

Tak Mak

The only constant in Tak Mak's career has been change. After jumping from a Jesuit seminary to engineering, to immunology and genetics, the scientific vagabond says he has finally found his true passion.

Newspaper clips, comic blurbs and glossy photos fill three large albums in Canadian researcher Tak Mak's office. Collectively labeled 'the Mak-a-tak!', the books chronicle every milestone of the scientist's career. But what is most striking about the stories they tell is their remarkable diversity: this is not a man with a single focus.

Director of the University of Toronto's Advanced Medical Discovery Institute, Mak has spent the past 25 years chasing one scientific challenge after another in immunology, genetics and cancer. Next year marks the twentieth anniversary of the discovery that hoisted Mak into the global spotlight at age 36—the cloning of the β -chain of the T-cell receptor, a key component of the human immune system.

Technically, the anniversary also belongs to Stanford University immunologist Mark Davis, who described the T-cell receptor gene in the same issue of *Nature*—something that shocked both researchers. "Thousands of people were working on the problem and we thought we were alone [in solving it]," Davis recalls. "We weren't, and there's some trauma that comes with that, but it was fun competing with [Mak]."

Davis soon stopped worrying about Mak as a competitor, because five years after the T-cell work, Mak astonished many by leaving the field completely. "I was getting bored," Mak now says. The scientist cajoled his team to drop all ongoing research and turn instead to making transgenic knockout mice—which lack specific genes—to better understand cellular pathways. Only 5 out of 20 lab members agreed to join him, but they never looked back. The reason, Mak says, is that his new idea led to "another grand slam."

Mak's long-time acquaintance, immunologist Douglas Green of the University of California in San Diego, recalls how scientists at the time regarded Mak's theories about knockout analysis as "wild." "It was far too difficult to make even one knockout mouse, let alone the many required for analyzing pathways," Green says. "But Mak assembled a team of brilliant technicians ... his approach not only worked, it is now one of the central ways we analyze signaling."

The propensity to change direction—successfully—has been a persistent pattern in Mak's life. A descendant of three generations of wealthy Chinese silk merchants, Mak grew up in Hong Kong and was raised a Catholic. His first career choice took him to a Jesuit seminary; he spent three months there before realizing his passion lay in science. He then dropped religion, moved to the US and enrolled in chemical engineering at the University of Wisconsin in Madison. A year in, Mak changed his mind again and switched to his true love—biochemistry. After completing his doctorate at the University of Alberta, Mak moved to Toronto as a postdoctoral fellow at Toronto's Ontario Cancer Institute.

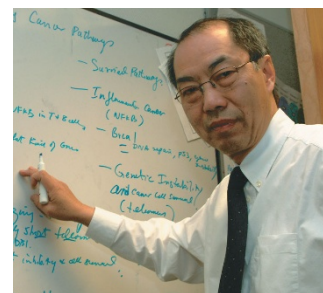
Following Mak's success with knockout mice, Amgen, a California-based biotechnology company, in 1992 gave Mak US\$100 million to build the Amgen Institute with six sparkling new laboratories and a talented staff of 50 researchers. Free of financial worry, Mak and his team dove into scientific discovery. In five years, Mak says, he delivered at least 100 knockout mice and six potential cancer drug targets to his benefactors. In 1999, Amgen gave Mak another \$50 million and pledged funding until 2008.

But the bubble burst last year. A new chief executive officer at Amgen pulled the institute's funding to lower company costs. With the funds that remained, Mak formed the Advanced Medical Discovery Institute. Mak's students sensed the sweeping changes, but say he made sure their research went uninterrupted. "[Mak] kept saying everything was under control," says Hitoshi Okada, a postdoctoral candidate who has worked with Mak for four years. "Nothing changed for me."

Still, some changes were brewing, particularly in Mak's relationships with the institute's other faculty members. In one highly publicized confrontation, Mak accused Josef Penninger, an Austrian immunologist who had worked with him since 1990, of shoddy science and irreproducible results. Penninger denied Mak's allegations and, amidst increasing hostility, resigned.

The rift is still palpable. Penninger and Mak's labs are side by side on the same floor of the Princess Margaret Hospital, but relations between the two remain cool. Scientists in Penninger's lab, which is moving to Austria this fall, say Mak's fame gives him the leeway to mistreat younger scientists, using them to further his own research

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goals even at the expense of their careers. Mak declines to comment on the episode but concedes it was very upsetting. "[The feud] has nothing to do with politics," he says. "It's about science."

Once the controversy died down, Mak drifted toward his growing obsession: cancer. Always drawn to cancer research, Mak's interest magnified when the disease infiltrated his private life. Mak's first wife died of breast cancer five years ago. Shortly after that, his sister also succumbed to the disease. One of his two daughters is a medical geneticist who works with breast cancer patients, and his second wife is an oncologist. "Now till the end of my life I will be immersed in getting at cancer," Mak says.

Many pharmaceutical companies are developing cancer drugs to retard the cell cycle of cancer cells. But that approach is misdirected, says Mak, because once a patient goes off the drug the cells can grow back. Instead of targeting the cell cycle, Mak says, drugs should block survival genes of tumor cells. Researchers in his lab are already cloning survival genes to determine their potential roles in cancer.

In case pharmaceutical companies don't buy into his approach, Mak has raised \$4.25 million to start his own company and isolate potential drug leads. The company's name, Miikana Therapeutics, means 'my path' in Ojibwa Indian. Mak says he chose the name because he realized that curing cancer is his true calling. "In the last five years I finally realized what I really want to do with the rest of my life," he says. "Before I was like a kid on a beach turning over rocks looking for anything interesting. Now I am very focused."

Paroma Basu, Toronto