DISCOVER

Medicine: Napoleone Ferrara
By Deborah Franklin - Photography by Jeff Minton
DISCOVER Vol. 25 No. 11 | November 2004 | Biology & Medicine

NAPOLEONE FERRARA

molecular biologist, Genentech

He trained to be a physician, but his curiosity led him into a job doing basic research. He had to go to Bay Area slaughterhouses to collect cow pituitary glands to study. A substance in the gland put him on the trail of the anti-angiogenesis proteins that could combat cancer.

On his favorite and least favorite parts of the research process:

"My favorite part is when you have an idea, you develop it, you do the right experiments, and things turn out. Everybody loves to see stunning results. They are addictive. You ask any scientist and all will tell you the same thing—looking at data is fantastic. . . . Even during periods when things don't seem to be so good, negative results can be useful to build up new ideas."

The idea seems so simple: Cut off a malignant tumor's food and oxygen supply by preventing it from growing blood vessels and the cancer will wither, unable to spread. But despite promising experiments in the late 1990s, when Boston researchers used the technique to shrink tumors in lab mice, repeated attempts to develop a drug that could do the same thing for people failed—until this year. In February, Genentech's Avastin, the first so-called anti-angiogenesis drug to significantly extend the survival of cancer patients, received Food and Drug Administration approval. The man responsible for this long-awaited development is Napoleone Ferrara, a 48-year-old Sicilian-born molecular biologist at Genentech. Back in the '80s, Ferrara discovered a naturally secreted protein known as vascular endothelial growth factor, or VEGF, that helps blood vessels grow. Years of tireless investigation produced Avastin, which works by selectively blocking the action of VEGF. In a large, randomized study, the drug extended the average survival of people with metastatic colorectal cancer by 30 percent—from 10 months to 15. Avastin is new to the clinic, so side effects are still being tracked, but doctors are cautiously hopeful that patients who get the drug in an earlier stage of their disease could fare even better.

When did you and your colleagues first get the idea that starving a tumor might be a good approach to treating cancer?
F: The idea that blood vessels are important for tumor growth has been around since the beginning of the century. But it was kind of forgotten because the biochemical and molecular tools to follow up did not really exist. Then, in the '60s or '70s, there was a revival of this idea, and the main champion at the time was Judah Folkman. He was the first one who understood the clinical implications of all this. What hampered the field was the difficulty in finding and identifying a tumor angiogenesis factor. Lots of molecules can induce angiogenesis, but very few turn out to be physiologically important.

Did you recognize VEGF immediately for what it was? And how long did it take to get from that point to an FDA-approved drug?
F: We did some early work when I was at the University of California at San Francisco and noticed some sort of factor in the pituitary gland that seemed to be very important in endothelial cell growth. We sequenced it in January 1989. From then until now was 15 years or so.

Has Avastin turned out to be everything you hoped it would be?
F: First, let's make sure the readers understand that the molecule that we isolated was VEGF, and it has turned out to be physiologically very important. It's essential for embryonic development, bone growth . . . it's one of the most fundamental genes. Knock out just one copy and the embryo dies. It's important also for female reproductive angiogenesis—really for many physiological processes. So it shouldn't be surprising that it's also important in many pathological processes: tumors, various bone diseases, probably also rheumatoid arthritis.

The drug—Avastin—is an antibody to VEGF. We first made a monoclonal antibody by injecting VEGF into mice, and then that antibody was humanized through engineering and is hardly immunogenic at all in patients because it is 93 percent human.

Why doesn't Avastin turn off beneficial processes that are important to good health when it blocks VEGF?
F: VEGF is extremely important in certain periods of development—in embryonic development or early postnatal development. In an adult, it turns out to be mostly important in cyclical angiogenesis, like the female reproductive cycle, and to some degree for wound healing. But other than that, mature blood vessels seem to be relatively independent of VEGF.

How do you pick which group of patients you'll test the drug in first?
F: In this case, the drug worked against virtually every kind of tumor in the animal models. And the early clinical data showed very broad efficacy. I still suspect that if you treat early in the process, the majority of tumors will respond to some degree. We chose colorectal cancer because, unfortunately, there are a relatively large number of people for whom bleeding is the first symptom that they have advanced, metastatic colon cancer. It was a big group of untreated people.

How is Avastin administered?
F: It's given intravenously—systemically—typically every two or three weeks.

Where is this field headed?
F: First of all, of course, anti-angiogenesis isn't limited to cancer. There are other exciting applications, such as against macular degeneration, a disease of the eye. Genentech is in phase III trials with a fragment of Avastin that could help there. And, in fairness, another company has a similar approach with positive data.

Is drug resistance still a major obstacle in chemotherapy?
F: Yes, I think it is, especially in the most lethal cancers. Eventually they stop responding to the drug.

So the only way to get around it at this point is to diagnose the cancer earlier and also hit it hard early on?
F: Yes, and also hit multiple targets. I think a good analogy is HIV. If you hit it only with one drug, you get a small effect, but if you hit it with more than one drug, each with a different mechanism of action, you can achieve a very powerful effect.

Along the spectrum from enthusiastic to critical, where do you think you stand?
F: I'm pretty enthusiastic. Science can be exciting. If you're always and only self-critical, you never produce a thing. You have to be both, that's the thing.