months, compared to five years in programs without CMMRF support.**
- **Provides funding to demonstrate to the U.S. Food and Drug Administration that cell therapy is safe in animal models.**
- **Provides funding to demonstrate that cell therapy may have a beneficial effect in patients by creating clinically relevant animal models of disease.**

GETTING A LEG UP ON PERIPHERAL ARTERIAL DISEASE

Peripheral arterial disease (PAD) afflicts over 8 million Americans and is as common as coronary artery disease. PAD is a result of hardening of the arteries of the legs due to atherosclerosis. It limits blood flow to the muscles and skin of the legs. Patients with claudication have inadequate blood flow to supply oxygen to exercising muscles, limiting the patient's ability to work or walk moderate distances. Patients with critical limb threatening ischemia (CLTI) have such a severe blood flow reduction they have foot pain, even at rest. Eventually they develop gangrene. In the U.S., over 53,000 leg amputations are performed each year for complications related to CLTI, with diabetics and minorities at highest risk. Amputation is the sixth most costly operation, a $10.6 billion expense to our health care system.

Thanks to the generous support of the Cryptic Masons, we have completed the Phase III MOBILE (Marrowstim Treatment of Limb Ischemia in Subjects with Severe Peripheral Arterial Disease) Trial. A landmark study, it was the first Phase III clinical trial in stem cell therapy to reach completion in the U.S. This achievement was possible because support from the Masons created the highly skilled team and support network at IU, which serves as national leaders of the study. The results of the MOBILE Trial clearly demonstrated a significant reduction in leg amputations for patients with CLTI, diabetics and non-diabetics with rest pain, and non-diabetics with gangrene. **This is a breakthrough for a condition which previously had no treatment.**

Using a diabetic mouse model with CLTI created at IU, Dr. Steven Miller discovered that mesenchymal stem cells grow in clusters called spheroids that can regenerate skeletal muscle. We have also found that those mice, treated with these spheroids, have complete return of muscle and limb function—a discovery that could lead to a clinical trial. With support from the Cryptic Masons Medical Research Foundation, we recently purchased the Buchi Encapsulator, a device which encapsulates cells and protects them from being cleared by the recipient's immune system. A recent paper in Nature Medicine showed that encapsulated human islet cells, injected into a diabetic mouse, survived 175 days and controlled the mouse's blood sugar. We plan to use this shield for our MSC spheroids. If the cells survive longer, they may be more effective in restoring blood flow to the leg and promote wound healing. Importantly, the Buchi Encapsulator is a sterile system and can be used in future human clinical trials.

Buchi Encapsulator

MEET DR. MURPHY

Dr. Mike Murphy leads the vascular research team at IU. He holds the Cryptic Masons Chair in Vascular Research.

- Columbia University, B.S. in Biochemistry 1985
- Columbia University Medical School 1989
- Harvard Medical School, Surgery Training
- Research Fellowship at Harvard Medical School
- Duke University, Vascular Surgery Training
- Faculty Position at Harvard Medical School and then Indiana University School of Medicine 2005

Dr. Murphy was on faculty at Duke University in 2003 when he felt the call to respond to the critical shortage of surgeons in Iraq. At 42, he joined the Army Reserves and was deployed to Iraq. Following heavy fighting at the Second Battle of Fallujah, he oversaw "Damage Control Surgery" at the 31st Combat Support Hospital. Dr. Murphy helped dramatically reduce deaths from combat injuries. He was awarded an Army Commendation Medal, a Meritorious Service Medal, and a Bronze Star.

PREVENTING AORTIC ANEURYSM RUPTURE WITH STEM CELLS

Abdominal Aortic Aneurysms (AAA) are a pathologic dilatation of the aorta, the main blood vessel from the heart. If untreated, this leads to aortic rupture and death. AAA is the 13th leading cause of death in the U.S. Approximately 200,000 new cases are diagnosed each year. Its incidence is probably higher as it has no symptoms until rupture. For patients who rupture, half die before reaching the hospital, and half of those die after emergency surgery. AAA has a 70% mortality rate. Surgical repair is indicated only when the AAA grows to a diameter of 5.5 cm. Thus, many patients with smaller AAA's must wait years before repair and describe it as having a ticking time bomb. There are NO current medical strategies to prevent or suppress AAA expansion and rupture.

Our team is near the completion of a Phase I clinical trial in which we are treating patients with a small AAA with intra-venous infusions of mesenchymal stem cells from a healthy young donor. Preliminary results show a significant reduction of inflammatory cells related to AAA development and a significant increase in regulatory T cells that suppress inflammation. We have shown that these stem cells decreased inflammation in the aorta and prevent AAA from enlarging.

HELPING FAILING HEARTS WITH STEM CELLS

Through the Cardiovascular Cell Therapy Research Network, a consortium of seven U.S. centers with expertise in stem cell research, our team participated in two clinical trials—SENECA and CONCERT-HF.

The SENECA study was a Phase I trial involving 60 patients with heart failure following chemotherapy treatment. Besides killing cancer, chemotherapy also kills heart muscle. Patients who survive cancer may end up with heart failure. SENECA assessed the effects of mesenchymal stem cells injected into the heart muscle of these patients. The study found that stem cells improved all seven measures of heart function. A larger, more definitive trial is planned.

The CONCERT-HF trial is assessing the ability of stem cells to improve heart function in patients with heart failure after a heart attack. Patients underwent a biopsy of their heart muscle and a bone marrow aspiration. The samples were sent to the University of Miami, where stems cells called c-kit positive cells were grown from the heart muscle and mesenchymal stem cells were grown from the bone marrow. The cells were sent back to the medical center and the combination of c-kit and MSCs were injected into the heart muscle. We will meet later this year to review the results of this study.

We are collaborating with Meijing Wang, PhD, in cardiothoracic surgery. Using our 3D bioprinter, we are creating scaffolds onto which heart cells can be implanted. This "beating" scaffold can be used to surgically replace parts of the heart damaged by a heart attack.

FOR MORE INFORMATION

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