



Chi Van Dang

LUDWIG WORKING FROM HOME

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Master of malignant metabolism

PEOPLE TEND TO DISMISS THE ROLE OF serendipity in their successes. Not Chi Van Dang. “My research career has been paved with luck,” Ludwig’s scientific director says with a chuckle. It was certainly there when Dang arrived in 1985 at the University of California, San Francisco, fresh from his medical residency at Johns Hopkins, for a fellowship in hematology-oncology and in molecular oncology, which he would do under the physician-scientist William Lee and two pioneers of the field, Harold Varmus and J. Michael Bishop.

“Varmus asked me what I wanted to work on,” Dang recalls, “I said, ‘oncogenes.’ He looked at me and said, ‘Which one?’ Dang confessed he had no idea. Unfazed, Varmus told Dang to go interview junior faculty on the team and pick one. “I hit it off with Bill Lee, and he was studying Myc,” says Dang. “At that

point we really didn’t know which oncogenes would be most prominent in human cancer. It was pure luck that I wound up focusing on Myc—it turned out to be a really important oncogene.”

Luck, for its part, found in Dang an amply prepared mind. Over the next three decades, his elucidation of Myc biology would expose the protein’s starring role in the orchestration of cellular metabolism and reveal how its dysfunction drives the malignant transformation of cells. Dang’s discoveries spurred a revival of the long-dormant field of cancer metabolism and led him into studies of phenomena as seemingly disparate as cellular oxygen sensing and chronobiology. In 2019, Dang’s Ludwig laboratory at the Wistar Institute in Philadelphia, in collaboration with researchers at Stanford University, added a new chapter to the winding tale of Myc

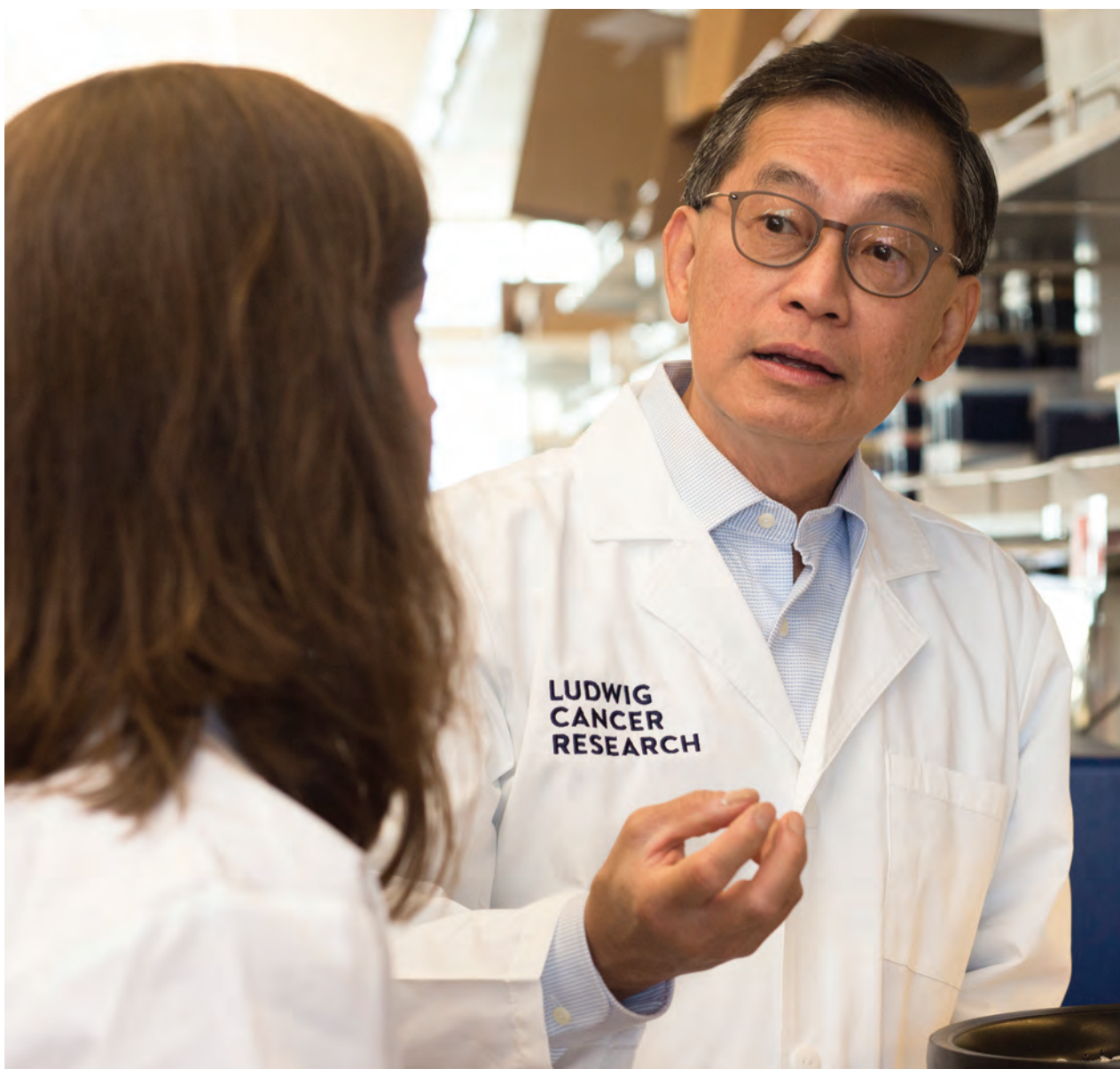


Photo by Flynn Larsen

and cancer metabolism. They reported in *Cell Metabolism* that cancer cells driven by Myc shut down their importation of fats and become highly dependent on their internal lipid-making machinery. That dependency, they showed, might be exploited for cancer therapy.

Lucky breaks

Dang was born in the former Saigon, now Ho Chi Minh City, in southern Vietnam. “My

mother was probably the best mother I know,” says Dang, “because she managed to keep track of ten children.” His father, Chieu Van Dang, was Vietnam’s first neurosurgeon and Dean of the Saigon School of Medicine. “He was a curious, eclectic man, very up about education,” Dang recalls. “He told us, ‘I won’t have a lot of money to leave you, but I will leave each of you an education.’ That was always his mantra.”

Dang's family frequently hosted foreign doctors and, as the Vietnam war heated up, an orthopedic surgeon from the U.S. who had stayed with them in 1960 and remained a friend offered to take a couple of the Dang children into his home in Flint, Michigan. Because they attended an English medium school, Dang and his brother Chuc were picked to go in 1967.

A bookish boy of 12, Dang found a welcoming community in Flint, learning about American culture from friendly neighbors and excelling in his studies. After a spell in refugee camps, the rest of his family migrated in 1975 to California, where Dang's father completed an internship and residency at the age of 56 to obtain a U.S. medical license. "That influenced me," says Dang, "the illustration that you can recover from adversity, recoup and get back on your feet."

Dang graduated with highest honors in 1975 from the University of Michigan, Ann Arbor, where he had majored in chemistry. But the fall of Saigon that year left him stateless and, despite his topping test scores and grades, medical schools put him on their waitlists as they puzzled over his immigration status. Ultimately, Georgetown University accepted Dang into its graduate program in chemistry with the understanding that he would join its medical school after earning his PhD.

But upon completing his graduate studies, Dang transferred in 1978 to Johns Hopkins University, where he earned his MD and continued honing his research skills, working on cell biology before moving into blood coagulation research. Both those experiences, along with exposure to cancer patients during his internship and residency at Hopkins, drew Dang to oncology. And so, in 1985, Dang and his new wife, Mary, packed up their belongings and drove across the U.S. to San Francisco, where Dang planned to start his career as a clinical and research oncologist—by learning, first, what makes a gene an oncogene.

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Profiling Myc

At the time, Myc was known to be a viral oncogene, but very little was known about the version of the protein encoded by cells. Working with Lee, Dang tested a leading hypothesis—that Myc was somehow involved in replicating DNA—and proved, with some disappointment, that it is not.

The two continued their collaboration after Dang was recruited back to Hopkins in 1987. Soon after he started his lab, Dang received a call from the molecular biologist Steve McKnight, whose team had noticed that another DNA-binding protein named C/EBP had some similarities to Myc. Dang and McKnight put their heads together and noticed that these and other cancer-driving proteins that bind DNA share a structural feature. McKnight's team argued in a landmark analysis in *Science* in 1988 that this feature, which they dubbed the "leucine zipper," allowed DNA-binding proteins to zip up with a partner protein bearing the same structure and so bind DNA.

Dang, meanwhile, returned to his lab to prove that Myc's leucine zipper indeed performed such a function. That work, reported in *Nature* and co-authored with Lee, experimentally validated McKnight's hypothesis, cementing a basic principle of

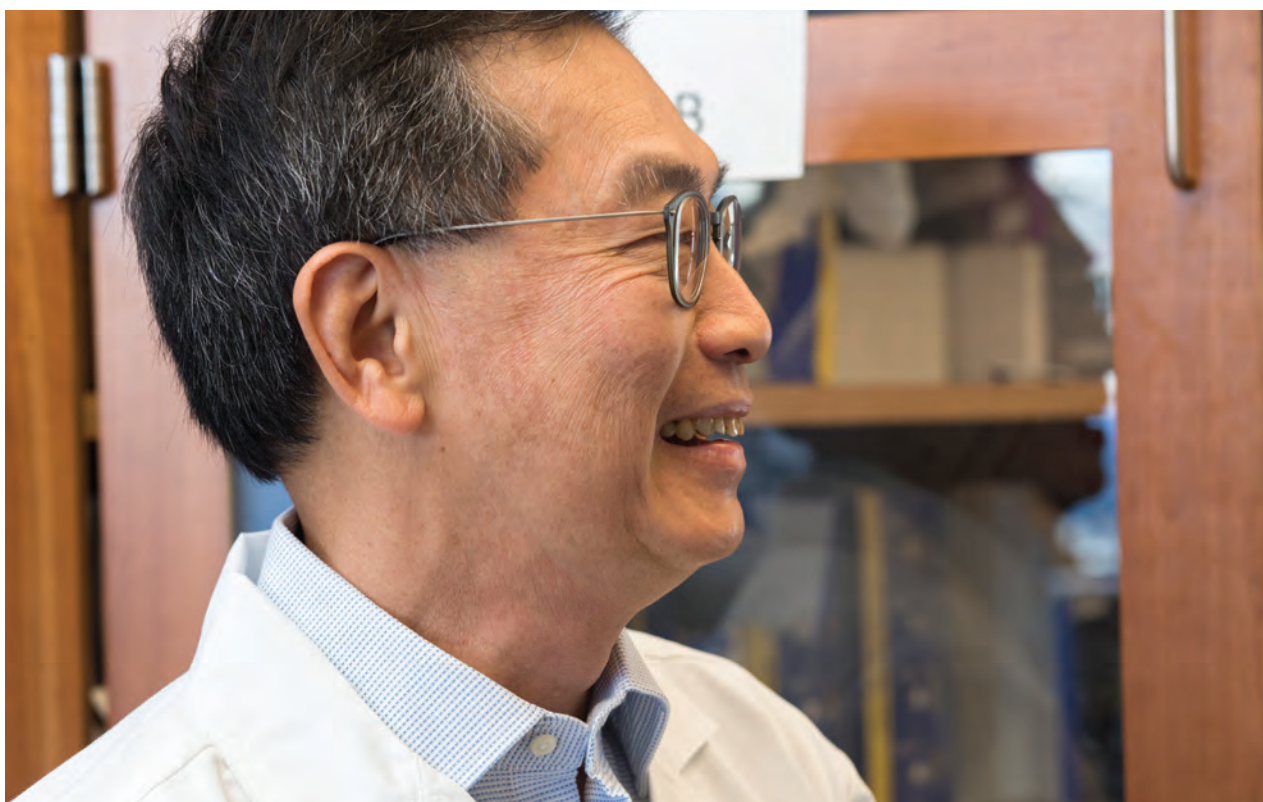


Photo by Flynn Larsen

molecular biology. “It was totally by luck that we made this discovery,” says Dang. “If McKnight hadn’t contacted me, we’d have been off working on something else.” Dang and Lee also discerned the molecular bar code on Myc that directs it into the nucleus and, most notably, proved that Myc is a transcription factor—a protein that controls the expression of genes.

Into malignant metabolism

Now the race was on to discover the genes turned on by Myc. Dang and others found that Myc activates many genes essential to cell division. But an entirely different kind of Myc-activated gene piqued Dang’s curiosity. “That gene was for lactate dehydrogenase A (LDHA), a metabolic enzyme that is seemingly very boring, just a housekeeping gene,” says Dang. Yet the discovery suggested to Dang an exciting possibility.

Cancer cells must rewire their metabolism to generate the extra energy and raw materials required to duplicate themselves. One way they do that is by switching on a metabolic pathway for burning sugar, known as glycolysis, in which LDHA is involved. Glycolysis is ordinarily employed only by oxygen-starved cells, but cancer cells keep it going regardless—a hallmark of cancer first identified the 1920s by the biologist Otto Warburg. Cancer cells like glycolysis because, though it generates relatively little energy, it produces large amounts of a key cellular building block, lactate, the acidic byproduct that makes overexerted muscles burn.

In 1997, Dang and his colleagues reported that Myc boosts the expression of LDHA in cancer cells, providing the first mechanistic link between an oncogene and the classical Warburg effect. Over the next several years, Dang’s lab would describe the myriad ways in which Myc controls metabolism by

modulating the production of key enzymes and the generation of cellular components like mitochondria—the powerhouses of cells—and ribosomes, which are required for the synthesis of proteins.

“The function of Myc is to turbocharge the production machinery of the cell so it can assemble all the building blocks required to double in size, copy DNA and then divide,” explains Dang. “If you get rid of Myc, cells can’t do this, so Myc is often permanently switched on in cancer cells. That’s a summary of about three decades of research on how Myc actually functions.”

Further afield

While Dang was exploring Myc’s rewiring of cellular metabolism, his Hopkins colleague Gregg Semenza had been investigating how cells adapt to oxygen starvation, or hypoxia. Semenza, who with Ludwig Oxford’s Peter Ratcliffe and Harvard’s William Kaelin won the 2019 Nobel Prize for that body of work, noticed that HIF, a transcription factor central to the cell’s hypoxic response, also activates glycolysis. In 1999, he and Dang began a fruitful collaboration exploring HIF’s influence on hypoxic metabolism and its interaction with Myc in cancer.

Hypoxia is a common feature of tumors and, in 2008, Dang and Semenza demonstrated that the pharmacological inhibition of LDHA could slow the growth of certain cancers, and worked for a few years to develop a drug for that purpose. Dang also explored the inhibition of another metabolic pathway activated by Myc—one involving the amino acid glutamine, to which many cancers cells are addicted—as a cancer therapy. Both efforts, which continued after Dang was appointed director of the Abramson Cancer Center at the University of Pennsylvania in 2012, were encouraging. Yet they have so far yielded mixed results in early trials and animal studies conducted by other researchers and companies.

“We think that if we make a drug that targets the cancer cell’s metabolic pathways, we can kill the cancer,” says Dang. “The mistake we made conceptually is that many cells, not just cancer cells, use those metabolic pathways. Most important, immune cells also depend on them.” Dang has thus adjusted his approach to look for metabolic interventions less likely to disrupt the immune response to tumors. (As it turns out, the targeting of glutamine metabolism seems to pass that test.)

Dang’s move to UPenn in 2012, meanwhile, exposed him to a cluster of chronobiologists, who study how circadian rhythms affect physiology. Those rhythms are coordinated by a central clock in the brain, subsidiary clocks in other organs and a network of clock-associated genes in cells.

Normally, cellular metabolism is in sync with the circadian clock, active during the day and slow at night. But ceaselessly proliferating cancer cells presumably do not rest. Dang and his colleagues wondered whether Myc—which binds to the same DNA sequences as a pair of proteins that control clock gene expression—has a hand in that circadian dysfunction. In 2015, they reported in *Cell Metabolism* that it does. Myc, it turns out, indirectly suppresses one of those genes to disrupt the cellular clock and reprogram metabolism to support cancer cell proliferation.

A basic discovery

Dang and his team were now curious about whether HIF too disrupts clock genes in the oxygen-starved cells of tumors, since HIF and Myc bind to similar DNA sequences. Their studies indicated, unexpectedly, that it does not. But the graduate student working on the project, Zandra Walton, found that acidity—caused by the lactate generated by glycolysis—suffices to disrupt the circadian clock and that the effect could be reversed by neutralizing the medium around hypoxic cells.

Figuring out how that happened continued

as Dang joined the Ludwig Institute for Cancer Research as scientific director and became a member of The Wistar Institute in Philadelphia in 2017. The following year, he and his team detailed in *Cell* a surprising molecular mechanism by which the acidity—caused by glycolysis in hypoxic tumors—pushes cancer cells, and all other cells, into a dormant state. The discovery has implications for cancer therapy because dormant cells in tumors cannot typically be killed by chemotherapy and are a major source of drug resistance and disease recurrence.

They also found that the effect, caused by the disabling of a protein complex named mTORC1, could be easily reversed. “In tumors grafted into mice, we saw mTOR activity in spotty places where there’s oxygen,” says Dang. “But when we added baking soda [which neutralizes acid] to the drinking water given to those mice, the tumor would light up with mTOR activity. The prediction would be that by reawakening these cells, you could make the tumor more sensitive to therapy.” Dang and his team also found that the activation of the immune system’s T cells, essential to most immunotherapies, is similarly compromised by acidity. “We’re looking now at whether that can modulate immunotherapy,” says Dang.

Back to basics

Dang and his team were at the time also examining how Myc influences the production of lipids—fat molecules that build cell membranes and play many other important roles in proliferating cells. A protein named SREBP1 normally monitors lipid levels and, when more are needed, activates the expression of genes involved in their synthesis. A graduate student in Dang’s lab, Arvin Gouw, discovered that Myc ramps up the production of SREBP1, putting it into overdrive. “We also found that MYC then binds to the same genes as SREBP1, and the two collaborate to push lipid synthesis to even higher levels,” says Dang. Those findings were

reported in a *Cell Metabolism* paper published in 2019 and led by Dang and Stanford University researchers Richard Zare and Dean Felsher—whose lab Gouw subsequently joined as a postdoc.

Myc, the researchers showed, controls the gene expression required for almost every stage of lipid synthesis in proliferating cells. Further, studies on mice engineered to develop Myc-driven cancers of the blood, lungs, kidneys and liver revealed that cells of such tumors are highly dependent on synthesizing their own fats rather than importing them. Inhibiting an early step of lipid synthesis led to the regression of the induced tumors and of Myc-driven human tumors implanted in mice. Even tumors primarily driven by other oncogenes are susceptible to the inhibition of fatty acid production if they indirectly activate Myc. The findings suggest strategies for developing drugs that could treat multiple tumor types, as Myc is overexpressed or activated in more than half of all cancers.

Dang remains eager to translate these and other such discoveries into cancer therapies, but now in a more nuanced way. “We’re still interested in metabolic inhibitors but are particularly careful about examining how they affect other cells in the tumor microenvironment,” says Dang. He and his colleagues are also engineering immune cells to withstand the enervating acidity of the tumor microenvironment, with the aim of improving cellular immunotherapy, and exploring how the circadian clock affects the anti-tumor immune response.

“These are the kind of projects where you take a shot at something that’s a little crazy, and then leverage your early results to compete for more traditional external funding—something I am encouraging all our Ludwig researchers to do,” he says. “That’s what’s important about Ludwig support—it allows you to innovate and not be fearful of trying something that’s way out there.” ■

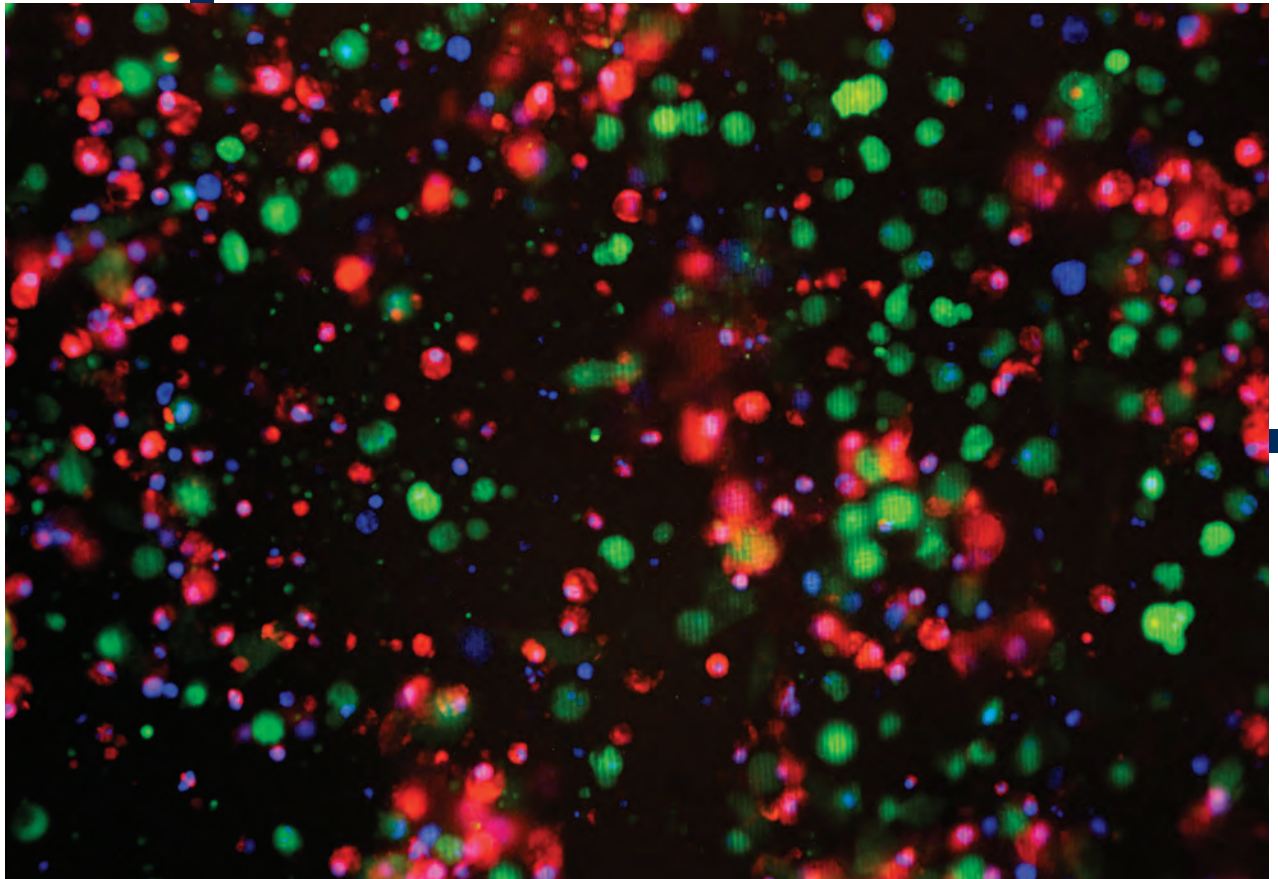


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