Craig Thompson, M.D., '75: Why not?

By Laura Stephenson Carter

Military brat, precocious medical student, controversial researcher, director of a cancer center: Craig Thompson has rocketed through a career that has taken him from Boston's Peter Bent Brigham and University Hospitals, to Seattle's Fred Hutchinson Cancer Research Center, to the National Naval Medical Center in Maryland, to the University of Michigan, to Howard Hughes Medical Institute, to the University of Chicago.

Eventually, he splashed down in Philadelphia, in 1999, as scientific director at the University of Pennsylvania's Abramson Family Cancer Research Institute. And he was just named director of the Abramson Cancer Center in September 2006.

Grew up: Born in Cambridge, Mass., and grew up all over the U.S., including in Hawaii

Education: Dartmouth College '74 and Medical School '75, University of Pennsylvania Medical School '77

Training: Peter Bent Brigham Hospital; University Hospital, Boston; Fred Hutchinson Cancer Research Center (University of Washington)

First paid job: Counselor in a Boy Scout camp outside Boston (at age 16)

College sports: Soccer and kayaking (then a varsity sport)

Instead of wondering why people get cancer, he asks, "Why do most people *not* get cancer?"

One might say that he rocketed through his formative years, too. "I was a military brat," says Thompson. "My dad was in the Coast Guard, so I grew up all over the place." In the 1960s, his father was an expert in long-range navigation and coordinated the deployment of ships from Pearl Harbor, Hawaii, to retrieve the Mercury space capsules from the Pacific Ocean. "Remember, they just shot those things at the Pacific and hoped they landed there," Thompson laughs. "We got to meet all the astronauts when they came back. They recovered [the capsules and] tied them up literally in my front yard—50 feet from my house. President Kennedy came out to my house one time, I remember. . . . It was really neat."

Thompson had been born in Boston, and his family made its way back there by the time he was in high school. There, his father ran a cutter that went out to sea for a month at a time, says Thompson, "and sat within a five-mile point in the mid-Atlantic and sent out a homing beacon for navigation."

Recruited to Dartmouth to play soccer, Thompson also joined the kayaking team. But, he confesses, "I didn't really graduate from college. In my second year I had a huge falling out with the soccer coach and quit playing soccer because he wanted me to give up science courses. And I wouldn't do that." He laughs. Yet he had come to college intending to play sports. The abrupt change in his focus forced him to think hard about what he wanted to do next. There was one thing he was sure of—he loved science.

And "one thing you could do in science that I understood was to be a doctor or a nurse," he says. "So I applied to [Dartmouth] Medical School in the middle of my sophomore year. I was 19 years old, a sophomore in college, applying to medical school. I'll never forget my interview with Dr. [Charles] Faulkner, who basically told me I wasn't living up to my responsibilities" by not honoring the commitment to play soccer. "We had a huge shouting match," Thompson recalls. Nevertheless, he was admitted to DMS. Faulkner "was incredibly nice to me afterward," adds Thompson, "and always told the tale that the reason he thought I could take it in medical school was because I could stand up to a professor who was telling me I was wrong."

Dartmouth wasn't about to let Thompson get away without a college degree, however. At the end of his first year in the two-year medical program, which Dartmouth was in the process of transforming into a full M.D. program, he was called into the dean's office and told to grade himself on the first year of medical school; they would use that work to give him credit for an undergraduate degree. "I have no idea who worked that out, but I've always been grateful because I do have an undergraduate degree in which my major is going to medical school," he says. He graduated from DMS with honors and completed his M.D. at the University of Pennsylvania.

Thompson had accepted a Navy scholarship to pay for medical school and expected to become a military clinician like those he'd met growing up. But he began working in naval *research*—in Boston, Bethesda, and Seattle—even before his training was completed. At the Fred Hutchinson Cancer Research Center, where he was both a naval officer and a research fellow, he cared for bone-marrow transplant patients who were given cyclosporine, an immunosuppressive drug that prevented the rejection of the new marrow.

But Thompson was puzzled by something. The drug should also have kept the patients' immune systems from fighting infections, but that wasn't the case. The patients seemed to handle infections fine. Thompson's attempts to find out why launched him on a journey exploring molecular pathways in the immune system and immune-based therapies to fight cancer. His lab pioneered the study of a family of cancer-related genes and their role in regulating cell survival and was the first to demonstrate costimulatory pathways in the regulation of cytokine production by T cells. He has since made a number of other discoveries that have contributed to the understanding of immune-cell development and cancer mechanisms.

Some of his discoveries have been controversial. Even the way he approaches cancer research is different. Instead of wondering why people get cancer, he simply asks, "Why not? Why do most people *not* get cancer?" After all, there are almost a hundred times more cells in a human body than there are people on Earth, he points out. Yet those cells "live together as an effective colony to make you an organism." With so many things known to cause cancer, "it's just a miracle that one of [your] cells hasn't come down with cancer and killed you."

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DMS graduate Craig Thompson, who holds some controversial scientific views, has just been named director of the University of Pennsylvania cancer center.

About six years ago, Thompson's lab proposed that the reason "collections of cells live together as a multicellular organism is because they have all given up the cell's autonomous ability to take up nutrients from their environment." Every cell in the body is constantly bathed in more nutrients than it would ever want or need—glucose, amino acids, other building blocks. Yet normal cells are unable "to take up those nutrients unless given permission by other cells" in a process called signal transduction. "A cell without those instructive signals will always starve to death despite the fact there's an embarrassment of riches outside," says Thompson. "A cell can't proliferate on its own because it can't even eat enough to actually survive." But in cancer cells, mutations control their ability to take up nutrients and allow the cells to grow and proliferate. Thompson and his research colleagues contend that increased glycolysis—the processing of glucose—is important for sustaining tumors but not necessarily for inducing them. Others disagree and say that the role of glycolysis is overestimated.

That's not the only controversial view Thompson holds. He also believes that cancer cells exploit autophagy—a process whereby cells eat themselves—in order to survive nutrient shortages, rid themselves of defective components, and even fight off chemotherapy. "We have found a variety of drugs that can intervene in that process that have never before been tried as cancer therapeutics, but are actually known to be safe and efficacious in patients," he says.

One such drug is chloroquine, an antimalaria medication that some suspect inhibits autophagy. When a mosquito injects the malaria parasite into the body, autophagy may help the parasite survive long enough to colonize its host. Thompson believes chloroquine interferes with that survival mechanism, killing the malaria parasite.

And he thinks cancer cells exploit autophagy in much the same way to protect themselves against chemotherapy. When "cancer cells metastasize, they move from a place where they can get enough nutrients to places where most of the mechanisms that have transformed them don't allow them to take up nutrients in a cell-autonomous fashion, until they've colonized a new organ." According to Thompson, when patients don't get better from chemotherapy it's because the cancer cells have used "autophagy to remodel themselves and to maintain themselves over the period of time of that treatment." He has shown that, in mice, chloroquine inhibits autophagy and enhances their response to the chemotherapy drug tamoxifen. Now he is conducting clinical trials to see if chloroquine will work in human cancer patients, too.

Other researchers have found, however, that autophagy suppresses tumor development in animals. "Everything that we have enjoyed doing over the last 20 years has started out as a controversial idea," Thompson says with a laugh. "The fun thing for us is that occasionally it's turned out to be of interest to the broader community."

On a more serious note, he adds, "I think it's incredibly rewarding to contribute to research that ultimately ends up in the hands of physicians treating patients and makes patients better."

Thompson's theories may have critics, but he has been widely recognized for his work. He is frequently invited to give talks, has received numerous awards, and has been elected to prestigious professional societies. Last year, he was one of only four cancer scientists elected to the National Academy of Sciences. He also holds leadership positions in a number of other organizations. He is associate editor or on the editorial boards of several important journals, including *Cell*, *Science*, *Immunity*, and *Cancer Cell*. What's more, he holds a number of patents related to immunotherapy and apoptosis and is the founder of two biotechnology companies.

He has also mentored more than two dozen students and fellows who have gone on to successful careers in academic medicine. "In the end," he says proudly, "they will have much more influence on the practice of medicine than I ever will."

And as busy as he is, he also makes time for his family—his wife, Dr. Tullia Lindsten, who jointly runs his lab; and their teenaged daughter and son. And though he refused to sacrifice science for sports back in college, he never really gave up sports. In fact, he organizes a weekly Penn faculty basketball game. "We play the medical students once a year," he says. And he approaches that contest as avidly as he does his matchup with cancer. "They beat us the last three years, so we're honing up again to beat them finally this year." ■

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