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Persistence—luck—Avastin

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News

"If I say I was delighted, it will be an understatement," said Napoleone Ferrara of Genentech (Figure 1) to the JCI when asked how he felt on February 26, 2004, when the FDA approved Avastin for colorectal cancer treatment. This culminated Ferrara's more than 15-year involvement in its development. FDA approval came after of one of the most successful phase III anticancer drug trials in history. The trial consisted of 925 patients diagnosed with previously untreated metastatic colon cancer. Comparison of the median survival time of patients treated with irinotecan/5-fluorouracil/leucovorin (IFL) chemotherapy and Avastin to that of patients treated with IFL and a placebo showed that those receiving Avastin had a median end-point survival time of 5 months longer than those without. This met the primary efficacy endpoint, and was also the greatest difference in median survival time ever seen in a phase III trial. Avastin is the first antiangiogenesis drug to receive FDA approval. It inhibits vascular endothelial growth factor (VEGF), a main protein involved in inducing angiogenesis. In the last several years, interest in finding antiangiogenesis drugs for anticancer therapy has peaked. The idea, though, of inhibiting new blood vessel growth as a means to block tumorigenesis is not really a new one. It has been around since the early 1900s: in a seminal study, Gordon Ide and […]

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While FDA approval of Avastin is only the beginning for a new line of anticancer treatments, it marks the end of Napoleone Ferrara's long road from the identification of an intriguing biological molecule to the development of a viable drug.

Ferrara's history with Avastin began in 1989, when he was working on another project — one focused on Genentech's then main research interest: cardiovascular disorders. He identified and purified a pituitary gland protein that stimulated vascular endothelial cell growth — that protein was VEGF.

At that time, "no one really thought this would be therapeutic," Ferrara said. "But [Genentech] has this great policy that allows people to pursue their own interests." So, Ferrara, thinking it might be useful for anticancer therapy, continued to work on VEGF.

A breakthrough came in 1993, when Ferrara and colleagues developed a mouse antibody that blocked VEGF function and inhibited tumor growth in mice (2).

At that time, Ferrara said, these results "were really surprising. It was thought that one would need to block many factors to inhibit angiogenesis."

Napoleone Ferrara's persistence pays off.

Ferrara said they then "had to convince management [to pursue this] — but overall they were very supportive." More difficult was the creation of a humanized form of the mouse anti-VEGF antibody. "Ultimately," Ferrara said, "we obtained what is now called Avastin, which is extremely effective and not immunogenic."

Ferrara told the *JCI* that when Avastin entered clinical trials, one very encouraging aspect was that the side effects seen in the trials were "very mild."

"What you see mostly," he said, "is modest hypertension. In phase II there was an indication of increased thrombosis, but [we] didn't really see this in the phase III trials." The resulting hypertension is not surprising, as VEGF induces nitric oxide, which is involved in blood pressure regulation.

"The beauty of a monoclonal antibody [as a treatment] is its specificity," Ferrara added. "Small molecule therapies can sometimes [have interactions] with other molecules, especially at higher doses, and cause side effects from activity unrelated to the targeted molecule." A monoclonal antibody specifically interacts with only one protein and therefore only affects the pathways in which that protein is involved.

Everything for Avastin looked incredibly good — until September 2002, when Avastin failed to meet its primary efficacy endpoint of progression-free survival in a phase III breast cancer trial.

"This was really disappointing," Ferrara said, but noted he still had some hope. "It did not increase the survival, but there was some evidence that the treatment shrank some tumors in the trial. Also, these patients were in third-line therapy [meaning they had already been treated by two other methods that had failed]. This is a very high bar for a trial. The patients were in a much more advanced stage and very sick."

Another positive sign was the preliminary results from a phase II renal cell carcinoma trial, which did meet its primary efficacy endpoint (3). That trial was the first step toward FDA drug approval. Most important, however, was the successful completion of the phase III colorectal cancer trial described above.

Avastin is currently in several other phase III anticancer clinical trials, as well as trials for other disorders where angiogenesis is involved; for example, a shorter form of Avastin, called Lucentis, is already in phase III trials for age-related macular degeneration.

When the *JCI* asked Ferrara how best to travel the entire road from isolated protein to approved drug, he answered with a laugh, "You need to be persistent — or lucky — or a combination of those."

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