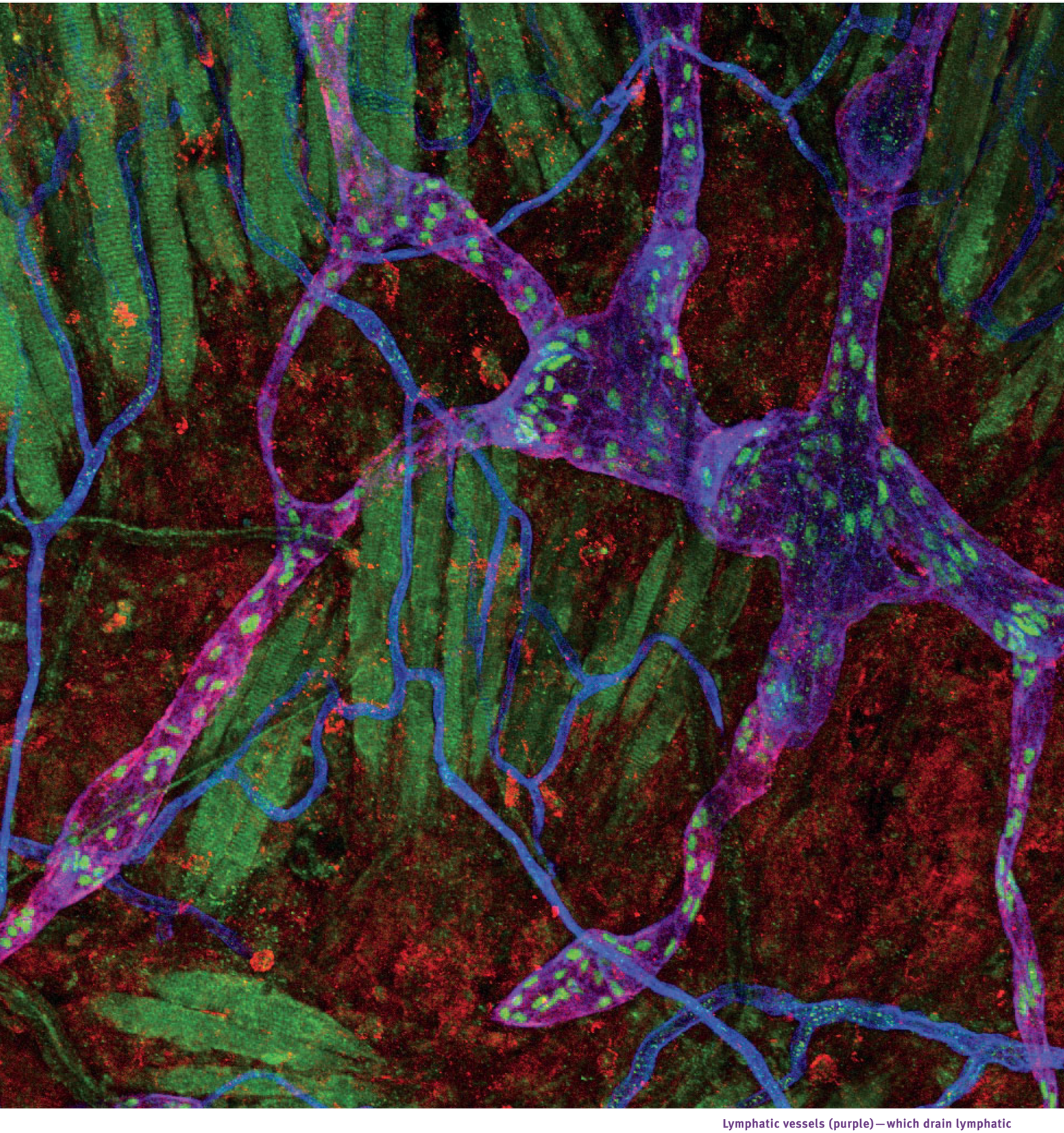
Explorations and revelations taking place in the medical school



Lymphatic vessels (purple)—which drain lymphatic fluid from tissue—next to blood vessels (blue)

THE FAMILY THAT ASSAYS TOGETHER

THE GENETICS OF LYMPHEDEMA REVEALED AT A REUNION | BY ALLISON A. CURLEY

Nearly two decades ago, Pitt's David Finegold (BS '68, MD '72, Res '75), professor of pediatrics and medicine, and Robert Ferrell, professor of human genetics in the Graduate School of Public Health, were chatting over a cup of coffee. Finegold mentioned that his wife, physiatrist Judith Esman (Res '87), worked with patients with lymphedema, an often-disabling retention of fluid (usually in the limbs) that results from abnormal drainage of the lymphatic system. Ever the curious geneticist, Ferrell asked his usual question: "Is it ever inherited?" As it happened, Esman was treating a father and his twin daughters for Milroy's disease, a hereditary form of lymphedema. In fact, many members of this family were affected, and they were willing to participate in research. Finegold and Ferrell couldn't pass up the opportunity to study an obscure disorder that was clearly genetic, and so they set out to identify the genes underlying Milroy's disease.

Some days later, the researchers rented out a local fire hall and hosted a family reunion. At one end of the hall were cookies and coffee and at the other, blood draws and clinical exams. The team collected DNA samples from 40 family members; others mailed in samples later. Such was the beginning of the largest-ever genetic study of heritable lymphedema, the Pittsburgh Lymphedema Family Study, which now includes more than 300 families worldwide.

Three years in, Finegold and Ferrell identified the first-known causative gene, which codes for a protein named VEGFR3 and is important in the development of the lymphatic system. They went on to find three more of the seven known causative genes—and have pinpointed the genetic culprits in about a third of the families they've studied.

The lymphatic system is a network of vessels that collect fluid from tissue throughout the body and deliver it to the bloodstream and lymph nodes. Hereditary (or primary) lymphedema, in which the system develops abnormally, occurs in roughly one in 6,000 people.

Far more common is secondary lymphedema. Secondary lymphedema occurs in about 30 percent of women treated for breast cancer; for many years, doctors assumed it was a result of the trauma of surgery, chemotherapy, or radiation. But not everyone in treatment gets lymphedema, so Ferrell and Finegold reasoned that trauma probably isn't the only cause. They suspected that genes played a role in this form of lymphedema, too, and set out to prove it. "If we're right, and we can identify a subset of women who are going to be at risk, we can potentially start preemptive treatment, such as massage and compression garments," says Finegold.

Secondary lymphedema occurs in about 30 percent of women treated for breast cancer.

In April, the team published results of a study that examined several candidate genes in a population of women with secondary lymphedema following breast cancer treatment. They found that these women—but not healthy women or those with breast cancer who hadn't experienced secondary lymphedema—had mutations in the gene coding for connexin 47 (Cx47). The researchers had previously implicated the gene in primary lymphedema.

Drawing on the expertise of research assistant professor of cell biology Catherine Baty, who joined the team in 2008, the researchers also examined the functional consequences of the Cx47 mutations. Connexins are the primary components of structures called gap junctions; recent evidence suggests they are important in the movement of lymph fluid. The investigators reasoned that the deficits resulting from the mutations may be subtle, because patients don't develop the condition until after the insult of cancer treatment. Using cultured human cells with mutations introduced, they showed that proteins trafficked normally to the cell surface but exhibited other functional impairments.

Ultimately, the team hopes that knowledge of the underlying genes could lead to a cure. In fact, drugs modifying the function of connexins are already available; they were initially developed for cardiovascular disease.

The findings could also have implications for wound healing among other conditions linked to fluid imbalance, says Ferrell. He calls lymphedema a "window on lymphatics" and a way to identify genes that are important in the functioning of the lymphatic system as a whole. ■

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