

A Research Mystery, Maclean's 2003
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Why has controversy dogged one of the world's hottest scientists?

AT HIS PEAK, a couple of years ago, Josef Penninger was one of the hottest, most charming scientists in the world. The now 38-year-old wunderkind from a tiny Austrian farming village had evolved into a delightful Leonardo da Vinci-style genius who quoted Picasso and Beowulf while talking about the mysteries revealed by his mutant mice. He even looked the part, a lithe soccer player with deep brown eyes, a slight German accent and a shaggy Albert Einstein hairdo dyed varying shades of brown.

From his lab on Toronto's hospital row, Penninger, a fearless anarchist, loved to demolish accepted wisdom as he swooped over a stunningly broad scientific landscape -- bone, pain, cancer, heart disease and the immune system. He churned out so many papers in the world's most prestigious scientific journals that for two years running, in 1999 and 2000, the trend-tracker Science Watch said Penninger was among the world's most quoted scientific researchers.

So why is Penninger leaving Toronto? He's been hired away to lead a new research institute in Vienna, but this is not the typical story of a brilliant young scientist lured abroad by money and the prospect of scientific renown. It is, instead, a scientific mystery that began when Penninger's own mentor questioned whether some of the groundbreaking research that made him such a big name in the scientific world was dead wrong. The bitter, vengeful battle that ensued between scientific father and son would undermine one of the hottest labs in the world and call into question some of the most exciting scientific research emerging from Toronto.

Penninger's boss was Tak Mak, the wiry, hard-driven 56-year-old Hong Kong immigrant who has won nearly every scientific prize, except for the Nobel, for his discovery of the holy grail of the immune system (last month brought his latest kudos, one of Canada's most distinguished achievement awards, a \$100,000 Killam Prize). Back in the early 1980s, Mak discovered how the body's mastermind detectives, the T-cells in the blood, pursue foreign invaders. The keys to the puzzle were the Y-shaped spikes on the surface of the T-cells that recognize viruses and bacteria that don't belong in the body. That discovery launched Mak into the scientific big league, a world of international travel, speeches and tempting offers from some of the most prestigious scientific research centres in the world.

Yet he chose to stay at the University of Toronto and, in the early 1990s, launched the Amgen Institute at Princess Margaret Hospital with a \$150-million commitment from Amgen Inc., the world's largest biotechnology company. Looking for six brilliant scientists to staff the institute, Mak spotted Penninger in the crowd of 600 contenders. Mak loved Penninger's roving mind and his driving ambition, and he treated the young scientist like a son, showering him with a couple of million of Amgen's dollars each year, far more than the average cash-starved Canadian lab gets. And Penninger exceeded all of

his mentor's expectations as he published an amazing string of reports in *Nature*, *Science* and *Cell*, the top three journals of basic research.

The relationship soured midway through 2001 when a scientist from the Toronto institute returned from a meeting at Harvard with some disturbing news: one of Penninger's most exciting discoveries might be wrong. A year earlier, Penninger had announced to the scientific world that he had discovered a gene that could block the growth of colon cancer, the second biggest cause of cancer death in North America. He had been studying some genetically engineered mice that were missing that gene, and they suddenly, unexpectedly, developed tumours. "It was really, really weird," Penninger said in an interview with *Maclean's*. "It's as if you expect sun and get hail."

But then three other labs in the U.S. and Europe checked their mice. These labs were studying the same gene as Penninger was, and they too had removed the gene from their mice to see how they did without it. But while Penninger said 40 per cent of his mice developed at least one tumour by six months, none of their mice got colon cancer. They could not duplicate Penninger's findings. These are ominous words in science. If a finding is true, other labs should be able to confirm the result. If they can't, there might be a technical or environmental reason. Or it just might be wrong.

After hearing the news, Mak walked down the hall to Penninger's tiny office, crammed with scientific papers, a tiny soccer ball, pictures of his young children, and some Japanese lucky charms. Why, Mak wondered, did Penninger's mice get colon cancer while the other labs' mice didn't? Penninger didn't have a clue, but he was certain of one thing: "Our mice got colon cancer. That we know. End of story."

Before Mak started asking questions, Penninger had sent some of his mice to one of those labs, in Switzerland, where scientists were trying to understand why the Toronto mice got cancer while the others didn't. But even when the Swiss bred Penninger's mice, the offspring didn't get cancer.

A couple of weeks later, Mak flew to Stockholm for a conference. Immunologists there were saying they couldn't duplicate several Penninger discoveries. Then Hans Wigzell, head of Sweden's Karolinska Institute, which hands out the Nobel Prize for medicine and physiology, challenged one of the discoveries that had made headlines. In 1999, Penninger said he had found the first biological proof that the bacterium *chlamydia* could cause heart disease. It was big news because scientists had long suspected a connection, but hadn't been able to prove it.

But Wigzell was puzzled. His group had injected mice with *chlamydia* and hadn't noticed any heart disease. Later Wigzell would retrace Penninger's exact steps, even using a tiny bit of protein from Penninger's lab. "We saw nothing," he says. In Toronto, alarm bells were sounding. Why were so many scientists saying they couldn't duplicate Penninger's work?

Even a year later, Penninger clears his throat and coughs repeatedly when asked about Mak's investigation. "People in the U.S. were told we were reporting garbage," he says. "People in other hospitals were e-mailing my [researchers]: 'Oh, I hear you're retracting your papers.' We had no chance to defend ourselves. We didn't even know what we had done wrong." He shifts in his seat. "It's such a vicious thing because, psychologically, what can you do worse to another person than say things like that? They're going after your life. They could have ruined everything I worked for. All of a sudden you're in a complete free fall. What do you do? You have no idea what hit you."

"Josef was freaked out," says Mike Crackower, a scientist who worked with Penninger at the time and still counts himself as a friend and admirer. "We all knew it was BS. We all knew everything was real. We know every personality. Nobody would do this." To Crackower, this is a simple story of a jealous mentor trying to undercut his brilliant protege. "Josef got bigger than [Mak] wanted him to be," says Crackower. "It's not any more complex than that."

According to Wigzell, Mak was reluctant to complain about Penninger to his employer, Amgen. "He said, 'Let it go, let it go. It will disappear,'" he says. "But I told Tak, you have a moral obligation, if you feel this is something bad, to ask for an independent review. You owe this to science. At the same time, if you're a whistle-blower, you get shit out of it, for sure. And [Mak] sure got shit out of it. He really suffered."

All through the summer of 2001, Mak waited for Penninger to explain why other scientists couldn't duplicate his results. Dissatisfied with the answers, he finally snapped. Researchers at the institute heard that Mak had e-mailed his protege: "You're not well. You'll bring us all down." The gloves came off. Penninger complained to Amgen's headquarters in Thousand Oaks, Calif., that Mak had been telling fellow scientists that the Penninger lab had been "cheating."

Amgen acted promptly. First, its human resources department chastised Mak for making statements that were "not appropriate" for someone in his position. Then Amgen set up a panel of five scientists -- including three from the company -- to investigate whether Penninger did commit any scientific misconduct. "I never asked them to decide if the research was correct or not," says Roger Perlmutter, Amgen's executive vice-president of research and development. "Things we take as the absolute truth now are going to look pretty silly a few years from now. The real question was: did the investigators make the observations they claimed to make, or did they make it up?"

Meanwhile, at least three scientists complained in writing to the panel that half a dozen of Penninger's results couldn't be reproduced by dozens of researchers around the world. They suggested something was wrong with Penninger's lab practices, or the way he interpreted the results. The panel met in Toronto for two days, behind closed doors, to decide whether a full-fledged investigation was warranted. It examined Penninger's overall lab practices and his approach. It didn't interview the scientists who had tried, unsuccessfully, to duplicate Penninger's results or retrace the steps of his most controversial experiments. On the colon cancer experiment, for instance, the panel never

asked for physical evidence to settle the question of whether the Penninger rodents had colon cancer.

The unanimous conclusion, announced to the University of Toronto medical community in June 2002: total exoneration. Penninger's lab displayed "scientific rigour and good laboratory practices" and "allegations to the contrary were unfounded." Dr. David Naylor, U of T's dean of medicine, issued a letter of support. "As is well known, Josef Penninger's accomplishments have been recognized in multiple ways," it said in part. "I personally count Josef among the most distinguished young scientists in the Faculty of Medicine at the University of Toronto."

"I cried when I heard it," says Penninger of the panel's decision. "Jesus Christ. It was completely unnecessary, a complete waste of our time. A whole year of our work was lost." By that point, though, Penninger had announced he was taking a job as head of the Institute of Molecular Biotechnology in Vienna, which will have an annual budget of nearly \$12 million from the Austrian government. It was a professional coup, and a handy exit. "I'm just happy to get out of here," he says.

By the time Penninger was exonerated, the ground had shifted under Mak, too. Just before Christmas of 2001, Amgen severed its connection with the Toronto research institute, five years earlier than planned, but insisted the move had nothing to do with the Penninger controversy. Mak declined comment to Maclean's, saying he was under an obligation not to talk. He still works in Princess Margaret Hospital, where the Amgen Institute was housed, and is seeking a new sponsor. His friend Wigzell lambastes the Amgen inquiry. "If you're kind, you call it amateurish," he says. "If you're more of an outsider, you call it scandalous -- you may consider it a cover-up." The fact that several Penninger reports could not be duplicated should be enough to launch a full investigation, says Wigzell. "It would make me extremely worried."

These days, Penninger is thinking about the scientific nirvana he hopes to create in Vienna. "This is a brilliant job," he says. "This place will be flying." He's supervising construction of the building and hiring 80 scientists, technicians and staff. He wants to make Austrians just as excited about genetics as they are about classical music and coffee. Genetics, he says, is very simple: "I always think good research is like a good book. Everyone can understand it; everyone can relate to it." Asked about the colon cancer mice, Penninger starts coughing again. "We are trying to figure out what the hell was going on," he says carefully. Although he didn't mention it in the original report, Penninger told Maclean's last fall that the mutant mice in his colon cancer experiment were infected by *Helicobacter pylori*, a bug known to cause ulcers and even stomach cancer. He thinks it might be the culprit. "Maybe we are completely wrong, but just imagine if we are right!" he said. "Can you think: a vaccination against colon cancer!"

A leading expert on *H. pylori* is skeptical. Long before Penninger came up with his theory, scientists explored the potential connection between the bug and colon cancer, says Barry Marshall, the Australian microbiologist who proved the organism can cause

ulcers. "There was an early flurry of interest," he says, "but a colon cancer-*Helicobacter pylori* link was small or non-existent, so we all lost interest."

In any case, three years after publishing his report, Penninger still hasn't published anything on his bug theory. So the mystery remains unsolved. Was he just plain wrong, a victim of an affinity for weird coincidences and novel connections? Or will it take the rest of the scientific world a while to catch up with him? Or was he so eager for the headlines, and the international scientific celebrity, that he cut some scientific corners in his research? Without a thorough investigation, which the panel found unnecessary, it's impossible to tell.

How would Penninger feel if it turns out he is completely wrong? "You know how many scientists are proven wrong?" he responds. "Many. It happens all the time. Please." His body tenses. "At the end, they got colon cancer," he states. "This is real. The interpretation may be wrong under experimental circumstances." That's always the risk when you venture out to the edge, and it's a risk that Penninger has been willing to take.