NEUROSCIENCE

Breaking the Brain Barrier

A new understanding of the blood-brain barrier as a living, mutable organ may revolutionize the treatment of diseases such as cancer and Alzheimer's

By Jeneen Interlandi

During one of his famous staining experiments of the late 1800s—the kind that would eventually lead to a cure for syphilis and a Nobel Prize for Medicine—Paul Ehrlich stumbled on a conundrum that would haunt medicine down to the present day. When he injected dye into the bloodstream of mice, it penetrated every organ except the brain. Kidneys, livers and hearts turned a dark purplish-blue, clear and stark under his microscope, but the brain remained a pale whitish-yellow. When a student of his injected that same dye directly into the brain, the opposite happened: the brain itself turned blue, whereas the other organs did not. Clearly, the student thought, a barrier—in German, *Blut-Hirn-Schranke*—must exist between brain and blood.

It would take half a century and a microscope roughly 5,000 times more powerful than Ehrlich's for anyone to actually locate this barrier, hidden as it was inside the brain's blood vessels. The average human brain houses roughly 400 miles of such vessels. They bend and twist in an endless array of tangled loops, ultimately ensnaring every single one of the human brain's 100 billion or so neurons. The walls of all these vessels are lined with endothelial cells. To be sure, endothelial cells line the interior of all of the body's vasculature, but they are much more tightly packed in the brain's vessels than they are anywhere else in the body, which explains why neither Ehrlich's dyes nor most of the medications in existence could cross from the bloodstream into the brain.

But long before they could visualize the barrier, doctors had come to both revere and avoid it. "For ages we saw it as like a

Illustration by Alex Nabaum