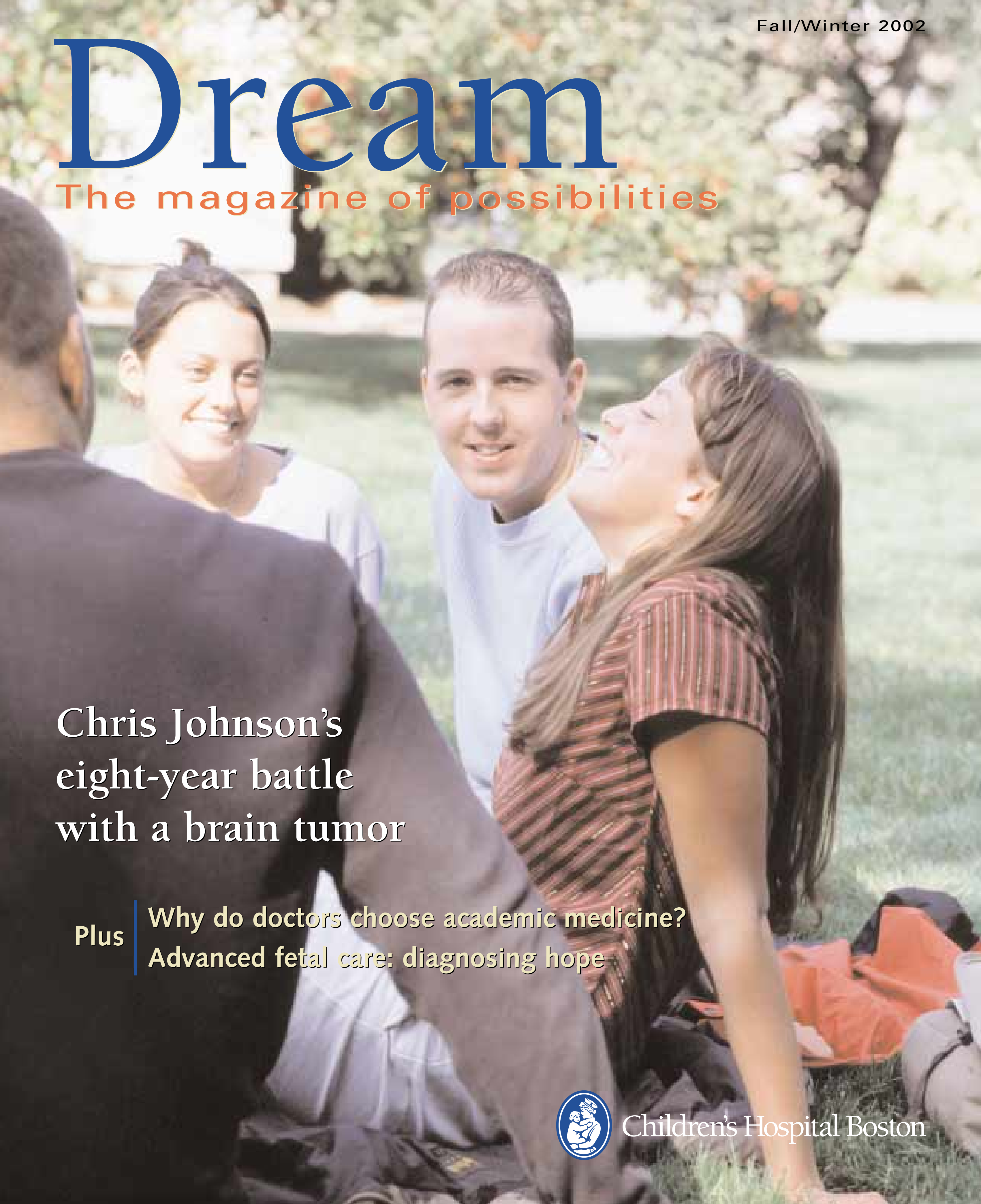
Fall/Winter 2002

Dream

The magazine of possibilities



Chris Johnson's eight-year battle with a brain tumor

Plus
Why do doctors choose academic medicine?
Advanced fetal care: diagnosing hope

Children's Hospital Boston

A new science comes of age

Thirty years ago, Dr. Judah Folkman revolutionized cancer research when he found that blood vessels feed disease. Today, his Children's colleagues are applying that discovery to eye diseases.

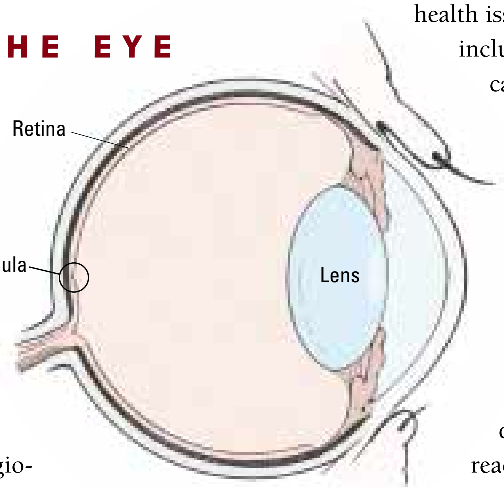
Karen Moulton, MD, mulls over the best way to characterize the Surgical Research Laboratories at Children's Hospital Boston. She pulls out an old article and underlines a favorite quote about how to plan and organize scientific inquiry. "Find a bunch of very bright and very imaginative investigators," it instructs, "pack them together in quarters as crowded as possible, consistent with free breathing, and hope for the best."

The words capture the essence of the 10th floor of the Enders Research Building, where hallways are plastered with posters summarizing recent discoveries, cluttered lab benches in each room overflow with files, reference books, beakers and instrumentation, refrigerators rattle and hum as if overwhelmed by their task of preserving tissue samples and newly isolated proteins, and workspaces are crammed so close that intimate collaboration and sharing seems inevitable. Here, Moulton and dozens of other investigators are learning how to control angiogenesis—the body's process of forming new blood vessels—and studying the role of that process in everything from cancer to eye disease.

It was in the Surgical Research Laboratories more than three decades ago that Judah Folkman, MD, director of the labs, pioneered the field of angiogenesis with his insight that new blood vessel formation is essential to the growth and proliferation of tumors, and that by cutting off that blood supply a cancer could be starved into remission. What began as a revolutionary approach to cancer has evolved into one of the most exciting areas of scientific inquiry today. Over the years, Folkman and a growing team of researchers have isolated the proteins and unraveled the processes that regulate angiogenesis. They studied a chemical that triggers blood vessel growth, called vascular endothelial growth factor, or VEGF, and have found a growing number of ways to inhibit it and other growth factors. Folkman's quest for safer, more effective cancer treatments has led to a field with nearly 50 anti-angiogenesis drugs already in clinical trials. Meanwhile, a new generation of angiogenesis research has emerged as well, widening the field into new areas of human disease and deepening it to examine the underlying biological processes responsible for those diseases.

When Children's completes construction of its new research tower in 2003, the Surgical Research Laboratories will move into a new, state-of-the-art facility dedicated to the ever-growing clinical applications of angiogenesis. These applications span many areas of human health, including cancer, arthritis and fertility. And some of the most promising investigations involve two eye diseases known as macular degeneration and diabetic retinopathy. These leading causes of blindness result from pathological blood vessel growth, and the search for ways to treat them holds important implications for all health issues involving angiogenesis—including the field that started it all, cancer treatment.

THE EYE



Blood vessels and blindness

One area of promise is the potential to treat the most debilitating complication of macular degeneration, known as choroidal neovascularization (CNV), which is associated with aging. With 200,000 new cases diagnosed every year, CNV is reaching epidemic proportions. CNV occurs when abnormal blood vessels begin to grow from a normal layer of blood vessels under the retina. The vessels then leak and bleed, lifting up the retina in the same way tree roots can break apart a sidewalk. Currently there are very few treatments available for CNV.

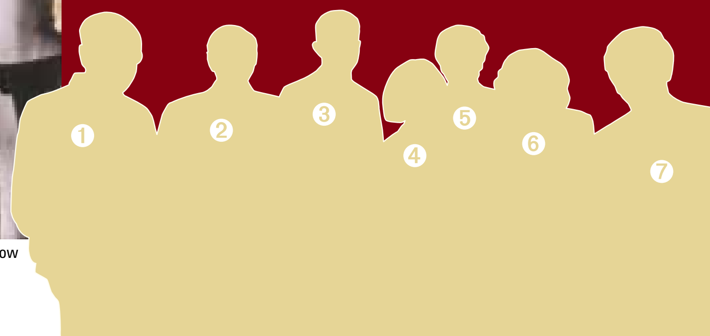
One option is a laser surgery that burns away retina cells along with the runaway blood vessels. But work done by Robert D'Amato, MD, PhD, a senior investigator in the Surgical Research Labs, recently demonstrated that a drug he discovered in 1993, known as 2ME2, can prevent macular degeneration in animals. D'Amato and his colleagues delivered 2ME2 to rats and rabbits via a tiny eye implant like the ones they hope could eventually deliver such drugs to human eyes. The method successfully stopped the animals' new blood vessel growth—and the onset of blindness.

Illustrations: Harriet Greenfield

Photo: Mark Ostow

A new generation

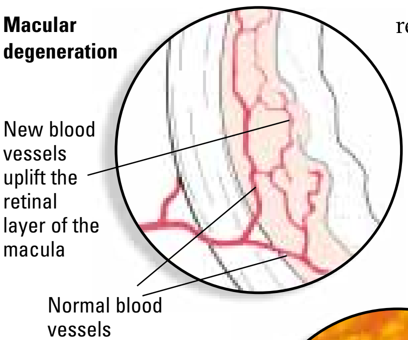
More than 30 years ago, Judah Folkman, MD, found a revolutionary new way to think about cancer. He postulated that in order to survive and grow, tumors require blood vessels. The growth of new blood vessels is called angiogenesis, and Folkman's quest to control this process—and ultimately starve cancers into submission—established a new field of medicine. While research on anti-angiogenic cancer treatments continues at Children's and around the world, a new generation of angiogenesis researchers are working to better understand the process and its effect on a host of other conditions.



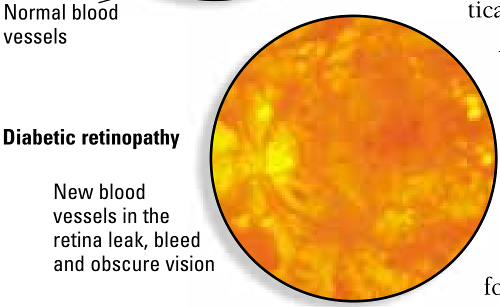
1. **Judah Folkman, MD,** is considered the world's preeminent expert on angiogenesis and the father of this new field of medicine.
2. **Michael Klagsbrun, PhD,** studies the structure, function and mechanism of chemicals that trigger blood vessel growth.
3. **Robert D'Amato, MD, PhD,** discovered that thalidomide, a drug abandoned for causing birth defects, is an angiogenesis inhibitor effective in treating certain cancers. His work is discussed in depth in the feature story.
4. **Patricia D'Amore, PhD,** is a world leader in understanding the abnormal growth of new blood vessels that cause many eye diseases. Her work is discussed in depth in the feature story.
5. **Donald Ingber, MD, PhD,** studies how cellular structure and mechanics affect biochemical function. His work led to the development of one of the first angiogenic inhibitors.
6. **Marsha Moses, PhD,** focuses on the enzymes involved in angiogenesis and the development of tumors.
7. **Yuen Shing, PhD,** is known for finding the naturally occurring chemicals that control angiogenesis.
8. **Bruce Zetter, PhD,** (not pictured) investigates how various chemicals responsible for controlling angiogenesis provide clues for better cancer diagnosis and prognosis.
9. **Joyce Bischoff, PhD,** (not pictured) has contributed to understanding capillary formation. Her major focus is the function of cell adhesion in angiogenesis.

Researchers have had even more success understanding angiogenesis in diabetic retinopathy. This late-stage complication of diabetes is the leading cause of blindness in American adults and is characterized by the abnormal growth of blood vessels across the surface of the retina. As in macular degeneration, these vessels are leaky, and fluid and blood escape into the eye, obscuring vision. These vessels grow because the regular blood vessels in the eye are damaged by the glucose irregularities of diabetes and cease to transport blood, leaving parts of the retina with insufficient nutrients and oxygen. The retina then releases VEGF, stimulating new blood vessels to grow in a botched attempt to fix the problem. It's a biological error that creates maverick blood vessels and leads to blindness. The solution? Blocking VEGF—which is exactly what a number of drugs currently being tested in humans attempt to do. Some of the most promising drugs in this area are being developed by a privately held pharmaceutical company with the expertise of Anthony Adamis, MD. Adamis pioneered much of the Surgical Research Laboratories' work on CNV and diabetic retinopathy before taking temporary leave from his Children's and Harvard Medical School positions to conduct research for the company.

Macular degeneration



Diabetic retinopathy



Raising basic questions

Cell biologist Patricia D'Amore, PhD, an investigator with both the Surgical Research Laboratories and the Schepens Eye Research Institute in Boston, began studying diabetic retinopathy as a way of posing questions about the basic mechanisms of angiogenesis. Because the blood vessels formed in diabetic retinopathy sit across the top of the retina, they are relatively easy to see and study. Also, since the onset of VEGF seems to be linked to the glucose irregularities of diabetes, D'Amore has a good idea where to look, on a molecular level, to understand how VEGF is triggered. "What you'd really like to do is go far enough back in the origins of the disease that you never get that VEGF production," she says. "So my group's research is looking not just at blocking the angiogenic factor after it's made, but at preventing it from being made in the first place." This fundamental understanding of the mechanisms of angiogenesis is medically significant far beyond the problem of eye disease, D'Amore explains, with implications for any biologic process related to the growth of blood vessels. "The same molecules are involved in all of these cases, with some fine-tuning in how the angiogenesis is controlled, depending on the tissue and the disease process."

> "If you just knock on the door and say, 'how does this relate to what you're doing?' you get amazing interactions and cross-disciplinary thinking."

While D'Amore is using eye disease to investigate the molecular mechanisms of angiogenesis, Robert D'Amato is looking even deeper, to examine how genetics influence the likelihood of different individuals growing new blood vessels (or conversely, to inhibit their growth). While studying the clinical applications of 2ME2 for treating CNV, D'Amato was intrigued by the fact that almost no African Americans develop the disease. Guessing that pigmentation might be linked to an ability to resist new blood vessel growth, he decided to test the theory in mice. To do this he exposed both white and black mice to growth factors that encourage new blood vessels to grow—and found that not only did different strains of mice have different sensitivity to the chemicals, but in fact black mice were ten times more likely to inhibit angiogenesis than white mice. (D'Amato notes that it isn't pigment itself that inhibits blood vessel growth. In genetic code, unrelated traits are often packaged together, and it seems that some of the genes involved in controlling angiogenesis just happen to be linked to the genes for pigmentation.)

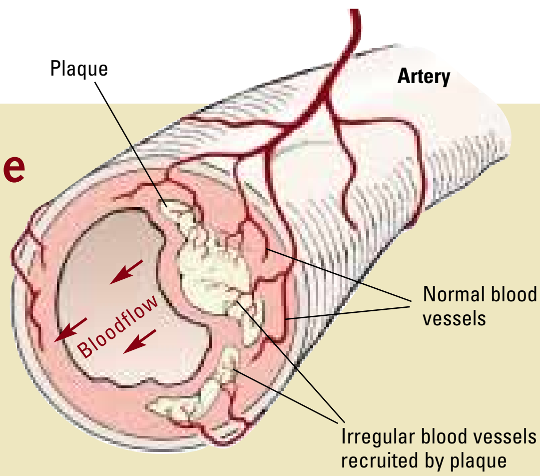
"This was really strong support for the idea that genetics control individual angiogenic potential," says D'Amato. And because he was able to associate this trait so strongly with pigmentation, investigators now have a good idea of where they should look on the mouse genome to find the gene or genes that control angiogenesis; if they find it, the mouse gene may provide a map to the corresponding human gene. And if they can manage that, they may be able to mimic that response with a clinical treatment.

D'Amato says it was immediately obvious that his finding was even significant for the disease that started it all. "It got us to think about cancer in a totally different way. Standard thinking has always been that cancer spreads faster in some people because their disease is more aggressive. But perhaps it's not the tumor, but the person who's more susceptible." Clearly, D'Amato found more than an answer to his original question.

Cross-disciplinary thinking

Maria Rupnick, MD, PhD, who studies the angiogenic properties of fat tissue, explains that the breakneck pace of angiogenesis research is why the labs on the 10th floor of Enders are so collaborative. "The growth of blood vessels requires a lot of different biological processes," she says. "The

Cancer treatment holds hope for heart disease



In 1999, Karen Moulton, MD, a clinical cardiologist and investigator in the Surgical Research Laboratories, discovered that anti-angiogenesis drugs designed to fight cancer had the potential to treat another devastating illness: heart disease. Moulton found that in mice, the drugs dramatically reduced the growth of arterial plaque—the accumulation of tissue and cholesterol that blocks blood flow in large blood vessels, and causes heart attacks and strokes.

That's because the plaque tissue in the wall of the large artery signals new, smaller blood vessels to grow into the plaque—but these tend to leak, bleed and attract cells that inflame the major blood vessel. The growth of these small blood vessels is typically restrained until some molecular cues flip the "on" switch, and the small blood vessels proliferate. Moulton's challenge now is to find the molecular "on" and "off" switches and learn how to control them. "I think these blood vessels can explain the precipitous change in the plaque that leads to heart attacks," she says.

Moulton's discovery could eventually lead to better prevention, and perhaps even reversal, of heart disease. That may be a long way off, but Moulton predicts that the cardiovascular systems of cancer patients on some anti-angiogenic treatments may show benefits that will raise a lot of basic scientific questions. When they do, she says, "Hopefully, I will have some of the answers."

relationship between these processes touches the work of investigators throughout the lab. It requires change in cellular shape, and it requires breaking down the membrane and the stuff in between the cells. These are the kinds of things people are studying here. And if you just knock on the door and say, 'how does this relate to what you're doing?' you get amazing interactions and cross-disciplinary thinking."

It is the same cross-disciplinary thinking that pushed angiogenesis beyond the realm of cancer research to begin with. "Processes that we learned about in tumors have turned out to be universal principals," D'Amore says. At the same time, new research in other areas is making contributions to the study of cancer. "My group started studying VEGF in the eye, and then we got a grant to study its regulation in breast tumors. Now we're also involved in a project with Dr. Folkman specifically studying a model of pancreatic cancer," says D'Amore. "The difficulty is not in translating the work to other fields. It's in keeping up with all of the angiogenesis research that Dr. Folkman's discovery has inspired, not just here but all around the world."

"What often happens in science," explains Rupnick, "is that you publish your results after you've sorted out the questions you were going to ask, what your conclusions are, and what their significance is, and you put it together so that it's easy for people to understand. But the work certainly didn't happen that way. It never goes so smoothly from question to methods to conclusion." In the Surgical Research Labs at Children's Hospital Boston, every conclusion opens up ten more questions, every interaction opens up ten more possibilities, and ideas flow from bright and imaginative people, packed together as close as possible—consistent, of course, with free breathing.

—*Cyril Manning*

Children's Hospital Boston is seeking $25 million in philanthropic funding to establish a state-of-the-art Angiogenesis Research Institute in the hospital's new research tower. The institute will advance angiogenesis research and clinical applications in fields including cancer, blinding eye diseases, heart disease, arthritis, psoriasis, fertility and hemangiomas. For information on funding opportunities, contact Lynn Susman in the Children's Hospital Trust at (617) 355-5344 or lynn.susman@chtrust.org.

wonder why? children's provides answers

Children's Hospital Boston researchers developed a new screening tool to detect the prevalence of teen alcohol and drug disorders, and found that nearly one in six teens had a diagnosis of substance abuse or dependence, and 43 percent said they had been in cars when the driver was high or had been using drugs or alcohol. The tool, called CRAFFT (an acronym for the six questions on the screening), was developed by John Knight, MD, and his colleagues in the Center for Adolescent Substance Abuse Research.

Not the same old song and dance

Children's programs show value of alternative therapies

While acupuncture and massage are often used as alternative therapies for people in need of relief from pain or stress, two Children's Hospital Boston programs show that sometimes all patients need is an alternative *to* therapy to make them feel better. After all, sometimes the best medicine is the kind you don't even know you're getting.

Berklee College of Music student Lorrie Kubicek plays a duet with patient Timothy O'Brien.

The music therapy program, established in 2001 with funding from the Children's Hospital League, brings the joy of music to patients' bedsides. For the patients, playing instruments takes their minds off of a sometimes frightening place. "Engaging these children with songs truly puts their minds and bodies at ease," says Child Life Specialist Ingrid Dahlin, who often uses her guitar to raise the spirits of cancer patients.

Another hospital program brings children with special needs together outside the hospital to socialize. Mickey Cassella, PT, acting director of Physical Therapy at Children's, came up with the idea of a dance class where children with Down Syndrome could interact in a fun and active atmosphere. She contacted the Boston Ballet, who agreed to lend the use of a studio, and her friend Gino DiMarco, a Boston Ballet dancer, who volunteered to run the class.

Boston Ballet dancer Gino DiMarco congratulates Isaiah Lombardo on completing the class.

DiMarco taught the children some unique steps, including chugging around the studio as a train, doing the wave and ending every class with a group hug.

Janet Slemenda, whose son Nicholas didn't want to take part in the class because "ballerinas wear dresses," noticed a big change by the time the class was over. "He was really disappointed when it ended. He's still talking about how much fun he had."

Cassella hopes the program can be expanded and used as a model for dance companies throughout the country. "Even though these children have special needs they love playing with others their age and need activities to boost their self-esteem, just like any other child."