

Yuan Chang and Patrick Moore: Teaming Up To Hunt Down Cancer-Causing Viruses

By Charles Schmidt

Yuan Chang was an undergraduate student in biology at Stanford University when a friend mentioned a teaching assistant whom she might want to meet. His name was Patrick Moore, and he was a doctoral candidate in biophysical chemistry, also at Stanford. Ironically, Moore had also been tipped off about Chang, but as fate would have it, the pair didn't actually connect until they were both in medical school at the University of Utah. They married in 1989, 7 years later.

Ever since, Chang and Moore have sustained not just a marriage but also an increasingly celebrated research collaboration in tumor virology.

The pair achieved global acclaim when they identified human herpesvirus 8, the cause of Kaposi sarcoma, which is the most common malignancy in AIDS patients. The finding excited cancer researchers because it confirmed that tumors found predominantly in immunocompromised patients could be virally induced.

That was in 1994. Now, Chang and Moore have succeeded once again, revealing what appears to be the viral trigger for Merkel cell carcinoma, a rare and aggressive skin cancer that afflicts 1,500 Americans annually. The newly discovered agent is a member of the polyomavirus family, which includes several varieties that produce tumors in animals. Dubbed Merkel cell polyomavirus, this is the first variety linked to human cancer. Chang and Moore, who acknowledge the need for replication of this finding, reported their discovery online in *Science* on January 17, 2008.



Patrick Moore, M.D., and Yuan Chang, M.D., may have discovered the virus that causes a rare skin cancer, complementing their previous discovery of Kaposi sarcoma-associated herpesvirus.

“Assuming it holds, this is a major discovery,” said Robert Yarchoan, M.D., chief of the human immunodeficiency virus (HIV) and AIDS malignancy branch at the National Cancer Institute. “The notion that polyomaviruses might cause human cancer had been discredited in recent years; this finding brings that family of viruses back into the limelight.”

Chang and Moore identified the virus from their laboratory at the University of Pittsburgh Cancer Institute, where she is a professor of pathology and he is a professor of microbiology and molecular genetics and director of the molecular virology program. What drives their success, colleagues say, is the complementary nature of their specialties.

Moore got his start in infectious disease epidemiology. He worked for the U.S. Public Health Service from 1987 to 1993, investigating outbreaks of yellow fever, encephalitis, bacterial meningitis, and other

illnesses, often in the developing world. “He was always going off to Africa when it came to setting a date for the wedding,” Chang said with a chuckle.

In fact, both often went to different places as their careers evolved. After medical school, Moore went to Montreal for his internship, hoping to learn more French, a language common to many African countries. But he ultimately did most of his rotations at Jewish General Hospital and, Chang noted, picked up some choice Yiddish phrases instead. After completing the internship, Moore went even farther east to Atlanta to train with the Centers for Disease Control and Prevention (CDC) in

their epidemic surveillance program. Chang, meanwhile, went in the opposite direction for a residency in anatomic pathology at the University of California, San Francisco.

“We finally got married in 1989 after completing these training programs and lived in a small, idyllic cliffside apartment in Pacifica, Calif., with a panoramic view of the ocean,” Chang recalled. “For 2 years, I drove down scenic [highway] 280 for fellowship training in neuropathology at Stanford University, while Pat commuted by subway to the Centers for AIDS Prevention Studies at the UCSF.”

Chang and Moore left California together in 1992 for their first posttraining jobs in Fort Collins, Colo. But almost immediately, she accepted a teaching job at Columbia University College of Physicians and Surgeons in New York, whereas Moore stayed behind in Fort Collins with the Public Health Service,

working in the CDC's arbovirus disease branch.

During that time apart, Chang began collaborating with Moore on what became their seminal discovery of human herpesvirus 8, also known as Kaposi sarcoma–associated herpesvirus (KSHV). In Fort Collins, Moore had become increasingly intrigued by Kaposi sarcoma. A team of CDC epidemiologists, led in part by Harold Jaffe, M.D., now at Oxford University in England, had reported that gay men infected with HIV were more likely to have the cancer if they had been sexually active with partners from either the west or east coast. That finding led Jaffe and his team to propose that Kaposi sarcoma was caused by some sort of sexually transmitted virus. Their conclusion cemented a growing suspicion that the cancer was virally induced. However, Jaffe said, laboratories looking for the virus had been unsuccessful because they limited their search to known varieties.

Moore raised the topic with his wife while they were chatting about new methods to identify unknown pathogens. He mentioned a new method called representational difference analysis (RDA), recently published in *Science*, that might help scientists find the mystery virus. Chang had been thinking about using the method to study genetic profiles in brain tumors. But RDA, which reveals genetic differences in pairs of biological samples, might also be useful for viral discovery, they speculated. Using it in this way could be straightforward—simply compare genetic profiles of diseased and nondiseased tissue from the same patient and then subtract the human DNA. The leftover sequences, Chang said, might then be ascribed to a nonhuman pathogen.

When Moore moved to the New York City Department of Health in 1993, he proposed that he and Chang use RDA to analyze Kaposi sarcoma lesions collected

from the autopsy service at Columbia Presbyterian Medical Center. Luckily, they began that side project just as the autopsy service was handling the last patient that it would see with these lesions for a year. And that patient turned out to carry KSHV.

“We were in the right place, at the right time, looking at the right patient,” Moore said. Within 5 weeks, using RDA, they had isolated human herpesvirus 8, the previously unknown version of the herpesvirus that was associated with Kaposi sarcoma. Within several months, they had validated the finding.

The discovery, published in 1994 in *Science*, was a major finding for tumor virology. It not only obliterated false hypotheses

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about Kaposi sarcoma etiology—that the cancer was caused by HIV or even the use of amyl nitrates (“poppers”) during sex—but also paved the way for future studies when the pair confirmed KSHV's role in two other illnesses: primary effusion lymphoma and Castleman disease, a proliferation of benign tumors involving the lymph nodes.

“It really opened up a very large field of investigation into the molecular biology [of KSHV], including how it interacts with cells and how it might cause malignancies,” Jaffe said.

Over time, the accolades poured in. Chang and Moore were awarded many top prizes, including the Robert Koch Prize, the German Cancer Research Center Meyenburg Prize, and the General Motors Cancer Research Foundation Mott Prize.

But reflecting the challenge of their field, 15 years would pass before they made another viral discovery—that of Merkel cell polyomavirus. Even though viruses may account for up to 20% of all tumors, Yarchoan said, only five such varieties, in addition to KSHV, have been linked to human cancer thus far: the hepatitis B and C viruses, to liver cancer; the human papillomavirus, to cervical cancer; Epstein-Barr

virus, to cancer of the nose and pharynx and to Burkitt lymphoma; and human T-cell leukemia virus.

One reason cancer viruses are so hard to find is that after they integrate with or become latent within a target cell, little of their genetic material remains detectable. The first clues, of course, come through epidemiology; viral cancers predominate in immunocompromised patients suffering from AIDS, the effects of chemotherapy, or old age. In contrast, prevalence rates for nonviral cancers, such as lung cancer, do not rise when immune systems falter. Scientists believe that viruses cause cancer by one of two ways: either by inducing genetic mutations directly or by expressing oncoproteins that do it for them.



Robert Yarchoan, M.D.

Chang and Moore elected to study Merkel cell carcinoma because it bore similar features to Kaposi sarcoma—in particular, a high rate of occurrence in AIDS patients. By the time they launched the study, after coming to the University of Pittsburgh in 2002, many new genomic tools were available. These tools allowed them to modify RDA in a crucial way: instead of subtracting nonhuman sequences from samples of diseased and nondiseased tissue, they aligned Merkel cell carcinoma tumor sequences with sequences extracted from genomic databases.

This *in silico* method, which they call digital transcriptome subtraction, gave them access to vast stores of human and nonhuman genomic information. The study ultimately pointed them to the polyomavirus family, an exciting direction because it had been suggested, but never proven, that this class of viruses was linked to human cancer.

“It makes you wonder if other members of that family might also cause tumors,” Yarchoan said. “And it reminds people that many new viral causes of cancer have not been discovered and that they may be tricky to find.”

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So where does the research go from here? Chang says future replication of this work is key. “This is just the first time the virus has been identified, so we can’t say it’s causing the cancer until people see that as a generalizable phenomenon,” she said. “But that said, we are getting reports now that the finding is being confirmed in other laboratories.” Another mystery, Moore added, is that only 80% of the Merkel cell carcinoma tumors were infected with the virus, raising questions about negative findings among the rest. Future investigations will have to resolve that issue, he said.

Chang and Moore are both hopeful that their discovery will one day lead to new treatments for Merkel cell carcinoma. But they worry that the KSHV experience raises a disheartening precedent. Even though scientists know the viral cause of Kaposi sarcoma, efforts to base a cure on that finding have made little headway.

“That’s been our biggest disappointment,” Moore lamented. “[Kaposi sarcoma] is the most common cancer in sub-Saharan Africa, driven mostly by AIDS, but pharmaceutical and biotechnology companies haven’t developed any therapeutics, preventatives, or even tests for it. It’s a scandalous failure on their part—KSHV appears to have been lost in translation.”

Jaffe shares those concerns. He said that one reason new treatments for Kaposi sarcoma have yet to appear is that drug developers assumed that they could do better by treating HIV as the underlying cause. Whether this same reluctance applies to Merkel cell carcinoma is unknown.

Meanwhile, Chang and Moore may have given tumor virology a boost that will accelerate the pace of research. “We hope that this new finding will restimulate interest in this area,” Chang said. “There are some fantastic scientists working in tumor virology, and there’s still a lot of work to do.”

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