PROFILE CLAIRE FRASER

TIGR's Chief: Results Without the Roar

Since Fraser took the reins in 1998, The Institute for Genomic Research has doubled its budget and expanded its agenda

Claire Fraser shares a passion for molecular genetics with her husband, J. Craig Venter—but not his headline-grabbing style. The two have worked side by side for 20 years studying many of the same topics, from human brain cells to bacterial genes to the latest genomics techniques. But they couldn't be farther apart in the way they present themselves and their work.

Take DNA sequencing. Venter seemed to relish the attention he and his former company, Celera Genomics in Rockville, Maryland, got when they were competing with a public consortium to sequence the human genome. As the race rumbled to a noisy finish in 2001, Venter and his rivals traded barbs in the press about the quality of each other's data. In January 2002, when the race was over, Venter made news again by abruptly stepping down as Celera's president, saying he didn't want to be in the biotech business any longer. Three months later, he disclosed that most of the DNA in Celera's human genome was his own—and that he plans to write a book about it.

Venter is explosive—like a firecracker, colleagues say—whereas Fraser is a steady candle, a calming influence on those around her. The difference between the two is "almost like night and day," says W. Richard McCombie, a molecular biologist at Cold Spring Harbor Laboratory in New York. Fraser does not seek the limelight, yet her contributions have earned her a seat on many of the panels that have shaped the course of genome research in the United States.

Moreover, since 1998, Fraser has presided over one of the most influential DNA research centers in the country, The Institute for Genomic Research (TIGR) in Rockville. Venter founded the institute 10 years ago, but it was Fraser who led it to its recent triumphs. Since 1998, its budget has climbed from $24 million to more than $50 million, its staff has grown to more than 300, and it is now the undisputed world leader in microbial genomics. Just 7 months ago, the National Institute of Allergy and Infectious Diseases (NIAID) awarded TIGR $25 million to set up a functional genomics center that would enable researchers from all over the country to study gene expression and other aspects of pathogens.

Bugs and brains

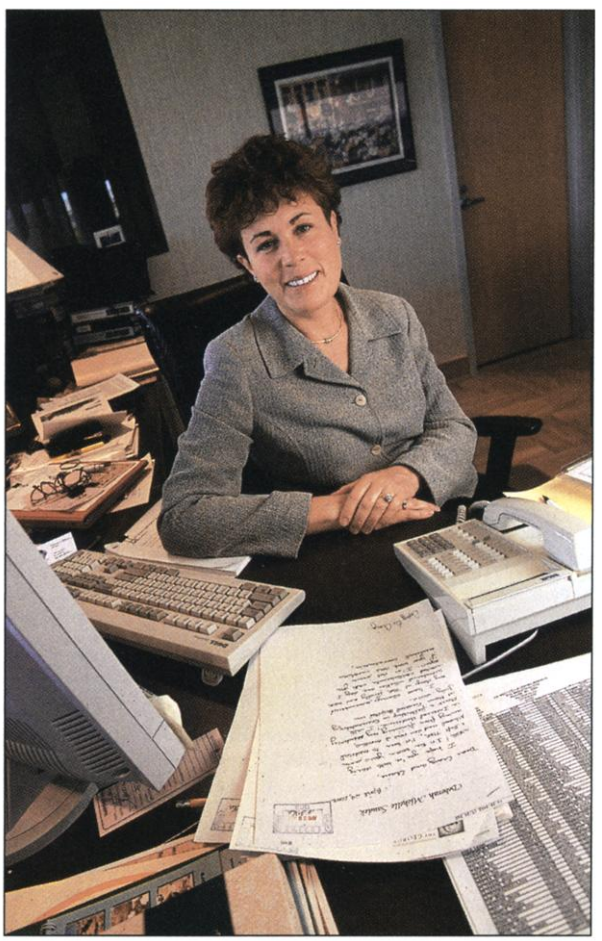
At first, Fraser didn't intend to study microbes; 25 years ago she was set on a career in medicine. But when she was a premed student in her senior year at Rensselaer Polytechnic Institute in Troy, New York, she opted to do an independent research project on nearby Lake George. She was looking for bacteria that could feed on pesticides and fertilizers and thus clean up pollution, a field now known as bioremediation. The taste of research made her hungry for more, although she hadn't settled on a field.

Indeed, she chose her graduate school—the State University of New York (SUNY), Buffalo—not because it was the best academic fit but so she could be close to a boyfriend in Toronto. "I ended up in a graduate program in Buffalo probably for the wrong reason," she concedes. Nonetheless, excited about the possibilities, she began checking out labs in her home department, pharmacology.

Fraser found a place in a lab Venter was running at SUNY—a move that would transform her life in unexpected ways. Venter was then studying how neurotransmitters interact with their receptors, and she joined in. Four years after working together, the two married in 1981, the same year she earned her doctorate. "Unlike so many men I had encountered, he was the first who was not the least bit threatened by my potential for success," says Fraser.

Three years later, she and Venter moved to the National Institutes of Health (NIH), "a dream come true," Fraser recalls. She continued studying brain receptors, first in Venter's group at the National Institute of Neurological Disorders and Stroke. By 1987 Venter had moved on to making gene sequencing faster and more efficient, and Fraser had taken on her own research group. But in 1988 she was denied tenure. "It was the first and probably only time that the old-boy attitudes of science really hit home," she says. Too "reticent" to fight the decision, Fraser instead started a new lab in molecular neurobiology at the National Institute on Alcohol Abuse and Alcoholism, where her group looked for receptors important in addiction and alcohol tolerance. But when Venter resigned from NIH in 1992 and invited Fraser to join him at a new nonprofit research institute, she didn't hesitate.

Together they became leaders in a gene-discovery project that Venter had tried to convince higher-ups at NIH to invest in but ultimately launched with private money. It worked by capturing random fragments of DNA—called expressed sequence tags (ESTs)—and using them to reconstruct genes. After NIH turned down his request to scale up his operation, a private investor offered to set Venter up in a specially tailored arrangement, giving him a nonprofit research center that would be partnered with a biotech company called Human Genome Sciences. Venter agreed, and TIGR's doors opened in 1992.



CREDIT: RICK KOZAK

Convert. Fraser began her career studying microbes and environmental remediation; now she is a leader in microbial genomics.

Despite her excitement about the new EST project, Fraser was not convinced she was in the right place. "I was not fully into the genome thing," she says. She was hoping to use ESTs to learn about a group of cell-signaling molecules called G protein–coupled receptors, important in a wide range of nerve cells, including those involved in taste. But TIGR's agreement with Human Genome Sciences imposed an 18-month delay on the publication of many of her discoveries. "I was increasingly frustrated," she recalls.

By early 1995, Venter and his crew were midway through sequencing the first microbial genome, *Haemophilus influenzae*, and were eager to take on a second—*Mycoplasma genitalium*, which has the smallest genome among free-living bacteria—hoping to begin to define the minimum requirements for life. They were using a fast new approach called whole-genome shotgun sequencing, a method that some had called unworkable. Fraser agreed to shepherd the *Mycoplasma* genome to completion. Some 580,070 bases later, she was hooked. "I had never been so intellectually engaged as when the first gene list was in hand and we had to make sense of the information," she recalls. She and her colleagues spent weeks perusing biochemistry books and journals, "trying to reconstruct the biochemistry of these bugs."

Hitting her stride

Although TIGR's agenda was growing, it faced an unexpected challenge in 1998: Venter left to create a sequencing company down the road, Celera Genomics. When Fraser took the reins, no one was quite sure what to expect. "People were cautious and curious" to see how well she would do, says molecular and cell biologist Rob Fleischmann, who was one of the first scientists TIGR lured away from NIH.

Any doubts are now gone. "TIGR has flourished since [Venter's] departure," says Cold Spring Harbor's McCombie. When TIGR broke with Human Genome Sciences and lost some $38 million in support, Fraser helped her researchers get grants—a new strategy for the institute. Today, TIGR scientists are funded primarily by the Department of Energy, NIAID, and the National Science Foundation.

There were some tradeoffs, however. "Some people miss Craig's approach of always wanting to stir the pot," says Fraser. Impatient, he'd get an idea, call spur-of-the-moment meetings, and expect his ideas to be implemented by the end of the week. "He took up an awful lot of time," she adds. Fraser has guided TIGR with a gentler hand. "When [Venter] was around, people scurried," says Fleischmann. In contrast, "there's a calmness in [Fraser's] leadership." TIGR molecular biologist Malcolm Gardner agrees: "She is perhaps a more steadying influence at the top." Researchers seem to have more time to pursue their own interests, he adds.

Fraser mentors young scientists, such as TIGR microbiologist Karen Nelson, and also goes to bat for them. When several funding agencies turned down Gardner's proposal to sequence a relative of the malaria parasite along with the parasite itself, thus enabling comparative studies, "[Fraser] was so taken by the science that she went to the board of trustees" and got the necessary funds from TIGR's private endowment.

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Under Fraser, TIGR now has a broader focus, expanding its analyses to include more comparative genomics and studies of gene function. Scientists at TIGR are using the institute's vast data collection to study evolution, probe for traits that create pathogenicity, and trace changes in gene expression over time. "They are getting more university-like and doing more science as well as genomics," says W. Ford Doolittle, an evolutionary biologist at Genome Atlanta at Dalhousie University in Halifax, Nova Scotia.

Sequencing remains a major thrust, however. TIGR has now completed a stunning 25 genomes, including that of anthrax, reported online by *Science* on 10 May and appearing on p. 2028 of this issue. About 40 more microbes, two fungi, eight parasites, and five plants are in the works, although not all will be sequenced in toto. The group has also contributed extensively to the *Arabidopsis* and rice genome efforts and has become a central repository for *Arabidopsis* data.

As TIGR celebrates its 10th anniversary this year, Fraser and colleagues are charting an even broader course. Sequencing, TIGR's mainstay, will continue to be important, says Fraser. That means TIGR must stay ahead of rivals and on top of rapidly changing sequencing technology. The same is true for bioinformatics. Microbial and plant genetics will remain key, but the institute's scientists might also move on to mammals. They're also talking about joining the proteomics bandwagon.

Fraser expects that there's "going to be some synergy" between TIGR and Venter's latest ventures: two new institutes, one dedicated to ethics and the other to clean energy and the environment (*Science*, 3 May, p. 824). But the lines of responsibility will be clearly delineated. Although these new ventures will share TIGR's $170 million endowment, they will be independent entities with different, but related, foci.

Whereas Venter's new energy institute will explore how to use microbes to solve energy needs, for instance, TIGR will continue its basic research on these and other microbes. In this way, Fraser and Venter will complement each other, as in the past. "I've been together with Craig for more than 20 years," she explains. "[The relationship] works because we are so different. We represent parts of each other's personalities that each of us wishes we had more of." That winning combination has ensured them a place as pioneers in this very dynamic field of science.

—ELIZABETH PENNISI