

HEARTBEAT



Healthy Heart Report

TAPPING THE POTENTIAL OF ADULT STEM CELLS

Can adult stem cells help regenerate the damaged blood vessels in patients with peripheral vascular disease?

A multidisciplinary team of researchers at the Indiana Center for Vascular Biology and Medicine is experimenting with a novel adult stem cell therapy, using patients' bone marrow cells that are involved in arterial formation and repair. The Stem Cell Mediated Angiogenesis Study is an FDA-approved Phase I clinical trial to examine how safe and effective adult stem cells are for stimulating the development of new blood vessels in the legs of patients with severe peripheral vascular disease—a painful condition that, according to the American Heart Association, affects approximately 12 million people. When blocked or destroyed, arteries in the leg are unable to transport essential nutrients and oxygen, resulting in tissue death and

gangrene. Many patients suffering from advanced peripheral vascular disease often exhaust all conventional means of therapy and face amputation.

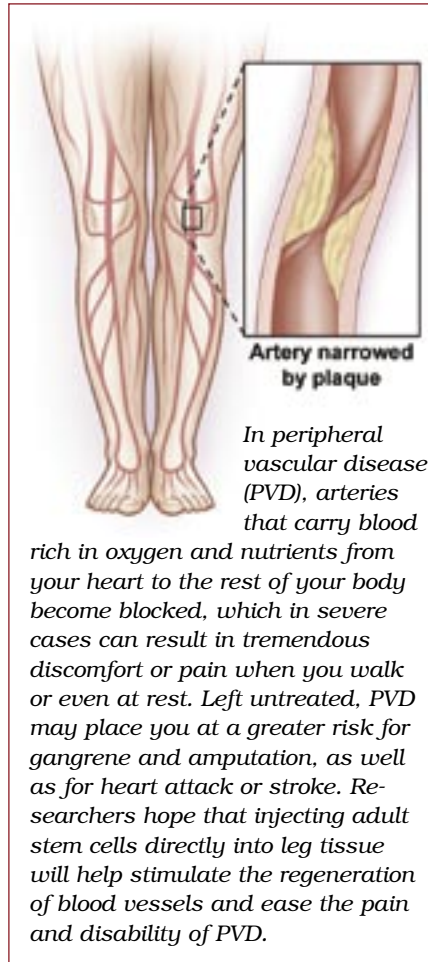
Researchers hope that the specialized adult stem cells—known as endothelial

progenitor cells (EPCs), involved in the repair of the inner lining of blood vessels—will help restore enough blood flow to lower limbs to help regenerate blood vessels and avoid amputation.

One day, the innovative therapy might benefit other areas of the body, such as the heart muscle.

To learn more about the trial, the *Post* spoke with Michael Murphy, M.D., at the Indiana Center for Vascular Biology and Medicine at Indiana University School of Medicine.

Post: Could you outline your research utilizing adult stem cell-based therapy to treat cardiovascular disease?



Murphy: Basically in the last five years, researchers have isolated a cell in the bloodstream of humans called an endothelial progenitor cell—a special type of stem cell. Subsequent studies have demonstrated that the endothelial progenitor cell, or EPC, comes from the bone marrow. Clinical evidence from an NIH study showed that patients who have a greater number of cardiovascular risk factors—high blood pressure, diabetes or cigarette smoking—have fewer endothelial progenitor cells. The conclusion was that these cells are involved with

arterial repair and may help prevent the development of atherosclerosis. The cells also participate in the development of new blood vessels. Animal studies have demonstrated that when EPCs from bone marrow are injected into lab animals, they develop new blood vessels in response.

Post: How do you retrieve and administer the adult stem cells in your study?

Murphy: Under anesthesia, we remove about 500 cc, or one-half a liter, of bone marrow from the patient—about 2 to 2½ cups of bone marrow. We process the bone marrow in our stem cell laboratory at University Hospital. We separate out what we call the buffy coat—the mononuclear cell layer—by spinning the cell preparation at very high speeds.

To administer, we basically inject the cells, or the mononuclear cell fraction containing a subpopulation of progenitor stem cells, right into the calf muscle of the affected leg that has insufficient blood flow. In the future, we plan to grow the cells in culture and increase the number of endothelial progenitor cells before injecting. Right now, we have strict limitations on what we can do from the FDA, because this is the first such study in the United States.

There is evidence the injected progenitor cells directly incorporate into new capillary beds and produce the necessary protein messengers—so-called cytokines—that induce existing blood vessels to grow.

By using the cells from the patient's own bone marrow, we avoid the problem of rejection and so avoid the ethical issue of using embryological cells.

Post: Is this one of the first U.S. stem cell therapy-based trials?

see Heartbeat on page 95

HEARTBEAT

Murphy: Yes. It is what we call translational medicine and modeled after a Japanese study published in 2002. Unfortunately, the U.S. is several years behind our colleagues in Japan and Germany, especially in adult and embryological stem cell research.

Post: Have foreign researchers reported success using this approach?

Murphy: I have communicated with researchers in Japan who have treated over 100 patients with very good results.

The patients we're treating in the United States, and those treated in Japan, have such severe peripheral vascular disease that their only other option was amputation. The patient population has no other alternative, which is why the FDA approved the study of this, to date, unproven mode of treatment. In short, the patient has little to lose.

Post: Are patients with diabetes eligible to participate in your study?

Murphy: Patients with diabetes are eligible. In Japan, patients with diabetes were treated.

Post: What are the enrollment criteria for your current study?

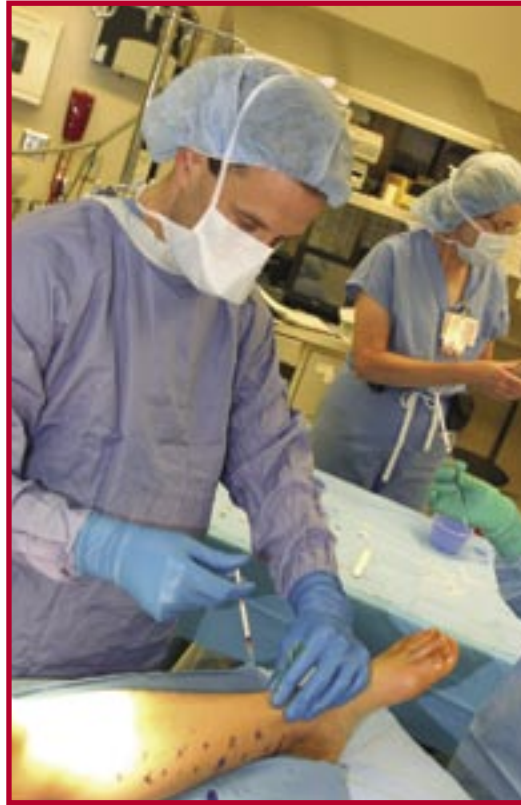
Murphy: The enrollment criteria are: patients need to be over 21 years of age; have severe vascular disease; are not candidates for any surgical procedure or angioplasty; have normal renal function; and have no history of cancer.

Post: Before the current controversy over the use of stem cells, haven't we employed bone stem cells for decades?

Murphy: For over 30 years, we've been using stem cells from the bone marrow or bone transplantation to reconstitute the bone marrow in patients who have various hematological disorders or bone marrow depression from chemotherapy, such as with Stage IV breast cancer.

Post: Are progenitor stem cells compromised in the bone marrow of patients with vascular disease, or are they abundantly available?

Murphy: That is a phenomenal question. Yes, the cells are compro-



Dr. Murphy injects the bone marrow-derived adult stem cells directly into the leg with PVD. This helps restore oxygen supply to the tissue, thus avoiding amputation.

mised. It may seem ironic that we are taking from a patient bone marrow cells that we think don't work well and using them as a mode of therapy, but evidence suggests that it works.

“What we learn from this trial could possibly apply to other areas of the body, such as the heart.”

—MICHAEL MURPHY, M.D.

A number of studies of patients with coronary heart disease, diabetes, rheumatoid arthritis, and renal failure have demonstrated that these progenitor cells are decreased in number and dysfunctional in the peripheral circulation. But those investigators have only looked at circulating progenitor cells.

Since we're harvesting bone marrow, we're going to see if the cells within the bone marrow are defective

as well. We will also be conducting a laboratory sub-analysis to investigate what role these cells play in the physiology of atherosclerosis.

We're also launching several other studies to look at alternative sources of stem cells.

My colleagues Dr. Keith March and fellow researchers have isolated a stem cell from fat or adipose tissue, and we're submitting an application to the FDA to conduct a trial using that stem cell population for the identical purpose.

These are Phase 1 studies to demonstrate that use of these fat cells is safe. Eventually if we demonstrate safety and some positive effect, we hope to expand the study to modify these cells in some way after we extract them from the body. Can we make them work better? In this instance, we return to gene therapy with a plan to genetically modify these cells with genes from VEGF and other proteins that are beneficial, and then inject the genetically modified cells back into the patient.

Post: Is the trial only taking place at your center in Indianapolis?

Murphy: Correct. The study is 12 weeks long and will require travel to and from Indiana University Medical Center at 2 weeks, 4 weeks, 8 weeks and 12 weeks after being treated.

Post: Whom do individuals contact if interested in participating?

Murphy: They could contact me via my e-mail address: mipmurph@iupui.edu.

Post: Are people aware of positive results emerging from adult stem cell research?

Murphy: The public is not aware of this second population of stem cells—adult stem cells. The media have been fascinated with embryologic stem cell research. We are now looking at the immediate potential of using adult stem cells. This is a novel approach to using stem cells for the treatment of vascular diseases. And it is the very first step and will probably lead to several different methods of treating not only vascular disease but cardiac disease as well. ♣

—Patrick Perry