Heart, Lung, and Blood Institute.

Nabel has worked on gene therapy for AIDS, therapeutic cancer vaccines, and a candidate Ebola vaccine, but he is a relative newcomer to AIDS vaccine work. He says, however, that his experience prepares him well for his new job, and he jokes that his limited AIDS vaccine research "should be an advantage because I'm not invested in old ideas that didn't work."

Nabel's background sits fine with Nobel laureate David Baltimore, head of NIH's AIDS Vaccine Advisory Committee—and Nabel's former postdoctoral adviser. "I have high hopes that Gary will be a great leader," says Baltimore, noting that Nabel is an "excellent manager" who is "widely knowledgeable in immunology and virology, giving him the perfect perspective for taking on this role."

One aim of the VRC—an idea first proposed by NIH immunologist William Paul—is to move fundamental research results more aggressively into clinical trials. But beyond that, its agenda is still largely up in the air. "It depends a lot on how Gary wants to build it," says Fauci. "We decided early on that we're going to put a lot of flexibility in the hands of the director."

A five-story building to house 100 VRC scientists is now going up at NIH's Bethesda, Maryland, campus. "The assumption is that the majority of the people are going to be brought in from the outside," says Fauci. Nabel, who starts his new job next month, plans to keep his Michigan lab running until the building is ready for occupants, by the middle of 2000. **–JON COHEN**

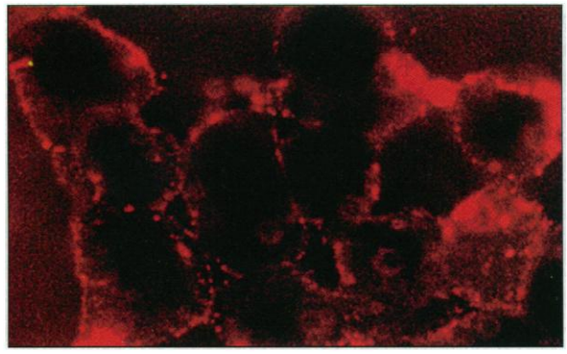
CANCER RESEARCH

A Surprising Partner For Angiostatin

The proteins angiostatin and endostatin have generated a lot of excitement in the past year or two because of reports that they can stop or slow cancer growth in mice, apparently by preventing the birth of new blood vessels needed to nourish growing tumors. But as potential therapies, they have a built-in drawback: Protein drugs can be fragile and hard to produce, as the pharmaceutical company Bristol-Myers Squibb acknowledged last month when it announced that it was giving up work on angiostatin. Efforts to get around those problems by developing small molecules that would mimic the effects of these proteins have been handicapped because little is known about how they act. Now, a research team at Duke University Medical Center seems to have solved part of that puzzle, at least for angiostatin.

The team, led by Salvatore Pizzo, reports in the 16 March issue of the *Proceedings of the National Academy of Sciences* that angiostatin binds to a surprising target on the surface of the endothelial cells responsible for blood vessel growth: an enzyme called adenosine triphosphate (ATP) synthase, never before found on the outer membranes of normal cells. The team can't say if this is angiostatin's only target on the cells, but they have evidence that the binding is necessary for angiostatin's antigrowth effects.

"This paper is important because of all of its implications," says Judah Folkman of Harvard Medical School in Boston, in whose lab angiostatin was discovered. For one, it may provide an explanation for endothelial cells' ability to grow in very low oxygen environments such as tumors. ATP synthase manufactures the energy-rich molecule ATP and thus may be providing endothelial cells with an extra energy source. If angiostatin's binding to the enzyme blocks its activity, that could be the means by which the protein prevents blood vessel growth. What's more, the work suggests that small molecules tailored to block ATP synthase might mimic angiostatin's effects and be useful as anticancer drugs. The paper "is sure to be very provocative," says ATP synthase researcher Gordon Hammes of Duke University.



Energized. Fluorescently labeled antibodies (red) to ATP synthase show the presence of the enzyme on human endothelial cells.

CREDIT: T. L. MOSER *ET AL.*, *PNAS* 96, 2811 (1999)

Tammy Moser, an associate researcher in Pizzo's lab, uncovered the enzyme in a search for endothelial cell proteins that bind angiostatin that she undertook on the assumption that such proteins help angiostatin stop cell growth. From a preparation of endothelial cell membranes, she fished out an angiostatin-binding protein and sent it to Peter Højrup at Odense University in Denmark. Using mass spectrometry, Højrup determined that what Moser had found was actually two proteins, the α and β subunits of ATP synthase. Because that enzyme was thought to be present only in the energy-producing organelles of higher cells, "our reaction was shock," Pizzo recalls.

By probing endothelial cells with antibodies that bind to the α subunit of the ATP synthase, the researchers soon confirmed, however, that it is indeed on the endothelial cell surface. They also found that the antibodies decreased angiostatin binding to the cells by more than 50%. This in turn led to an 80% decrease in angiostatin's ability to inhibit endothelial cell growth, which suggests that angiostatin works at least in part by binding to the ATP synthase. The Pizzo team recently acquired antibodies to the enzyme's β subunit and plans to see whether those block any of the remaining effects.

The ATP synthase could play a key role in the survival of endothelial cells, which live, Folkman notes, "in the lowest oxygen of all cells." Those in the capillary beds that drain tissues are bathed in blood that has been depleted of oxygen by the oxygen-hungry tissues. In tumors, which tend to compress their blood vessels, oxygen levels are even lower, but nevertheless, "you can see tumor vessels coursing through an environment where all the other cells are necrotic" from lack of oxygen, says Duke University tumor biologist Mark Dewhirst.

Normally, oxygen-deprived cells have trouble synthesizing enough ATP to survive. But the ATP synthase in the endothelial cells' outer membranes might produce ATP in a process that doesn't require oxygen. During energy generation in the mitochondria, the enzyme is driven by a gradient of protons across a membrane, produced by the organelle's oxygen-burning metabolism. But in endothelial cells, the gradient could result from the lack of oxygen, which tends to acidify the inside of cells compared to the outside. Endothelial cells could also have a plentiful supply of adenosine diphosphate (ADP) for conversion to ATP, Pizzo notes, because red blood cells release lots of ADP in low-oxygen conditions.

Hammes calls the hypothesis "speculative, but very intriguing." ATP synthase is a large enzyme, made up of many subunits, and the Pizzo team hasn't yet shown whether the whole enzyme is present and functioning in the endothelial cell membrane. The researchers are joining forces with biochemist Richard McCarty, who studies ATP synthase at Johns Hopkins University, to explore that issue. They will also look to see how angiostatin affects the enzyme.

If angiostatin does achieve its effects by inhibiting the enzyme, as Pizzo suspects, drug developers will likely start searching for small molecules that do the same thing. They might work as angiogenesis inhibitors that could be administered by mouth. "If I were a pharmaceutical company," says Folkman, "that's what I would do."

–MARCIA BARINAGA