



YIBIN KANG

LUDWIG PRINCETON

Disruptor of metastasis

Yibin Kang's ambitions were once nearly thwarted by a pebble.

Growing up in the 1980s in the small coastal town of Longhai on the southern edge of China's Fujian Province, the young Kang had decided by middle school that he wanted to be a scientist. In 10th grade, in pursuit of that goal, he participated in a national chemistry competition organized by the Educational Council of China to find and cultivate the nation's most talented young scientists. On the day of the exam, however, Kang found himself in a quandary. Playing basketball barefoot on a clay court a couple of weeks before, he had landed hard on a sharp pebble and the wound, impervious to treatment, was now festering. "My head was spinning, and I hadn't had much sleep due to the pain, but I decided to take the test anyway," he says. With his chemistry teacher pushing him on a bicycle in a downpour and his father holding an umbrella over his head, Kang made it

to the test and, winning first place in his school, got a seat in a specialized secondary school science program at Peking University High School in Beijing.

With that first hobbled step, Kang began a journey that would take him from the shores of the Taiwan Strait to the U.S. and the cutting edge of research on cancer metastasis, by far the single deadliest consequence of malignant disease. Now the Warner-Lambert/Parke-Davis Professor of Molecular Biology at Princeton and a founding Member of the Ludwig Princeton Branch, Kang has over the past two decades illuminated key mechanisms of breast cancer metastasis to the bone and described the molecular biology and residential niches of rare breast cancer stem cells capable of seeding new tumors. His research has also explored the complex molecular signaling that underlies the transformation of settled cancer cells into mobile agents of metastasis and their subsequent





Photo by Flynn Larsen

reversion to anchored, tumor-seeding cells in distant organs, processes known respectively as epithelial-mesenchymal transition (EMT) and MET. Aside from their scientific contributions, his studies have generated five experimental drugs—and counting—for treating metastatic cancer.

GROWING UP AND OUT

Born in the mid-1970s, Kang spent his early years running wild and playing along the shore. “I almost drowned once, trying to catch fish,” Kang recalls. “But it was a great way to explore nature. It made us observant and adventurous.” His father, a marine biochemist whose budding career had been derailed in the late 1960s by the Cultural Revolution, taught chemistry in Longhai, and Kang joined him there when he was six years old, followed a few years later by his mother, who was a primary school teacher.

His father often brought chemistry demo sets back home between classes, and Kang was experimenting with them by the time he was in 6th grade. “In the end, I had my own little laboratory, where I designed my own little chemistry experiments and made specimens out of animals I’d caught,” says Kang. “I feel very fortunate to be doing today what I always wanted to do.”

Completing the college level natural sciences course at Peking University High School, Kang went on to Fudan University in Shanghai, joining the Department of Genetics headed by the C.C. Tan (a.k.a. Tan Jiazhen), who had brought molecular biology to China. Finding classwork a breeze, Kang spent a good deal of time in the lab learning gene mapping and cloning, and became fast friends with a masters-level student, Yong Wei, who he looked up to as a prototype scientist. “What a crazy scientist!” says Kang. “He lived in the lab and only went

to the dorm to tidy himself up when his girlfriend was visiting. He lived and breathed science." Wei is today a staff scientist and manager of Kang's Ludwig Princeton lab. "He's a lifelong friend and a great mentor to my students."

After initially enrolling in a graduate program in Michigan, Kang transferred to Duke University in 1996 to earn his PhD in the laboratory of virologist Bryan Cullen, where he studied the processing and nuclear export of viral gene transcripts. "He was very insightful, always right to the point and blunt," Kang says of his mentor. "He would come to my bench and blast me with his ideas in that British accent, and initially I'd get maybe 30% of what he'd said." The remaining 70% was often salvaged in long discussions with Hal Bogerd, then a technician in the lab and today an accomplished research scientist, who was something of an extracurricular mentor to Kang and remains a close friend today.

With a PhD in hand, and eager to move out north, where he would be closer to his future wife, Kang applied in 2000 for a postdoctoral position in Joan Massagué's laboratory at Memorial Sloan Kettering Cancer Center. After the interview, he and Massagué decided over a few beers that Kang would work on two projects related to cancer metastasis. One concerned a signaling pathway involved in metastasis that is controlled by a protein named TGF β . But it was the other one that most excited Kang: an effort to capture the genes essential to bone metastasis.

INTO METASTASIS

With the sequencing of the human genome and invention of DNA microarrays (gene chips), the tools required to conduct an open-ended search of such genes were, if expensive, now available. And Massagué, it turned out, had the resources and the confidence in Kang to let him give it a try.

"I almost drowned once, trying to catch fish. But it was a great way to explore nature. It made us observant and adventurous."

After learning how to work with animals, Kang developed a mouse model in partnership with Massagué and Theresa Guise at the University of Texas, San Antonio, to uncover the genes required for breast cancer metastasis to the bone. Cancer cells derived from breast cancer patients were placed in the mice and assessed for their ability to colonize the bone. Gene expression profiling of the avidly bone-metastatic cells revealed a trove of highly expressed genes, which could then be subjected to functional analysis to identify true drivers of metastasis.

In 2003, Kang, Massagué and their colleagues reported a suite of overexpressed genes that enable breast cancer bone metastasis. They also described how a few of them help carve out a niche in bone to initiate a metastatic tumor. Conceptually, their study supported the hypothesis that only a small subset of cells in a primary tumor are capable of metastasis, and that distinct suites of genes such cells overexpress determine where they wind up. In practical terms, they had developed and tested a model system for the identification of cellular factors that control

metastasis to various organs, enabling assessment of their possible blockade for therapy. They went on to conduct similar analyses for breast cancer metastasis to the lung and brain.

PHARMA TAKES NOTE

In 2004, Kang joined Princeton as an assistant professor. Partly as a training exercise for graduate students rotating through his lab, he began a project to add an imaging capability to his mouse model to observe signaling events and tumor growth in living animals. "It was a crazy way to do a project," says Kang. But it worked. In 2009, Kang's lab reported the use of that model to show that TGF β signaling is associated with the destruction of bone, which occurs in the creation of a metastatic niche, and that its blockade is most effective in suppressing tumor growth in the early stages of metastasis.

The study snagged the attention of scientists at the drug firm Merck, who suggested a collaboration to examine possible links between the TGF β signaling pathway and another such pathway controlled by Notch, a protein involved in stem cell maintenance and embryonic development. Led by Kang and Nilay Sethi, then an MD/PhD student in Kang's lab, the researchers showed in 2011 how TGF- β stimulates a vicious cycle that fuels metastasis. Tumor cells respond to TGF β by expressing a protein named Jagged1, which activates Notch in bone cells to drive further bone destruction while prompting the release of a factor, IL-6, that stimulates tumor progression.

This time around, the results caught the eye of researchers at the biotech Amgen. "They contacted me and said, 'We have a Jagged1 antibody, which we developed for our anti-angiogenesis program, but it didn't work at all, so how about we test it in your model?'" Kang recalls. Working with the Amgen team,

Kang reported in 2017 that the Jagged1 antibody inhibits bone metastasis of breast cancer and makes existing metastases highly sensitive to chemotherapy. Amgen is now developing it for possible use in patients.

BRANCHING OUT

Developing increasingly sophisticated mouse models, Kang continued to broaden the ambit of his research through the 2010s. His investigations eventually encompassed the similarities and differences between normal and cancer stem cells in the breast and bone, their respective interactions with other cells in their niches and the cellular transformations that accompany the migration and resettlement of metastatic cells—or EMT and MET.

EMT promotes stem cell-like states in cancer cells destined to form new colonies. MET would presumably reverse that process as the cells settle down at a new location. Yet this presented a paradox, as the migrant cell would need to retain its "stemness" to establish a new tumor even as it underwent MET. Kang and his colleagues discovered that metastatic breast cancer cells engage a protein named E-selectin in the bone to undergo MET and settle down while still maintaining their stem-like properties. Partly on the strength of this work, a drug that inhibits E-selectin developed by the firm GlycoMimetics is now in clinical trials for treating breast and prostate cancer metastases.

In other work, Kang and his team discovered how certain small RNA molecules—microRNAs—that regulate gene expression support cancer stem cells and metastasis. One such RNA, miR 199a, they showed, helps maintain the stemness of healthy breast stem cells but is coopted by cancer stem cells to escape immune suppression. They also showed how members of another family of microRNAs (miR 200s) suppress EMT



Photo by Flynn Larsen

yet drive metastasis: by simultaneously blocking the cancer cell's secretion of a factor, *Tinagl1*, that inhibits metastasis. Kang and his colleagues demonstrated that supplementing *Tinagl1* undermined tumor progression and metastasis in mouse models of triple-negative breast cancer. This technology has been licensed to a startup trying to translate the discovery into a therapy.

In parallel with the studies modeling metastasis, Kang and his team began searching more generally for genetic factors that contribute to poor outcomes in cancer patients, developing new techniques for the analysis of cancer genomes to that end. The effort yielded an obscure gene

encoding a protein named *metadherin* whose expression was linked to aggressive metastasis and drug resistance in breast cancer. "There were maybe six papers out about this protein when we started working on it," recalls Kang.

Kang's subsequent studies showed that *metadherin* promotes cancer progression by supporting tumor cells under various stresses such as chemotherapy, and by suppressing the recognition of tumor cells by cancer-targeting T cells. His team demonstrated in mouse models that its inhibition suppresses the growth and metastasis of breast, lung and colorectal cancers, and that mice lacking the gene seem to suffer no ill effects. The protein,

“Cancer cells are under constant stress ... The reason they can survive and progress is due to the fitness pathways that allow them to cope with that stress.”

it appears, is not essential to healthy cells in animals—except perhaps under certain stressful conditions—and could therefore be safe to target for therapy. Kang and his colleagues have launched two biotechnology companies to develop drugs targeting metadherin and other cancer fitness genes for therapy.

NEW FRONTIERS

For the longest time, Kang notes, scientists have considered the genes that gain and lose function to initiate cancer as a set separate from those that enable metastasis. Based on his own studies, Kang considers this view inaccurate, noting that *Jagged1* is essential for bone metastasis but also plays a key role in the establishment of primary tumors. Ditto for metadherin, he says, whose loss in engineered mice compromises the formation of primary tumors as well.

“The concept steadily evolved in my lab that cancer is a continuous process and, in fact, many of the so-called oncogenes also play a role in metastasis, and so-called pure metastasis genes are essential for the formation of primary tumors as well,” says Kang. “The reason they behave like

metastasis genes is that they allow the cells to survive under stressful conditions. Cancer cells are under constant stress—mitotic stress, metabolic stress, immune cell attack, genomic instability, to name some. The reason they can survive and progress is due to the fitness pathways that allow them to cope with that stress, so if you target those pathways, they become very vulnerable to therapy. A lot of our research now is focusing on these fitness pathways.”

Kang’s interrogation of metastasis has also drawn him into cancer metabolism—the focus of Ludwig Princeton. Branch Director Josh Rabinowitz (see *accompanying profile, page 14*) joined Princeton the same year Kang did, and the two reported the results of their first collaboration in 2010. Employing Rabinowitz’s sophisticated technologies for the large-scale analysis of metabolism, the researchers analyzed metabolic changes associated with the metastasis of breast cancer cells. Though a relatively small paper published in the *Journal of Biological Chemistry*, says Kang, it remains one of his most highly cited studies, since it was among the first to attempt such an analysis.

The pair have since collaborated on other studies of cancer cell metabolism, examining the reliance of cancer cells on various energy-generating and biosynthetic pathways. “We are very complementary to each other,” says Kang. “Josh’s lab is very strong in metabolomics and chemistry, and we have all the resources in mouse modeling.”

Kang has also worked with Eileen White, associate director of the Princeton Branch (see *accompanying profile, page 22*), in a study on the metabolism of cancers driven by the oncogene Ras. He is, further, associate director for consortium research at the Rutgers Cancer Institute of New Jersey, where White is chief scientific officer.

Kang’s focus on cancer metabolism seems



Photo by Flynn Larsen

set to grow at Ludwig Princeton. He is, he says, very interested in exploring the role of exercise, diet and other lifestyle factors that influence the risk and treatment response of metastasis. (It bears noting here that, despite the pebble injury, Kang remains an accomplished athlete: he completed a half IRONMAN contest this summer and then a full IRONMAN in Arizona on November 21st—a triathlon that includes a 2.4-mile swim, a 112-mile bike ride and a 26.2-mile run.)

Kang is particularly excited about the many opportunities created by the establishment of the Ludwig Princeton Branch. “Cancer research used to be a relatively niche research area at Princeton, since we do not have a medical school on campus,” he says. “Now we are part of a large global family of Ludwig researchers, many of whom work on

areas that synergize with our main research interests: metastasis, tumor environment, cancer immunology, epigenetics, cancer stem cells, just to name a few. This will elevate our research to a whole new level.”

On the therapeutic front, Kang’s team is in collaboration with the Rabinowitz lab now developing candidate drugs targeting a family of metabolic enzymes for the treatment of cancer, stemming from research that will soon be published. Another area of interest to him in cancer metabolism, says Kang, is the role of diet in cancer metastasis to the liver.

“My ultimate goal,” says Kang, “is to make a medicine that really helps cancer patients.”

He seems well on his way already. ■