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# CVBT Banks on Fibroblast Growth Factor

## Potential Exists for Treating Blood-related Diseases

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**CardioVascular BioTherapeutics** (CVBT; www.cvbt.com) was founded in 1998, soon after Thomas Stegmann, M.D., demonstrated that fibroblast growth factor injected into the hearts of patients with coronary heart disease stimulates new blood vessel growth. Dr. Stegmann, a cardiac surgeon in Germany, published the findings in the February 1998 issue of Circulation. Daniel Montano, a California businessman, read a report of the study in the Wall Street Journal and called Dr. Stegmann. The two teamed up to start CVBT, with Montano as co-president and CEO and Dr. Stegmann as co-president and CMO.

In addition to coronary heart disease, fibroblast growth factor holds the potential to treat several other medical conditions that involve inadequate blood flow to organs and tissues, including peripheral artery disease, diabetic skin ulcers, wound healing, bed sores, stroke, back pain, intestinal ischemia, and hypertensive renal disease. "Half of all people in the developed world suffer or die from lack of blood flow to a tissue or organ," says Dr. Stegmann. CVBT's mission is to develop regenerative therapies based on fibroblast growth factor to help millions of people suffering from such diseases.

Coronary heart disease, peripheral artery disease, stroke, and other ischemic disorders all result from the underlying condition of atherosclerosis, which causes significant morbidity and mortality. Fibroblast growth factor reverses the complications of atherosclerosis by stimulating the growth of new blood vessels, called angiogenesis.

Dr. Stegmann first heard of unwanted angiogenesis in oncology, where blood vessel growth enhances the growth of cancerous tumors. "What they didn't want, we would like in cardiovascular patients who have occluded, calcified vessels," he recalls. Dr. Stegmann reports that he was the first doctor in the world to treat atherosclerosis with fibroblast growth factor in 1995. By injecting it directly into ischemic tissue, the procedure does not raise the risk for tumorigenesis. As a safety precaution, patients with a history of cancer are excluded from CVBT's studies of fibroblast growth factor to treat ischemic disorders.

Human fibroblast growth factor is the active ingredient in the company's biopharmaceutical product, CVBT-141, previously called Cardio Vascu-Grow. CVBT manufactures its fibroblast growth factor at a GMP facility that it maintains in San Diego and uses bacteriophages as a biofactory. Compared to E. coli or mammalian cell methods, "phages are more elegant and less expensive," says Dr. Stegmann, and the resulting protein emerges already folded and active.

### Mending More Than Hearts

The company just completed a Phase I study and is starting a Phase II trial of fibroblast growth factor in coronary heart disease. Angiography reveals that, in just 12 weeks, fibroblast growth factor injected close to clogged blood vessels induces the formation of new blood vessels and capillaries. Once blood flow is established through the sprouting of new blood vessels that bypass the damage site, patients with cardiovascular disease experience an increase in life expectancy and quality of life.

CVBT is also evaluating fibroblast growth factor in peripheral artery disease. When atherosclerotic lesions block blood vessels in the legs, it becomes painful to walk, a condition called intermittent claudication. Circulation to the foot and leg can become so reduced that amputation is needed.

"If left untreated, peripheral artery disease increases the risk of heart attack, stroke, amputation, or death," says

Dr. Stegmann. The multicenter Phase I trial will treat patients with intermittent claudication with injections of fibroblast growth factor. Patients' legs will be evaluated before and after treatment with MRI to quantify changes in blood flow.

In another Phase I trial, fibroblast growth factor formulated as a cream will be applied externally to treat wound, such as diabetic ulcers. "Chronic wounds often never heal because they need perfusion, an arterial blood supply, and oxygen," Dr. Stegmann explains.

Also, a proof-of-concept study conducted in Russia will study patients with chronic back pain caused by degenerative disc disease. Many of these patients have atherosclerosis of the lumbar arteries that nourish back muscle and tissue. "Some orthopedic surgeons believe that degenerative disc disease is an ischemic condition," Dr. Stegmann says. Patients whose angiograms show occluded or calcified lumbar arteries will be injected with fibroblast growth factor to regenerate blood vessels.

A similar feasibility study will take place at the Orthopedic Education and Research Institute of Southern California in Orange, coordinated by orthopedic surgeon Vance Gardner, executive director of the facility.

In the near future, Dr. Stegmann plans to use fibroblast growth factor to treat stroke. Animal experiments indicate that angiogenesis could repair the damage done to blood vessels by blood clots during a stroke. However, before starting a Phase I trial in stroke patients, "we want to advance our studies in other conditions first," Dr. Stegmann adds.

In all of these medical conditions being treated, fibroblast growth factor works the same way. The protein stimulates the growth and multiplication of two main cell types found in blood vessels—smooth muscle and endothelial cells. Receptors in hypoxic cells are sensitive to fibroblast growth factor, which promotes angiogenesis locally.

### Next Standard of Care

Dr. Stegmann first treated coronary heart disease patients 11 years ago, and the angiogenesis induced by fibroblast growth factor remains permanent for most of them. A few coronary heart disease patients require a second injection years later if the disease progresses to a different location in the heart muscle. Since the treatment acts locally and is not a cure, other sites may require injections over time, "but most patients need only one injection," Dr. Stegmann says.

At the start of 2006, Dr. Stegmann resigned his position as director of the department of thoracic & cardiovascular surgery at Fulda Medical Center in Germany, to work full time at CVBT. "It is the logical next step for me to intensively advance CVBT's drugs and to finally get FDA approval," he says. His goal is to make fibroblast growth factor the standard of care for people suffering and dying from cardiovascular diseases that are characterized by lack of blood perfusion.