



On The Cover/Top Stories

Medical Merlins

Robert Langreth Zina Moukheiber, 06.23.03

Behind every breakthrough drug is a handful of unknown geniuses who conjured up what no one had dreamed of before.

"Discovery consists of seeing what everybody has seen and thinking what nobody has thought."

--Albert Szent-Gyorgyi, 1937 Nobel Laureate in Medicine

The Single-Minded Sleuth

Twenty years ago biologist **Napoleone Ferrara** discovered a mysterious protein in the pituitary gland of cows that seemed to make blood vessels grow. He foresaw a new weapon against cancer--block the protein and tumors may be unable to proliferate--but the finding was so obscure that even his boss was skeptical. Last month the drug that resulted from Ferrara's work began to look like a success: **Genentech** (nyse: [DNA](#) - news - people) unveiled trial results that showed it extended colon cancer patients' lives by a median of five months, or 30%, one of the bigger advances in years.

The drug, Avastin, could hit the market by year-end, joining existing anticancer chemicals and radiation as standard therapy for colon cancer--and it could end up working against other cancers. Thus, Avastin, which blocks VEGF, the protein Ferrara first isolated, could become the first entry in a new way to treat cancer--antiangiogenesis, which shuts down tumors by quelling their ability to form the new blood vessels that feed their expansion.

"It is a big achievement," says Judah Folkman of Harvard's Children's Hospital Boston. He was an early proponent of antiangiogenesis and is known for the experimental drugs angiostatin and endostatin. "Napoleone had the vision to see before other people that many tumors make VEGF and that you might be able to make an antibody to block it. Everyone said the approach wouldn't work, but he kept going."

In biology every solid clue emerges after a dozen red herrings that can waste years of effort. Ferrara, a charming 46-year-old with a Sicilian accent who is known as Napo ("NAP-oh") to friends, is a medical detective with an unerring knack for knowing what to pursue. "Many people fly by the seat of their pants in science," says Genentech pathologist Kenneth Hillan. "Napo has an incredible nose for knowing when to follow up on something. Even when his ideas seem wacky to start, they pan out." Rivals at other drugmakers, Hillan says, are students of virtually

every experiment he has done.

Dr. Ferrara joined Genentech as a junior scientist in 1988, and his colleagues were charmed by the slightly disheveled Sicilian who drove to work on his Yamaha VMAX motorcycle and paced the hallways, muttering to himself, when his work was going well. He had grown up as the only child of a judge and graduated from medical school in Catania, Sicily in the early 1980s, intent on practicing obstetrics. Curious about research, he snared a two-year postdoctoral stint doing biology research at the University of California, San Francisco. There he was handed the low-priority task of exploring the basic science of the pituitary gland. That meant frequent treks to the slaughterhouse to collect cow samples.

One day he mixed follicular cells (an extract from the cow pituitary) with blood vessel cells. To his great surprise, the blood cells started multiplying like mad. He theorized that the pituitary cells were secreting a protein--some unknown elixir among several thousand proteins the organ churned out--that instructed blood vessels to sprout tendrils. Skeptical colleagues believed he had merely rediscovered the well-known fibroblast growth factor. Ferrara couldn't prove otherwise because he wasn't able to isolate the protein and lacked enough evidence to publish his theory.

But his gut told him he was right, so he scrapped plans to begin an obstetrics practice in Sicily, instead staying in San Francisco to devote himself to research.

Though he was hired by Genentech in 1988 to work on a pregnancy drug, he concentrated on the tedious work of isolating the cow protein he had stumbled upon years earlier. Driven by the idea that he might discover something totally new, he labored nights and weekends for months, filtering out thousands of other proteins until he finally separated the right one in 1989 and cloned the human version of the gene that produces it. He named it Vascular Endothelial Growth Factor, or VEGF (pronounced "VEJ-ef"), for its ability to act as a molecular fertilizer for blood vessels while having little effect on other tissues. (Monsanto found it at around the same time.)

He realized, five years before Harvard's Folkman would discover angiostatin, that blocking VEGF with a specially tailored drug might lead to a totally new type of cancer therapy. Ferrara's team and others showed that many tumors secrete large amounts of VEGF to spur nearby blood vessels into growing new branches to supply the tumor. The more VEGF a tumor contains, the more it is likely to grow. By 1993 Ferrara's Genentech colleagues had engineered a monoclonal antibody that latches on to the VEGF molecule and disables it so it can't dock onto its receptor in blood vessels. The antibody dramatically slowed the growth of tumors in mice, but persuading executives to launch costly human trials was a struggle. At the time Genentech focused on heart disease, not cancer. Ferrara kept coming back at them with more data. "He is kind of unstoppable," says Hillan. "He keeps pushing and pushing his ideas," until they prevail.

Human trials of Avastin began in early 1997 and proceeded with little fanfare until mid-1998, when Harvard's Folkman landed on the front page of the New York Times. A media frenzy ensued over Folkman's success at wiping out tumors in lab mice. Ferrara's bosses fretted over whether Genentech was pursuing the right strategy. He urged them to stay the course, noting that the mechanism of Folkman's drugs was unclear and that the results hadn't yet been reproduced. Sure enough, it took years to reproduce those animal findings, and angiostatin and endostatin have been delayed while their backer Entremed looks for a new partner.

Initial trial results for Avastin in colon and kidney cancer were promising, prompting Genentech to start large-scale tests. But Avastin failed to help breast cancer patients in a study of 462 women completed last fall. Many analysts wrote off the drug entirely. Ferrara felt as if he'd been punched in the stomach. Everything now was riding on the big colon cancer trial, with results due in May 2003. As the outcome neared, Ferrara found it harder to sleep. He was in Italy on May 18 when he received an urgent message to call Genentech Chief Arthur Levinson. He expected mixed news at best. Levinson told him to sit down: The drug had far exceeded expectations. Ferrara, feeling a wave of relief, was speechless.

Ferrara hopes Avastin is just the start. He has been mulling other diseases involving VEGF, including eye problems characterized by a proliferation of blood vessels. Genentech is testing a derivative of Avastin, rhuFab V2, in patients with macular degeneration, a leading cause of blindness. It is now in final-stage human tests. Some 25 trials of Avastin are under way, targeting tumors of the kidney, lung, pancreas and liver. VEGF research has become a cottage industry, with hundreds of new studies emerging every year. Resulting drugs could help heal severe wounds and treat heart and liver diseases.

Back in his lab Ferrara is working furiously to figure out how tumors can become resistant to Avastin. One theory, which may explain its failure against breast cancer, is that there may be tissue-specific proteins that spur tumor growth in the absence of VEGF. "This is a long-term quest, and we can't assume that blocking VEGF alone will be enough," he says. "I try to do my work and move on--and not get stuck waiting for Godot."

The Chemical Cobbler

Most chemists in the drug industry go their entire careers without working on a drug that makes it to market. **John J. Talley**, 51, has four on sale. In the 1990s he led the tiny team of chemists at **Monsanto** (nyse: [MON](#) - [news](#) - [people](#)) that invented the stomach-friendly painkillers Celebrex and Bextra. The two drugs, now sold by Pfizer after myriad mergers, reap \$3.5 billion in combined annual sales.

Now Talley is searching for his fifth hit. Last year he quit his secure job at **Pharmacia** (nyse: [PHA](#) - [news](#) - [people](#)) to lead research at a no-name biotech shop working on antifungal drugs. It is a vexing pursuit; only one new drug class has emerged in 15 years. The firm, Microbia in Cambridge, Mass., has spotted 80 genes that fungi use to morph from harmless to deadly form, infiltrating vital organs in patients with weak immune systems. Talley must invent a compound that gums up the action of bad genes and their proteins.

Designing a drug is akin to machining an oddly shaped part to fit a slot whose exact design is not yet known. Drugmakers can synthesize 10,000 new chemicals before finding one that can slip harmlessly through the body and disable one bad protein without disturbing good ones. Talley has an unusual ability to feel his way toward the right component.

"He has almost an innate taste for what is the right molecule, a feel for the direction he wants to go," says Mark Currie, a longtime colleague. Adds Peter Isakson, who led the Celebrex team: "It's an instinct that you can't teach. You either know it or you don't."

A heavy-smoking, baseball-capped Iowan, Talley has an encyclopedic knowledge of chemical compounds. He can draw from memory the precise structure of almost any drug, dissecting their flaws and attributes atom by atom. "I like to think every atom is there for a reason," he says. He always carries a black leather notebook so he can scribble down new molecular structures as they float into his mind at any time of the day. At home he sometimes relaxes by reading USAN, an annual dictionary of newly named compounds, to get ideas.

Talley stumbled into chemistry at the University of Northern Iowa after finding business classes unbearably dull. After grad school at the University of Minnesota and a stint at GE's labs, he ended up at Monsanto's Searle unit in St. Louis in 1986.

His first years were frustrated by near misses. He spent years on a blood-pressure project, but the molecular target was a dud. He designed early protease inhibitor drugs for AIDS, but the lead molecule failed in trials. In 1991 a new research head, Philip Needleman, shifted the focus to

aspirin substitutes that avoid causing ulcers. Needleman's theory was that one could spare the stomach by selectively blocking the enzyme responsible for inflammation, COX-2 (cyclooxygenase-2), while avoiding the one involved in maintaining the stomach lining, COX-1.

It proved to be devilishly difficult. The only difference between the two types of cyclooxygenase is a small pocket that protrudes, like the thumb of a glove, from the main binding site. Talley needed to modify existing painkillers so that they attached only to enzymes with the protrusion. Six chemists spent long nights paging through piles of dusty chemistry journals in the Monsanto library to see if anyone had invented a COX-2 inhibitor without realizing it. In early 1992 two colleagues got wind of an old DuPont compound that seemed to fit the bill. Talley's chemists rushed to dissect the DuPont compound and improve it. The crux: a six-atom side chain that fit neatly into the thumbhole. Talley tweaked it to boost potency and limit potential side effects.

Merck also was working on COX-2, but Monsanto beat it to market, getting Celebrex out in January 1999, five months ahead of Merck's entry, Vioxx. Talley's second COX-2 entry, Bextra, was approved last year, beating out Merck's second version. Talley got a \$40,000 bonus for his breakthrough.

Monsanto merged with Pharmacia in 2000, and the new guard emphasized computerized gene-hunting, robotic chemistry and other gizmos. Talley grew disillusioned, convinced the tech glitz was diverting drugmakers from the way medicines were really discovered--by individual artists.

When Microbia wooed him last year, he was intrigued. He knew firsthand how badly new drugs are needed: His father-in-law, weakened by cancer, died from a fungal infection in 1998. Upon his arrival he dumped two of Microbia's three lead compounds. His gut said they would be prone to side effects, so he bet everything on the third.

Each day Talley's researchers inch closer to that magic combination of properties that is a drug. They hope to have a compound ready for human trials next year. But the competition is intense--both Merck and Pfizer sell antifungals and are pursuing advances. Talley is back in his element: chasing another win. "I'm really close to something," he says, eyes afire. "I feel really good about this."

The Maverick and the Maestro

Some scientists are almost apologetic about their hunches. **Craig Smith** is anything but. Smith, 52, is the voluble half of an odd couple of **Amgen** (nasdaq: [AMGN](#) - [news](#) - [people](#)) scientists whose early work led to Enbrel, the billion-dollar blockbuster targeting rheumatoid arthritis. He is a passionate, messy, untamed biochemist bursting with more ideas than he could ever pursue. "His mind is going 47 different directions at once," says a former colleague.

Everything is magnified in Smith's world. One drug he is working on "is the most exciting development in cancer research in eons;" another "cures lupus" in lab animals. He heaps scorn on distracting projects. A drug that flopped in the 1990s was "ludicrous beyond human comprehension," and another "had no chance of working" but the study went on because the company brass at what was then Immunex (now Amgen) "didn't have the slightest idea of what was going on."

"Craig drives some people crazy, but I trust him. He tends to be right," says Smith's research partner, **Raymond Goodwin**, who stays out of the spotlight. Goodwin, also 52, is the counterbalance--a quiet, neat, hyperefficient gene cloner. In the days before the genome was decoded and posted on the Internet, he was a master at fishing new genes out of the cellular soup.

In an eight-year heyday in the 1990s at Immunex, the two men helped discover some of the most important new drug targets in decades, unearthing a family of immune-system genes. Enbrel, concocted in 1989, targets the prototype member of this gene family: tumor necrosis factor. The drug, remarkable for attacking the molecular causes of autoimmune disease, was the main reason biotech giant Amgen acquired Seattle-based Immunex for \$17.7 billion last year. Amgen says Enbrel's sales, now at \$1.3 billion, could hit \$3 billion in a few years.

And Enbrel is just the beginning. Smith and Goodwin and their Immunex colleagues discovered nearly a dozen new TNF relatives. Drugs targeting them may one day treat diseases as diverse as psoriasis, multiple sclerosis, lupus, osteoporosis, heart disease, even cancer.

The two biochemists met in the late 1980s, soon after Smith arrived at Immunex. Goodwin recalls seeing a terrific mess inside a nearby lab and wondering who made it. Craig Smith was the culprit. He had been hired to work on a class of immune-system proteins called interleukins, but he had a better idea: He proposed, instead, that the two of them work on cloning the receptors for TNF.

It was an unlikely choice. Tumor necrosis factor, named for its ability to make cancer cells shrivel and die in the test tube, had largely fizzled in human tests because it was too toxic. But Smith figured excess TNF might cause autoimmune diseases such as rheumatoid arthritis or lupus.

The two used a new technique called expression cloning to fish out the TNF receptor in a mere three months. They devised the Enbrel molecule by fusing a copy of the receptor to the base of another protein, so it would float in the blood and sponge up excess TNF. After a bumpy road through human trials--Enbrel flopped as a sepsis remedy before Immunex found the arthritis application--it won approval in late 1998.

Smith and Goodwin, believing TNF had sibling receptors that also influenced the immune system, eventually found several more. Smith chanced upon one gene, dubbed 4-1BB, one night at 2:30 a.m. while surfing the Internet; it may play a role in lupus. Now others are in the hunt for new TNF genes. The most promising is Trail (TNF-related apoptosis-inducing ligand), spotted in a database in 1995 by Steven Wiley, a protégé of Goodwin and Smith at Immunex. In the test tube, Trail causes cancer cells to kill themselves while sparing normal cells. The possibility of liver damage has delayed human trials, but Smith is, as ever, impatient. "It's the perfect cancer killer," he says.

So far his new bosses at Amgen are letting him be, but he dreams of going off on his own. He has received thousands of Immunex options for his work on Enbrel; at his own boutique, Smith would reap far bigger riches for his next blockbuster.

The Tireless Hunter

Some miracle drugs emerge from eureka moments, but more often a new compound results from years of meticulous, plodding work championed by a relentless true believer. And so it is for a drug approved last month to treat a deadly cancer of the blood known as multiple myeloma.

Velcade, from **Millennium Pharmaceuticals** (nasdaq: [MLNM](#) - news - people), is the first new treatment approved for myeloma in a decade. Myeloma afflicts 50,000 people a year and kills 70% of patients within five years of diagnosis. Yet in middle-stage trials Velcade shrank tumors in 28% of 188 patients who had failed two other therapies; 20% went into remission. Those results so impressed regulators that they approved the drug in only four months. "It's a dream of a lifetime," says chemist **Julian Adams**, 48, head of drug discovery for Millennium.

Eight years earlier, when Adams first tested his drug on six lab mice, every one of them died from side effects. But Adams is a hunter who never gives up. He doggedly shepherded Velcade through development and believed in it when no one else would, saving it from oblivion when two successive mergers could have killed it. "Velcade is a testament to Julian's tenacity and brilliance," says John Littlechild of HealthCare Ventures, a backer.

Adams developed his relentless style after graduating from the Massachusetts Institute of Technology and joining Merck & Co. in 1982, working with Robert Zamboni, who created the popular asthma drug Singulair. Zamboni taught him the importance of seeing a drug from inception through human trials. "He imbued in me the spirit of the drug hunter," Adams says of his onetime mentor.

Adams left Merck in 1987 to make a name for himself at the German drug firm Boehringer Ingelheim. Two years later, as head of the company's Ridgefield, Conn. chemistry lab, he led the team that synthesized Viramune, the first in a new class of HIV drugs called non-nucleoside reverse transcriptase inhibitors. (Viramune grossed \$370 million last year.)

Five years later Adams joined ProScript, a startup in Cambridge, Mass. founded by a quartet of Harvard professors. The four were focused on the proteasome, a complex of proteins in cells that work as molecular garbage disposal units, engulfing and chopping up proteins when they are no longer needed. Only a handful of papers had explored the proteasome. "It was fresh. I love the thrill, and the thrill seemed perfect."

The Harvard profs tinkered with ways to block proteasomes in the hopes of treating disease; in need of an expert drug hunter, they signed him up. Clues hinted that some proteins might be signals for cancer cells to multiply. Adams theorized that blocking the proteasome with a drug might overload tumor cells with proteins, causing the signaling mechanism to short-circuit. Adams tracked down a researcher at the Max Planck Institute in Germany who had just mapped the 3-D structure of the proteasome, which was shaped like a six-ringed cylinder. Using this data, Adams in 1995 concocted an unusual boron molecule that snuggled into one of the enzyme's active sites and blocked its function. In test tubes the compound destroyed tumor cells. ProScript then raised \$37 million from HealthCare Ventures, Aventis and Roche.

Adams' team of 35 scientists spent two years tinkering with dosages to reduce toxic side effects, settling on twice-weekly injections that slowed tumor growth in mice but didn't kill them. "We built up our courage," he says. In 1998 he began a trial of 60 patients with various tumors.

The following year he received some results that gave him hope. One patient's prostate tumor temporarily shrank, and two patients, one with lung cancer and one with neck cancer, also responded positively. But the drug's potential toxicity still was a problem, and ProScript was running out of cash. At one tense meeting a scientific adviser told Adams he wouldn't give the drug to a relative.

"It was a new target and a new mechanism; people looked at it and said this is way too risky," recalls HealthCare Ventures' Littlechild.

In a last-ditch rescue effort Adams lined up \$2 million from private investors and put up \$250,000 of his own money to try to buy the drug. HealthCare Ventures nixed his offer and sold ProScript to LeukoSite, one of its portfolio companies, for \$2.7 million in June 1999. Angry, the Harvard founders quit, but Adams stayed on, determined to see the project through. Six months later his efforts were disrupted again when Millennium bought LeukoSite for \$635 million. Millennium was mostly interested in LeukoSite's leukemia drug, Campath.

Adams began lobbying hard for his drug. "He was in my office all the time, saying, 'We need more money, more people,'" says Mark Levin, Millennium's chief. Adams even arranged for Levin to

have dinner with doctors who were testing the drug. More data trickled in, showing the drug was especially helpful in myeloma. One 41-year-old North Carolina woman went into remission and is still alive.

The data--and Adams' unwavering faith--persuaded Levin to make Velcade the centerpiece of Millennium's cancer program. Midstage trial results were so promising that Millennium applied for federal approval this year, even before final-stage trials were completed. Now Adams is rushing to test Velcade on tumors of the colon and lung. He aims to boost the response rate by combining it with chemo. Always restless, he is plotting his next hunt: "We have a lot of exciting drugs."



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