Fierce Competition Marked Fervid Race For Cancer Gene

By NATALIE ANGIER

WITH the discovery of a gene that causes inherited breast cancer, the many competitors in this most impassioned and publicly visible of all genetic races find themselves blinking in the sun, still a bit shocked that the long hunt is over.

No one is more surprised, and gratified, than Dr. Mark H. Skolnick of the University of Utah, whose team plucked the gene from a crowded stretch of chromosome 17, and out of the grasp of 12 other teams that had thrown hats and hopes into the ring.

"It was a hard problem and it took almost two years just to get to the right region," said Dr. Skolnick, who worked with 44 colleagues from five institutions. "It's very exciting to win such a race."

With the welcome advantage of hindsight, Dr. Skolnick ascribed his success to relentless hard work, a few missteps by his competitors and an extraordinary genetic resource: Utah's large, stable families and the vast genealogical archives of the Mormon church. Others on the team admitted there was also a strong component of the scientist's best friend. "What do I attribute our success to?" said Dr. Roger Wiseman, one of Dr. Skolnick's collaborators. "Luck."

The losers in the contest express a mixture of relief that the fugitive gene has been found, disappointment that it was not found in their laboratories, and, in some cases, frustration at knowing they probably had a piece of the desired gene but had failed to recognize it for what it was. A number of the defeated had devoted the entire effort of their laboratories for the last four years to the search for the gene, called BRCA1, and some are questioning whether the extreme competition accelerated or impeded the quest.

The medical, emotional and economic stakes were unusually large for a gene hunt. Not only is breast cancer the most hated scourge among women today,

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and a subject on many a politician's and activist's lips, but the identification of a gene linked to the disease offered great practical value in the form of tests to identify women at high risk of the disease and perhaps even new therapies.

Matching the high profile of the coveted gene were the high profiles of many of the contenders. Dr. Skolnick, 48, a former mathematician, made a name for himself 15 years ago, when he helped invent the technique that led to DNA, or genetic, fingerprinting. He has restlessly migrated from one project to another, working in Italy to track genetic changes among different human populations and this spring discovering a widely publicized gene linked to melanoma, a deadly skin cancer.

Three years ago he helped found a biotechnology company, Myriad Genetics Inc., of Salt Lake City, to seek out genes involved in common human diseases. The fledgling company now has a bonanza in BRCA1, for which it has filed a patent.

Among his most fervid and celebrated competitors were Dr. Mary-Claire King of the University of California at Berkeley, who got the race going when she announced the approximate chromosomal location of BRCA1 in 1990; Dr. Francis S. Collins, the director of the National Center for Human Genome Research at the National Institutes of Health and a certified gene jockey who helped find such previous prizes as the genes for cystic fibrosis, Huntington's disease and neurofibromatosis, and Dr. Raymond L. White, another geneticist at the University of Utah, who also helped discover the neurofibromatosis gene and genes involved in colon cancer.

The race was enlivened by longstanding feuds among the principal players, all of whom are known for their intensity, ambitiousness and competitiveness. Many of the quarrels, which are well known in the biomedical field, stem from past collaborations that fell apart, as high-powered scientific collaborations so often do. Like rock musicians, scientists thrive on recognition, and it is harder to get full recognition when one is part of a band.

"There's always competition for a limited resource, and here the resource is genes," Dr. White said. "We're in a world where affiliations

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Dr. Mark H. Skolnick led team that found gene on chromosome

come and go, the rules are rather poorly defined and there are lots of opportunities for misunderstanding." Besides, he said with a whooping laugh, "some of us take pleasure in people not liking us."

Perhaps the main reason behind the intensity of the race was the clarity of the goal. Most scientific problems are amorphous and difficult to frame. In this case, researchers knew that a gene associated with familial breast cancer was located somewhere on the bottom half of chromosome 17. Dr. King and others had demonstrated as much through molecular studies of families in which many women suffered from breast cancer, ovarian cancer or both.

Researchers knew that mutations in the gene gave carriers an 85 percent lifetime risk of contracting breast cancer, often before the age of 50. And they estimated that as many as 5 percent of all cases of breast cancer might be due to inherited defects in the gene.

Knowing the approximate neighborhood of the gene, scientists had only to narrow it down to a particular address. They had to pick through an undifferentiated morass of about a million subunits, or base pairs, of DNA, which probably held scores and scores of genes, as well as confounding stretches between genes.

To do that, all who leapt into the fray took fairly similar approaches. Looking through the DNA in blood cells from families with hereditary breast cancer, they searched for telltale patterns, or genetic markers, that would point toward the gene proper. And when they unearthed promising candidate genes, they checked to see if the gene differed at all between a family member who had the cancer, and one without the tumor.

As always happens in a scientific race, the contenders knew through the genetics rumor mill roughly where everybody was positioned from one month to the next. For a long time, nobody seemed to have the advantage. "Six months ago, I don't think you could have predicted from looking at anybody's strategy who would get there first," said Dr. Collins.

But in mid-July, the Skolnick team realized it had what almost certainly was the gene. "When we finally got toward the end, my first reaction was disbelief, that we can't possibly be correct, we must be missing something," said Dr. P. Andrew Futreal, who works in Dr. Wiseman's laboratory at the National Institute of Environmental Health Sciences in Research Triangle Park, N.C. "But the data kept coming back from Utah, confirming that we had finally landed on the right gene."

In recounting his triumph, Dr. Skolnick emphasized the importance of his team's access to the unusually large families of Utah. One of them, for example, had 40 women who suffered from breast or ovarian cancer. A few revealing patterns in the family's chromosomes allowed the scientists to narrow down the DNA region of study to almost half what the other groups were scratching through.

Some groups went down a dead end by seeking the gene through comparisons with the DNA of other animals, thinking that BRCA1 would very likely be conserved from one mammalian species to the next. As it turns out, said Dr. Wiseman, the breast cancer gene has changed significantly in its passage through evolutionary time, so the zoological approach was doomed to disappointment.

Dr. Walter Gilbert of Harvard University, a co-founder of Myriad Genetics, suggested that Dr. Skolnick succeeded because he kept his collaborative team running smoothly and relatively harmoniously, while some other groups worked under a kind of fission-fusion system, with collaborators sort of collaborating, and sort of competing.

For some of the scientists in the race, those with less astral reputations than the celebrity contestants, the search for the gene was at least partly motivated by pragmatic career concerns. A big discovery brings attention and all the essential sequelae.

"You get more grants, more money, more speaking engagements at scientific conferences, better graduate students and postdoctoral fellows applying to your lab," said Dr. Barbara Weber of the University of Pennsylvania, an unsuccessful contender who said her entire laboratory had devoted every minute of the last three years to finding the gene. "It's also very glamorous. So of course I'm disappointed and frustrated." On the other hand, she said, "you can still look around and say you have your kids and your health. On a scale from 1 to 10, good to bad, this is really no worse than a 5, or maybe a 6."

Dr. Wiseman said of his successful search for BRCA1, "It was the most extraordinary scientific endeavor I've been involved with in my short career." Nevertheless, as someone who came from the relatively obscure and comparatively civilized world of mouse genetics, he found the vitriol surrounding the search for the breast cancer gene hard to believe. "I was shocked by the competitiveness," he said. "It was a real eye-opener."

The winning team has filed for a potentially lucrative patent on a gene.

Despite any lingering grudges, the losers conceded the race with graciousness, complimenting Dr. Skolnick and his 44 collaborators at five institutions for their evident hard, meticulous work. Dr. King, for example, who may have been the scientist most obsessed with finding the gene — "It was her reason for getting up in the morning," said Dr. Collins — and whose personal less-than-tender feelings about Dr. Skolnick are well known to her colleagues , nonetheless described the discovery as "beautiful" and "lovely" and deserving of all the praise it might win.

The researchers realize that their ego disappointments must take a back seat to the considerable and far more pressing problems at hand. Among them are figuring out how the newly discovered gene works in both its healthy and mutant state; how many different mutations in the gene give rise to cancer, and whether some mutations are associated more strongly with breast cancer, and others with ovarian cancer, which is also linked to BRCA1; and what can be done to reverse the effects of a mutation in the gene, resulting in a cure for the disease.

The next question for all researchers in the field is, of course, what now? Some say they plan to study the gene in mouse experiments. Others are already trying to learn where the protein produced by the gene labors in the cell, and what its task is.

Myriad Genetics is moving forward as swiftly as possible to develop a screening test to check for mutations in the gene. Who will benefit from the test and how is not yet clear. Women from high-risk families with mothers, sisters and aunts affected may want to know if they inherited a faulty gene. Others who have only a relative or two with breast cancer may also consider being tested. Yet should a woman test positive, her choices are limited. She can watch and worry and go in for regular mammograms. She can opt for prophylactic mastectomy or try taking the experimental drug tamoxifen, but neither course has been proven to prevent cancer. And she can always hope that a medical breakthrough arrives before her cancer.

"Women will have to be very careful," said Frances Visco, president of the National Breast Cancer Coalition in Washington. "You're talking about giving them a test telling them they have an 85 percent chance of getting a disease that we don't know how to prevent, and for which there is no known cure."