be salvaged in association studies where the focus is not so much on the correct call of a particular base in the sequence, but instead on pattern alterations when the hybridization signals from two genomes are compared. The pattern changes could then be followed up using other types of analyses. Finally, it goes without saying that analytical tools and algorithms capable of analyzing data generated from whole genomes must be developed to handle the comparisons. It is no easy task to compare two genomes from each of 1000 patients with a particular disease against those from 1000 normal controls in order to identify the genetic factors associated with a disorder.

Despite the obstacles, Patil *et al.* have shown us that when one sets out to achieve the almost impossible and does something about it, we are one step closer to realizing the dream.

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RETROSPECTIVE

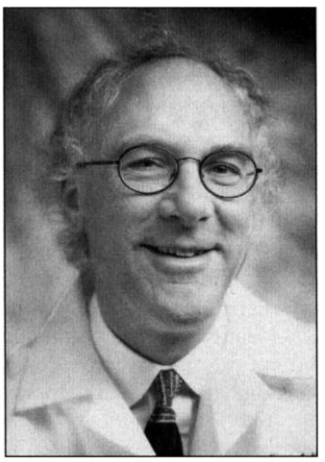
Jeffrey Isner, 1947–2001

Judah Folkman

A pioneer in cardiovascular research and gene therapy, Jeffrey M. Isner died at age 53 of a cardiac arrest on 31 October 2001. His loss is a terrible blow to the world of medicine, and particularly to the field of cardiovascular biology. A professor of Medicine and Pathology at Boston's Tufts University School of Medicine, he also held the positions of chief of Cardiovascular Research, chief of Vascular Medicine, and director of the Human Gene Therapy Laboratory at St. Elizabeth's Medical Center in Boston.

Isner's vision was to revascularize the blood-deprived (ischemic) heart using gene therapy to promote the sprouting of new blood vessels, a strategy called therapeutic angiogenesis. He began to treat ischemic limbs as a bridge to eventually treating the heart. In December 1994, after years of laboratory studies, he and his team at St. Elizabeth's performed the first human cardiovascular gene transfer for a patient suffering from peripheral vascular disease in the legs. Initially, patients received an intra-arterial injection of naked DNA encoding the angiogenic protein vascular endothelial growth factor (VEGF). Subsequently, patients received intramuscular injections of the DNA for VEGF, and many were spared a leg amputation. By 1999, Isner's team was able to report that injecting ischemic heart muscle (myocardium) of patients with naked DNA improved collateral blood flow to the heart. The VEGF gene was delivered by a catheter that reached the heart's left ventricle through a percutaneous insertion into the femoral artery. The tip of the catheter entered the left ventricle, and the DNA was injected into ischemic sites in the wall of the heart, as determined by an elegant method of electromechanical mapping. By August 2000, Isner reported that in 9 of 13 patients with advanced heart disease, inactive heart muscle was working normally. Recently, his team had submitted for publication a paper reporting the beneficial results of a placebo-controlled double-blind trial of VEGF gene therapy for ischemic myocardium. This week, investigators in Switzerland also reported a successful placebo-controlled clinical trial of angiogenic gene therapy of the heart, using a different gene but confirming the principle that Isner had pioneered (*1*).

In 1997, Isner's laboratory reported the surprising discovery that endothelial progenitor cells enter the circulation from the bone marrow and that their numbers can be boosted by systemic administration of VEGF. When Isner first presented this result at a Gordon Research Conference in 1995, it was met with disbelief. But Isner persevered because he could foresee the possibility of isolating these cells from a patient's blood and returning them to the myocardium to augment revascularization. What no one could foresee was how rapidly this discovery would be confirmed by other investigators—within a year—and how important it would turn out to be for tumor angiogenesis (the growth of new blood vessels that nourish tumors). This month's *Nature Medicine* carries a landmark paper detailing how circulating endothelial progenitor cells contribute to tumor angiogenesis (*2*).



I knew Jeffrey as a colleague and friend, and had the greatest respect and admiration for his pioneering research. His patients were devoted to him. He was always in good humor. He made them laugh. He gave hope to the hopeless. Even if a leg had to be amputated, the patient felt deeply that everything possible had been done to avert this course. Isner was devastated by a temporary Food and Drug Administration (FDA) hold on his clinical trials, not for personal reasons, but because he worried about sick patients denied therapy. He was elated when the FDA subsequently gave him approval to move ahead. He was a wonderful mentor to his staff, students, and postdoctoral fellows. He cared for them as though they were family. He always gave them credit and worked hard to develop their scientific self-confidence. He was especially proud that of the 24 postdoctoral fellows that he trained, 16 had either won Young Investigator Awards from the American Heart Association, or were selected as finalists. When Takayuki Asahara's paper on endothelial progenitor cells was accepted by *Science* (*3*), he was invited by Isner to celebrate at one of Boston's finest restaurants. Isner's work has received worldwide recognition and numerous awards, including a 10-year MERIT Award from the National Institutes of Health, and in September of this year a 5-year Program Project grant for a Center of Excellence in Gene Therapy.

Jeffrey Isner left a path for others to follow. His legacy will continue as physicians learn to treat ischemia of the heart as a chronic manageable disease. The clarity of his vision is best evoked in a recent essay by Lance Morrow (*4*), who described the similarities of his own heart attacks and their therapy to those of U.S. Vice President Cheney. Morrow wrote, "A couple of years ago, I drew ahead of Cheney in the fancy-therapy category by having DNA injected into my myocardium in order to induce the growth of new vessels—angiogenesis, a still experimental but highly promising technique which has, in my case, worked miraculously well."

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