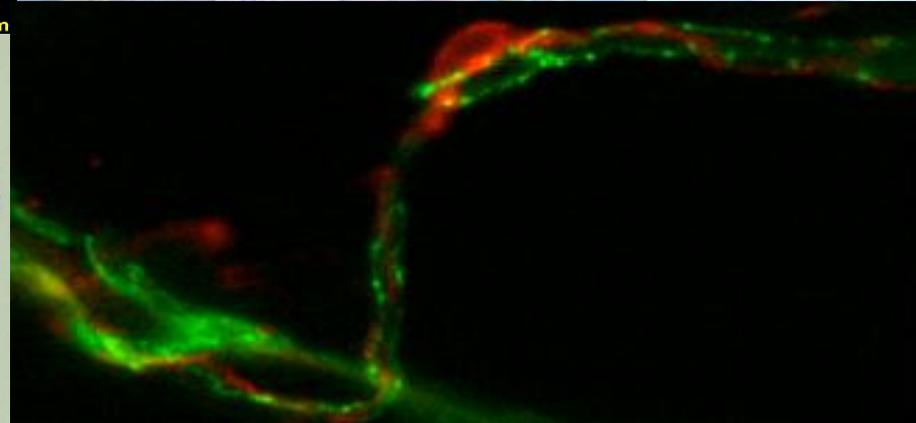
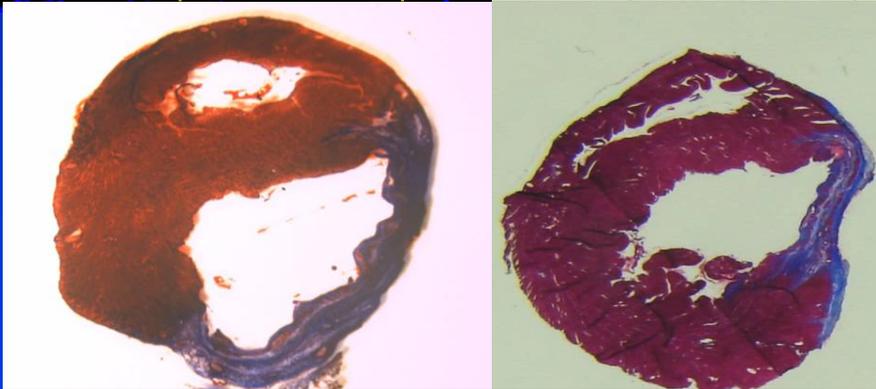
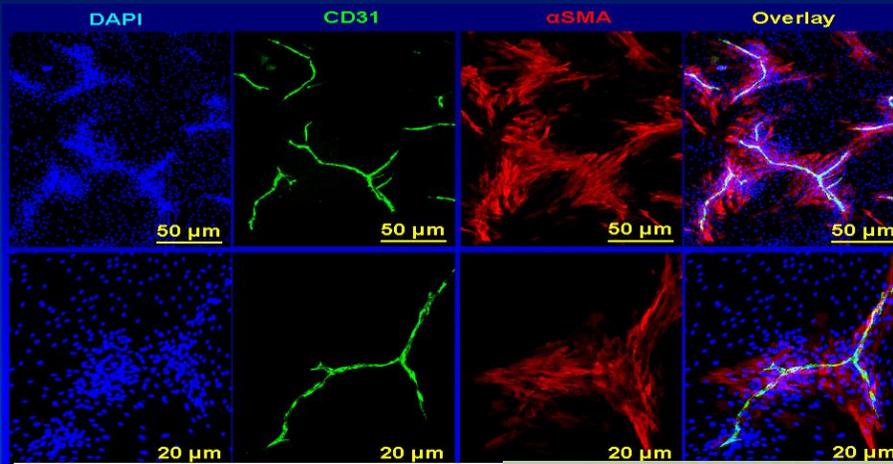




Indiana Center for VASCULAR BIOLOGY & MEDICINE



Vessels from Bench To Bedside

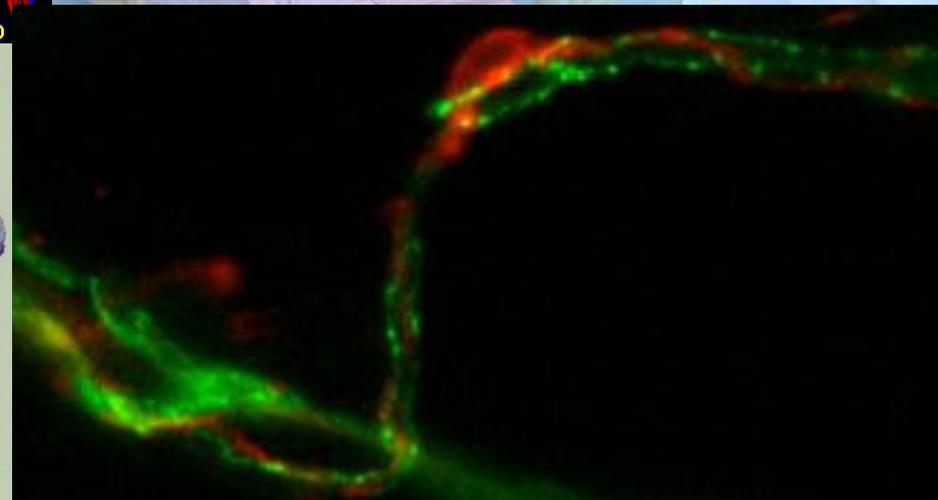
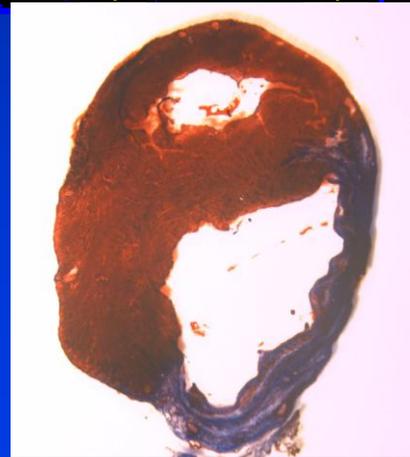
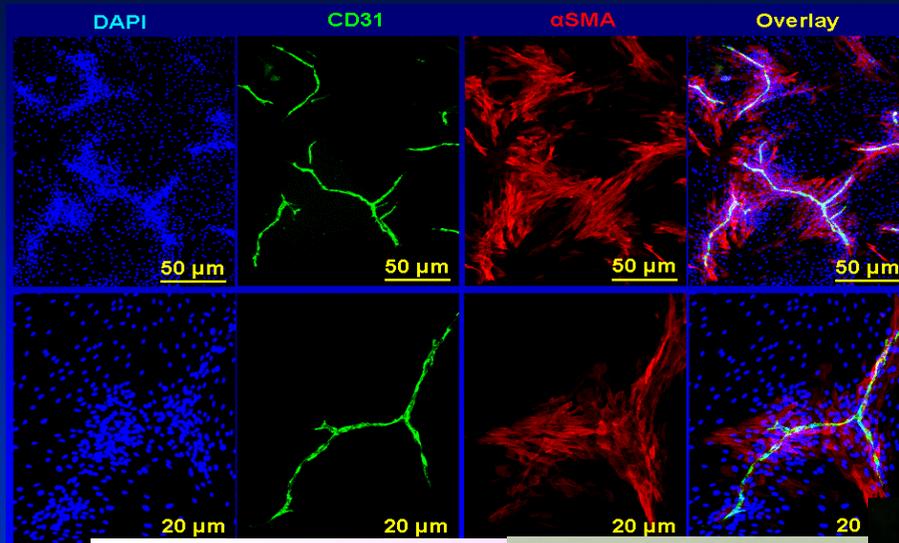


Vascular and Cardiac Center for Adult Stem Cell Therapy

Indiana Center for VASCULAR BIOLOGY & MEDICINE



INDIANA
UNIVERSITY
SCHOOL OF
MEDICINE



Vascular and Cardiac Center for Adult Stem Cell Therapy

Proposed Efforts of the ICVBM and VC-CAST Focusing on Diabetes and its Complications

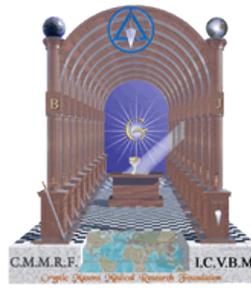
The goals that we would specifically like to address with new support directed to our vascular and adult stem cell diabetes initiatives, will include:

- Testing the effects of one's own fat-derived (adipose) stem cells on the progression to diabetes in children in the early stages of juvenile onset diabetes
- Testing the effects of one's own fat-derived stem cells on the progression to diabetes in adults with Type 2 diabetes.
- Developing and improving new models of islet transplantation which may be able to reverse diabetes in some patients.
- Creating the ability to watch vessels providing blood flow to transplanted islets in real time.
- Building a bank of fat-derived stem cells from patients with and without diabetes to determine the effects of diabetes on one's own stem cells.
- Investigating the ability of fat-derived stem cells to reverse kidney damage associated with diabetes.
- Retinopathy leads to blindness in both diabetes and macular degeneration. We believe that both problems may be addressed with fat-derived (vascular) stem cells that may have the ability to stabilize new blood vessels in the eye, and we are prepared to test this concept.

Additional Target Diseases to be Pursued as Support becomes Available

- We hope to address lung disease known as adult respiratory distress syndrome (ARDS). This occurs in the ICU, and has no good treatment. Our results in COPD suggest to us that this is a very viable target, such that we might be able to save patients with ARDS very soon, if animal models support this idea.
- We have determined that adipose stem cells can be modified to become similar to liver cells and to secrete the factors needed for hemophilia treatment. We plan to take the findings in hemophilia from the laboratory to the animal, to determine whether this concept can work in vivo.
- Up to 50% of patients have erectile dysfunction after certain types of prostate surgery for cancer, and this ED does not respond to drugs like Viagra. There is significant evidence suggesting that fat-derived (vascular) stem cells could reverse this problem by enhancing nerve sprouting to the penis. We would like to attempt this concept as well, in collaboration with local Urology colleagues.
- Fat-derived (vascular) stem cells may well also address certain types of arthritis, like rheumatoid arthritis. We would like to try this in initial animal studies; and move into patients as soon as feasible, if supported by the studies. We also anticipate initiating clinical trials in the area of osteoarthritis, where substantial animal data has already been accumulated.

*Cryptic Masons
Medical Research
Foundation, Inc.
(CMMRF)*



HISTORY OF THE CRYPTIC MASONS MEDICAL RESEARCH FOUNDATION

Updated May 2010

The Cryptic Masons Medical Research Foundation (CMMRF) was incorporated in the state of Oklahoma, March 6, 1986. The driving force behind the new corporation was General Grand Master Ben Mandlebaum, of the General Grand Council International. Companion Joe Lewis, Attorney at Law, was instrumental in getting the Foundation a tax-exempt status very quickly. We also had a tax lawyer, James A. Hogue, PMIGM in Oklahoma. These men donated their time to the Foundation. Companion Lewis & Mandlebaum are now deceased and Companion Hogue is no longer working with us. The current secretary also donated his time and efforts until the Foundation was well established.

The Foundation funds research at ICVBM, which is located at the Indiana University School of Medicine in Indianapolis, Indiana. Because all blood vessels are very important in maintaining the health or in repairing almost all tissues, nearly all diseases turn out to have a vascular component involved in their origin or in tissue repair. Diabetes, stroke, poor leg circulation, difficult wound healing and many more diseases share a common denominator, blood vessels! Centering our contributions to an organization that helps so many different health concerns around the world allows our contributors to share in the medical advancements, regardless of their state or country.

Through this research, we hope the causes and eventually a cure will be found for Diabetes and many other vascular related diseases. This research was previously funded by an Indiana corporation, which ceased to do business upon the death of Dr. Owen L. Shanteau, October 17, 1985. While CMMRF is not a part of that organization and the General Grand Council was not its governing body, we are continuing the good work that it started. Dr. Shanteau met with Dr. Nils Bang at the Medical Center in 1978 and discussed this new venture. He was able to give a grant of \$12,000.00 a year to this project, which was being done on a part time basis.

Contributions are urgently needed. As you know, most of our donations are voluntary. Only three states that we know of have included CMMRF in their per capita dues. This is a decision that must be made by each Grand Council and not the General Grand Council. This is one reason a life sponsor program is not attractive to our members, we cannot offer them a savings for being a life sponsor. The contributions may be tax deductible and that does have some appeal.

We now have two new brochures that are more graphic and colorful than the earlier ones. The older ones are still in demand. We also have one entitled INFORMATION ON GIFTS, WILLS & BEQUESTS. We will send a supply to anyone who requests them. We have a quantity of CD's available on request describing our research. They are available upon request or by visiting www.cmmrf.org.

There are six lapel pins presented to contributors for donations totaling \$50.00, \$100.00, \$150.00, \$300.00, \$500.00 and \$ 750.00. There are six different certificates that can be earned. They are for \$25.00, \$50.00, \$100.00, \$500.00, and \$1,000.00 and for one hundred percent participation by a council. A plaque is also presented for a \$1,000.00 donation. An individual receives a gold filled 9 Arch Pin with a diamond chip for each additional \$1,000.00 after the 1st \$1,000.00 a council is presented with

an extender for their plaque for each additional \$1,000.00. These donations may be a one-time gift or an accumulation over the years since 1986.

There is a Board of Directors that meets once a year, or as needed. The General Grand Master serves as the President during his triennial. The Current President is Joseph Vale, MPGGM. The Secretary is Marion K. Crum, P.O. BOX 1489 Nashville, IN 47448.

We have a triennial audit or review performed by a Certified Public Accountant. We also have charts available which show how much each state has given each year, and the total amount given since 1985. These are available to any Cryptic Mason upon request.

Each year we have continued to grow in financial assets. There are expenses that have to be paid and they are paid from the income from investments. As of December 31, 2008 we have received \$4,067,851.60 in contributions and we have \$2,176,702.21 in financial assets. CMMRF has given the I.U. School of Medicine \$2,524,000.00. We feel that is an excellent record and we are proud of it. Prior to restructuring the foundation in 1986, the former foundation had given \$96,000.00 to the Medical Center for research. Cryptic Masons have given Grants equaling \$2,428,000.00 from 1978 to the present time. Income from our investments helps to fund our grants. These figures do not include money earned from the endowment of the chair, which is \$100,000.00 per year. We get a report on this, but we do not run it through our books.

At the February 1996 Director's meeting in Washington D.C. we agreed to fund a "Chair" at the Medical Center at the cost of one million dollars. We contributed two hundred thousand dollars a year for five years to endow the chair. The final payment was made in December of 2000. The University offered as an incentive to guarantee a five per cent income on the endowment plus matching it with a five percent payout from the endowment. At the end of five years the Chair will be netting over one hundred twenty-five thousand dollars (\$125,000.00) a year for research in Vascular Biology. Sometime in 2001-2002 our Lab became a Center of Vascular Biology and Medicine (not Atherosclerosis). After a 3-year search for just the right person for this "Chair", Dr. Keith March was selected. The Creation of the ICVBM has attracted several million dollars from non-Masonic sources.

In 2007, a non-Masonic benefactor challenged CMMRF to match his \$50,000.00 donation to the Indiana Center of Vascular Biology and Medicine. By meeting his challenge, CMMRF contributed \$300,000.00 to ICVBM in 2007. In 2008 we had a Cryptic Mason to donate \$20,000.00 which we matched and it enabled us to give \$240,000.00 to the Center for research. Our support continues, as this year we have pledged to contribute an additional \$300,000.00. We will **match** \$10,000.00 donations up to \$100,000.00.

Our commitment to support research conducted at the ICVBM will translate into cures and treatments for almost all diseases! We urge you to consider partnering with the CMMRF mission to save lives and improve the quality of life. Thank you for your efforts on behalf of the Foundation. We could not achieve our goals without your help.

Fraternally and sincerely,

Marion K. Crum

Marion K. Crum, PMIGM
Executive Secretary

Selection of Current Projects

Peripheral Vascular Disease

Michael Murphy, M.D.

More than 100,000 patients in the US each year undergo amputation due to advanced atherosclerotic vascular disease in the leg. Ten to fifteen million more with this disease have crippling pain that limits their walking. More than half of these patients have this disease as a complication of diabetes. There is accumulating evidence that this PAD may be effectively treated with stem cells that stimulate new blood vessel development.

Dr. Michael Murphy has completed the first Phase I trial of stem cells (derived from one's own bone marrow) that was FDA-approved in the USA to treat vascular disease in legs for patients who have been told their only hope is amputation. Thus far, only three patients of 32 treated have required amputation. The autologous bone marrow mononuclear cells "SAVE" study is now being extended to a Phase III randomized study between patients receiving cells or no cells, to compare outcomes directly. The study has received conditional FDA approval and will be conducted at 10 centers throughout the US, with the ICVBM being the lead center for the study. Duke University in North Carolina and the University of Alabama in Birmingham are among those participating. This study forms a key platform to move into treatments of heart disease; developing new therapies in legs allows testing safety in leg muscle before moving into heart muscle.

Dr. Murphy's team also launched a new trial that evaluates a new source of stem cells; **A Laboratory Analysis of Endometrial Regenerative Cells (ERC)**. This study collects menstrual blood. The goal is to develop a sterile laboratory technique for expanding ERCs from a single donor to reach a target population of 1×10^8 cells with a normal karyotype. ERC appear to possess numerous advantages compared to other stem cell sources that make them attractive to further investigation. Firstly, the ease of collection of ERC allows for the creation of patient-specific cell banking (holding them back until needed). If the cells behave as expected, they may be expanded (multiplied) and may possess the ability to change into various tissues.

Isolation and Characterization of Endothelial Colony Forming Cells (ECFCs) from Human Adult Blood Vessels.

Michael Murphy, M.D.

Highly proliferative endothelial stem cells were isolated from human arteries and leg veins by Dr. Murphy, using colony forming assays developed by David Ingram, MD and Merv Yoder, MD (collaborators in Pediatrics). The significance of this study is that (1) we have developed the ability to isolate these cells from vessel endothelium, a critical step in the analysis of ECFCs in the pathogenesis of disease; and (2) we have shown that autologous vein, potentially available by minimally invasive harvesting methods, can provide a practical source of ECFCs that are available for autologous use in cell therapies. We are also studying how diabetes and aging affect these cells and may cause blood vessel disease by making them unable to fulfill their repair functions.

Adipose Stem Cells for Peripheral Arterial Disease. We are working with the FDA as well as a corporate partner, Tissue Genesis, to test the feasibility and safety of providing adipose (fat) stem cells (ASCs) in patients with severe peripheral vascular disease. Animal trials that we have conducted have suggested that ASCs are very potent in this regard; multiple other labs have also corroborated these data. We would like to be the first to complete testing of this concept in a human Phase I critical limb ischemia trial essentially identical in design to the ABMNC "SAVE" study.

Diabetes: working towards a cure

Carmella Evans-Molina, M.D., Ph.D.

Nearly 24 million people in the United States are affected by diabetes. Type 2 diabetes is the most common form of diabetes. In type 2 diabetes, either the body does not produce enough insulin or the cells ignore the insulin. Insulin is necessary for the body to be able to use glucose for energy. When you eat food, the body breaks down all of the sugars and starches into glucose, which is the basic fuel for the cells in the body. Insulin takes the sugar from the blood into the cells. When glucose builds up in the blood, the body cannot make efficient use of its main source of fuel, and over time, high blood glucose levels may hurt your eyes, kidneys, nerves or heart.

Type 1 diabetes is usually diagnosed in children and young adults, and was previously known as juvenile diabetes. In type 1 diabetes, the immune system attacks the insulin-producing beta cells in the pancreas and destroys them. Insulin is a hormone that is needed to convert sugar (glucose), starches and other food into energy needed for daily life. A person who has type 1 diabetes must take insulin daily to live.

Dr. Evans-Molina and Dr. Kono, in collaboration with Dr. Keith March, have been performing the first transplantation studies using two adult stem cell types (from fat and blood vessels) in combination with pancreatic islets. They have already obtained early information suggesting that this approach can prolong beta cell (the insulin-secreting cell) survival following islet transplantation. This has the potential to provide an exciting new treatment option for patients with diabetes. Our hope is that one day a patient will receive an under the skin implant of these cells (Bio-Pump) which will be able to augment their insulin levels and reduce or eliminate the need for supplemental insulin injections.

Furthermore, this team has discovered that these fat-derived stem cells can actually block islet death in animals that are newly acquiring type 1 diabetes. They are planning experiments to help lay a foundation for clinical trials to treat children at the time of initial presentation with diabetes (or after onset in their brothers and sisters) in the hope of significantly forestalling the onset of disease. These findings may also have potential benefit for patients with type 2 diabetes.

"Targeting diabetic retinopathy with low molecular weight inhibitors".

Rajashekhar Gangaraju, Ph.D., and Matthias Clauss, Ph.D.

Over 80% of people who have had diabetes for 10 years will develop eye related complications. Current strategies for treating diabetic complications are ineffective in targeting these eye disorders which include; laser photocoagulation, VEGF (a cocktail that encourages repair), injections of steroids, and the removal of leaking blood, and a few more experimental procedures. Although some treatments are successful in slowing down or partially restoring vision loss, they do not cure diabetic retinopathy. New evidence indicates that diabetes may be an inflammatory disease. We hypothesize that endothelium (single layer of smooth, thin cells that lines the heart, blood vessels, lymphatics, and serous cavities) exposed to inflammation and high glucose, leads to a condition resulting in increased blood vessels with abnormal leakiness. In order to address this hypothesis we use a unique diabetic mouse model that over expresses TNF in endothelium. We have found that diabetes and inflammation strongly support each other for generating diabetic retinopathy. Importantly we have identified a low molecular weight signal transduction inhibitor which reduces diabetic retinopathy and can be applied in the eye without injection. It thus may be superior to anti-VEGF therapy (trade names: Lucentis, Macugen, Avastin), which needs to be injected. Most current treatments involve an injection into the eye. Have you ever had a loved one receive an eye injection? Imagine requiring an 80 an elderly great grandmother, who already has some mild dementia, to hold still while her head is placed in a vise and contraptions put on her eyelid to hold them open. Then, the only way she has to quiet the eye from moving is to try to stare at a spot on the wall. Quickly, a 2 inch needle is used to inject into the fragile back of the eye. The Grandmother can be terrified....

The potential for a new therapy offers new hope to millions. Many people elect not to receive treatment strictly because they cannot hold still long enough for the procedure, and because it usually takes multiple injections, with very little improvement. At present, this project is awaiting additional support to further improve the inhibitor and test its application, as a safe and noninvasive therapeutic tool to treat diabetic retinopathy in patients.

Veterinary Medicine

In collaboration with Purdue Veterinary School, the ICVBM is designing research to determine whether the new treatments being developed by Drs. March and Evans-Molina, using fat-derived stem cells, could offer hope to thousands of pets as well as people. We are exploring a possible approach which would allow us to reduce the time table needed to get a product into human clinical trials by including diabetic pets (dogs) in the research plan. This idea recognizes that new therapies based on blood-vessel stem cells may offer hope to not only mankind, but "man's best friend" as well. Additional funding is required to support this project moving forward.

Adipose Stem Cells for Treatment of Heart Attack and Prevention of Heart Failure.

Keith March, M.D., Ph.D., Brian Johnstone, Ph.D., Peng-Sheng Chen, Ph.D.

Heart attacks and heart failure are major life-threatening complications of diabetes. Based on our prior findings that adipose (fat-derived) stem cells could protect leg tissue from injury due to poor blood flow, we wished to test the possibility that heart tissue would be protected in a similar way. We also have obtained data that the factors secreted by ASCs could protect nerves from injury due to low oxygen as well as other injurious factors that mimic degenerative conditions of nerves, and we hypothesized that this in turn could contribute to cardiac functional preservation. Indeed, we found that rats with heart attacks had less damage and more nerve sprouting following ASC injection. In a study of ASCs infused into normal pig coronary arteries, we also found that ASCs could self-aggregate, creating the possibility of microvascular obstructions and undesirable injury. We discovered that this problem could largely be avoided by the admixture of heparin and other selected agents with the ASC prior to infusion. This finding is potentially very important in directing future studies of ASC delivery into heart tissues.

Wound Healing

Keith March, M.D., Ph.D., Dmitry Traktuev, Ph.D.,

Burns and wounds are often slow to heal due to poor blood supply in areas of poor circulation like the legs of diabetic patients, or such as those seen after radiation to treat cancers. We have identified that fat-derived stem cells can function along with endothelial cells to build blood vessel networks. Dmitry Traktuev would like to use this observation to build new skin-like materials from the vascular stem cells and skin cells, and then test this approach in mice and in pigs. ICVBM research demonstrating this concept in pigs for the first time was recently published in the leading journal of plastic and reconstructive surgery. This sets the stage for clinical trials testing this in patients. Additional funding is required to support this project moving forward.

Lung Disease

Irina Petrache, M.D.

Emphysema as well as sleep-disordered breathing and sleep apnea are conditions associated with increased diabetes and insulin resistance (metabolic syndrome), as well as obesity, hypertension, and cardiovascular disease. In addition, the alteration in circulating endothelial progenitor cells found in respiratory disease, the metabolic syndrome and cardiovascular disease may reflect a common condition of endothelial dysfunction. Irina Petrache, M.D., and her team of investigators recently completed a study to determine if adult stem cells acquired from fat could help improve blood flow to the lungs, particularly those damaged by emphysema. In this study, mice were exposed to chronic cigarette smoke for up to 21 weeks. These "smoking mice" were then given injections of adipose (fat) derived stem cells. After injection of the cells, this study showed that the lungs were not only protected from typical damage, but that these cells even promoted repair of the lung tissue. These findings point the way to a new potential treatment option for COPD and emphysema patients; and may be helpful to diabetes in this context as well. As in the other studies, adipose (fat) stem cells used in this study are readily available and can be acquired in large amounts during liposuction.

Matthias Clauss, PhD, an ICVBM investigator that was recruited from Germany along with his research team, also is leading the field with cutting edge discoveries like: "**An Antibody That Can Reduce Cigarette Smoke-induced Lung Emphysema**". Over 3.1 million Americans have been diagnosed with lung emphysema, which is a fatal disease with no cure currently available and cortisone based therapy showing only partial reduction in disease progression. Chronic obstructive pulmonary disease (COPD) refers to chronic bronchitis and emphysema, a pair of two commonly co-existing diseases of the lungs. Emphysema is characterized by loss of both matrix and cellular elements of the lung, thus impairing gas exchange between the gas and the blood side of the lung. Recently, excessive programmed cell death of structural lung cells emerged as a key mechanism in addition to inflammation. Recently, he demonstrated that a pro-apoptotic protein, named EMAP II is sufficient on its own for lung emphysema development. Importantly, he could block progression of cigarette smoke induced lung emphysema in mice, which were previously exposed to prolonged smoke exposure, by application of a neutralizing anti-EMAP II antibody. This suggests that this antibody could be a suitable therapeutic tool for emphysema patients with a smoking or smoke exposure history.

For a clinical application this antibody, which had been developed in rodents, needs to become "humanized", which is an established technique to make antibodies tolerable to the immune system for long time treatment in patients. Given the high clinical significance of our findings we hope to make this antibody available to emphysema patients as soon as possible. It will be delivered as a nasal or inhaled spray.

ICVBM Vascular Solutions

Diabetic Retinopathy
(Retinal blood vessel damage of the eye)
Leaking blood vessels can cause irreversible vision loss. Fat-derived vascular stem cells may be able to stabilize the blood vessels in both diabetes and macular degeneration.

Emphysema and Pulmonary Disease
Antibodies, which can be inhaled have been developed which offer treatment options where there have been few. Injections of our fat stem cells also promise exciting treatment.

Prevention of Type 1 Diabetes
Fat derived stem cells have proven to prevent islet death in an animal models. Foundations for clinical trials in children are planned, bringing hope to stopping this deadly disease BEFORE it develops! There is promise this treatment may also benefit type 2 diabetes.

Islet Cell Transplantation
A Bio-Pump, under the skin transplantation of pancreatic islet cells with adult stem cells; may hold the future for a new method to deliver insulin.

Adipose Stem Cells to Treat and Prevent Heart Failure
People with Diabetes has twice the chance to have a stroke or heart attack. These fat derived cells come from ones own body and are easily collected at the time you will receive treatment.

Characterization of Stem Cells from Blood
Diabetes and aging affects stem cells in the blood and blood vessels making them unable to fulfill their repair functions.

Peripheral Vascular Disease (PAD)
Poor blood supply from unhealthy blood vessels can result in amputations. Current clinical trials are underway using adult bone marrow stem cells with remarkable results. Treatments using adult stem cells from fat are schedule for a new clinical trial starting soon.

Nerve Damage
Gangrene can result from loss of sensations. Several of our stem cell discoveries promise hope for restoring health to the nerves and growing new blood supplies.

Wound Healing
Burns and wounds are slow to heal in diabetic patients as well as those recovering from cancer treatment. Using combinations of special adult stem cells can build new blood vessels and speed up healing.

See Selection of Current Projects for Complete Descriptions

Indiana Center for Vascular Biology and Medicine



Keith March, M.D., Ph.D.

The Indiana Center for Vascular Biology and Medicine (ICVBM) is led by Keith March, MD, PhD, a physician, scientist and cardiologist. The ICVBM is committed to being a leader in basic as well as applied research in understanding vascular wellness and disease, and the development of leading-edge medical therapies to improve the care of patients with vascular problems. Because blood vessels are very important in maintaining the health of and repairing almost all tissues, nearly all diseases turn out to have a vascular component involved in their origin or in tissue repair. Centering our key research on the biology of cells that form blood vessels leads to knowledge that can readily translate from one disease to many others.

The ICVBM includes more than 30 investigators from a range of basic as well as clinical disciplines, and is thus well-positioned to approach vascular research and development from a highly cross-disciplinary perspective. The overall mission of our Center is the rapid development and extension to clinical application and commercialization of new knowledge in vascular biology. The ICVBM thus operates with the purpose of facilitating research while impacting delivery of novel and innovative medical treatment in order to achieve positive results within the health care community.

This ICVBM faculty as well as the staff and students work as a team to achieve the component missions of: Facilitating excellence in interdisciplinary basic and translational research; Leading a nationally-recognized interdisciplinary post-graduate education program in vascular biology and medicine; and implementing interdisciplinary clinical programs to provide excellent care to patients with all vascular diseases. Successes in these three areas distinguish the ICVBM from other programs relating to vascular issues, which rarely engage a strong linkage between research and clinical programs.

To harness the potential of the Center and its component institutions and investigators, an active interdisciplinary approach is implemented, capitalizing on our established premier academic resources and combined industrial, philanthropic, and Federal support. The Center operates on the well-founded principle that a properly implemented, multidisciplinary approach to the use of resources leads to a whole that is indeed far greater than the sum of its parts.

Partnership of the ICVBM and VC-CAST with the Indianapolis VA Hospital

Last year, the ICVBM and VC-CAST engaged in discussions with the RL Roudebush Veterans Affairs Medical Center (VA), and developed a strategy to establish the **VA Center for Regenerative Medicine (VA-CRM)**, as a direct outgrowth of the VC-CAST effort, and thus of the ICVBM. This center was created in order to facilitate the involvement and recruitment of veterans to participate in trials involving adult stem cells, thus providing a way to accelerate advancement in the field, while providing access for veterans to cutting-edge trials related in many cases to diseases that are common in aging and veteran populations.

BECOME A PART OF THIS TEAM; JOIN OUR EFFORTS IN SAVING LIVES AND ADVANCING MEDICINE.