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A conversation with Craig Thompson

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Conversations with Giants in Medicine

Craig Thompson, President and CEO of Memorial Sloan Kettering Cancer Center, is a medical oncologist and immunologist who has made fundamental contributions to our understanding of how cells — from B and T cells to stem cells and cancer cells — survive and replicate. See the full interview at https://www.jci.org/videos/cgms to hear Thompson's (Figure 1) stories about being a remedial reader, the future of cancer research and therapy, and leadership lessons learned from Watership Down. JCI: What were you like as a kid? Thompson: I grew up as a military brat. My dad was a career officer in the Coast Guard, and so I spent my life growing up on or near military bases. We started out in the midwest and moved to Boston, where I had my first science experience at Woods Hole, when my dad ran the Coast Guard base in Falmouth, Massachusetts. I learned to swim at the Woods Hole beach and had my first science lecture in the first grade there. We then moved to Hawaii and then many other parts of the US. I became quite open to new situations and new opportunities as a result of my upbringing. I was not the best student when I was in elementary school, nor was I a very attentive young man. The good news for me was […]

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I was not the best student when I was in elementary school, nor was I a very attentive young man. The good news for me was I was pretty good at math, and so that always carried me through, but I was a horrible reader.

JCI: At some point along the way, you kindled an interest in science.

Thompson: Before high school, we moved to outside Boston. My parents put my sister and me in an experimental public school funded by the Ford Foundation that was hooked up to MIT. I was put in a special computer homeroom and that exposed me to the science nerds of the school, and it turns out I was one. Almost all of us that were in that group went into science in some way. But when I grew up, one of the ways you learn as a military brat to break in, is that sports are the leveler. I was lucky enough to go to Dartmouth and play two sports there, which were the two sports I liked best in high school. I played soccer in the fall, and I did white water kayaking in the spring, which had just been made an Olympic sport.

I loved working in the chemistry lab, and I thought I would go on to a doctoral degree in chemistry. In 1974, the National Science Foundation stopped giving out doctoral fellowships in chemistry; everybody thinks today is the only time funding from federal government was withdrawn, but they decided we had enough chemists back then. I was disconsolate about this when one of the guys in my dorm invited me to come to a pre-med meeting. I had never thought about going into medicine. I fainted at the sight of blood and wasn't particularly interested in medicine and biology. I decided at that meeting, for no good reason, that I would apply to medical school. I only applied to one medical school, and I fortunately got in.

> We started to become interested in why cells die and how we could manipulate the apoptotic decision to learn more about cell death and proliferation.

JCI: The Navy paid your way through medical school, so how did you go about fulfilling your military obligation?

Thompson: I became entranced by intermediate metabolism in medical school, started working in the laboratory, and became very interested in the academic pursuit of medicine. That isn't what the Navy thinks they award a scholarship for, as quite rightly, they needed people that would take various service jobs to take care of the military workforce. I started exploring if there were any lab opportunities in the Navy and visited all the naval hospitals that have training programs. I was able to defer my Navy commitment and go to the Peter Bent Brigham Hospital to do my internship and residency.

Afterwards, I really didn't want to be an internist at a base hospital, and going to the NIH as a researcher wasn't possible. This is where being brought up in the military helps; you know that every government has loopholes, so I investigated where I could be assigned once I finished my deferment for my clinical training. I ended up at the Naval Blood Research Laboratory in Boston. It's an important place that worked out all the protocols everyone uses to freeze blood cells, cell lines, and all other frozen cell products.

JCI: What did your research entail while you were there?

Thompson: My actual job in the billet that I occupied in the Navy was twofold. One job was to take care of 37 big Revco freezers that were kept at –140, storing units of blood that had been collected from the Korean War through the Vietnam War. My second job was as a backup physician for a nuclear submarine in Groton, Connecticut. In my free time, I worked on why it is that we only need a platelet count of 50,000 for coagulation, but our normal platelet count is 350,000. So I worked on platelet physiology with the help of some great people who were willing to teach me how to design and carry out experiments.

I then moved to the Naval Medical Research Center in Bethesda. I was a General Medical Officer at the National Naval Medical Center, which was a great job for training as a general internist. I now also had my own laboratory and learned from Irwin Scher how to do immunology research. The military realized that they needed somebody trained in radiation injury and bone marrow transplantation; I agreed to serve, as did my friend Carl June, and I took out another four years of

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Figure 1. Craig Thompson on April 25, 2015. Image credit: Karen Guth.

obligation to the military in exchange for being sent to the Fred Hutchinson Cancer Research Center to do a fellowship in bone marrow transplantation and hematology/oncology.

In the early 1980s, we still didn't have modern immunosuppression, so graft-versus-host disease was horrible for many of the patients. Most patients had their leukemia come back because we hadn't figured out all the conditioning regimens. I was lucky enough to be one of the fellows that treated the first 100 patients with cyclosporine during bone marrow transplantation; cyclosporine had already been used for solid tumors, but we were using it as an immunosuppressant. It was transformative. There are many advances that have been made since then, but in my career, that was the one that transformed the treatment from a purely experimental procedure to something that could be practiced everywhere.

JCI: How did you transition from such an impactful clinical experience to become an academic immunologist?

Thompson: Carl and I were both interested in these patients that were dramatically advantaged by cyclosporine. Cyclosporine turned off proliferation in every known in vitro assay of lymphocyte function. And yet, even though no one thought they would be able to handle a virus or bacterial infection, if anything, the patients did better because they healed more effectively with immunosuppression. For three years, Carl and I played around, combining every way known to induce proliferation of lymphocytes. We found the key combination that allowed human lymphocytes to proliferate with industrial doses of cyclosporine onboard. Our research led to what we now know as the costimulatory or CD28 pathway.

JCI: During this time, you were introduced to the world of apoptosis.

Thompson: I really was interested in the problem of proliferation. In the standard proliferation assay, you add a mitogen to stimulate lymphocytes, and then after three days, you add tritiated thymidine. You would wait a day, harvest the cells, and count the thymidine that was incorporated, and that would be an index of proliferation.

At the Naval Blood Research Laboratory, I learned how to count cells better than anybody on earth, because that's what we did all day long. And I grew up in a family where my mother was morbidly fearful of radiation. We were never allowed to have a color TV, because she thought it gave off too much radiation, but we had a black and white TV. We weren't allowed to get any closer than six feet because my mother was worried that we would get too much radiation. So I always thought you should limit the radiation, and so instead of adding the tritiated thymidine, which is radioactive, I just counted the cells.

What is interesting is that less than 10% of the cells that were present on day one were present on day four. The professor in the laboratory said not to worry, as it was the trauma of taking them out and an artifact of the tissue culture system. And we couldn't study the phenomenon we wanted because the cells would die in culture. Around that time, Stan Korsmeyer and Carlo Croce were characterizing a gene called *BCL2* that modulated apoptosis. I had my first technician, who started a project cloning homologs of *BCL2*, and we cloned a gene that now is known as *Bcl-xL*. The rest is history. We had a way to reverse the cell death response. We started a long collaboration with Korsmeyer's laboratory to clone a wide variety of genes in the *BCL2* family that regulate apoptosis, and we never looked back. We started to become interested in why cells die and how we could manipulate the apoptotic decision to learn more about cell death and proliferation.

JCI: During this time, you were at the University of Michigan as an HHMI investigator, and you decided to take on a big leadership position at the University of Chicago. Why take on an administrative role when your research was so exciting?

Thompson: When I went to Michigan, I was a physician-scientist. I had an appointment in the Department of Internal Medicine, but because HHMI also requested basic science appointments for their people, I got a secondary appointment in Microbiology and Immunology. But it was under the condition that I would never be allowed to take a graduate student, because I didn't know what it would take to be a "real" scientist. I was never completely happy with that situation, and I wanted an opportunity where the science would be the more important part of my position, rather than secondary to my taking care of patients. Taking a leadership position in an institute where the understanding of medicine would be taken back into the science curriculum gave me the opportunity to concentrate on my science, and it was a good trade-off on many levels.

JCI: You then took on an even bigger role in terms of administration by moving to Penn to help start their Abramson Family Cancer Research Institute.

Thompson: The offer to go to the University of Pennsylvania to help start a new research institute came at an absolutely

perfect time. We'd completed what I went to Chicago to try and do; we had filled the place to a self-sustaining level. I was no longer primarily interested in apoptosis, because we had eliminated apoptosis in mice and found that there was still another mechanism of control of cell survival, and that was through the regulation of nutrient uptake in cellular metabolism. I knew I wanted to change the lab to study that, and there was no way I could do it because everybody counted on me to be the resource for apoptosis. I told the lab, three months after we moved, that we were going to abandon everything else to focus purely on the regulation of cellular metabolism as it informed cell proliferation and cell survival. This did not lead to a great deal of excitement in the laboratory, and in fact, Jeff Rathmell, who was the senior postdoc in the lab, was elected to come and tell me that they were going to rebel, because in fact, I was destroying all their careers. It took some convincing to keep them going, but in fact, all of them now work in cellular metabolism.

JCI: In 2010, you took on the presidency of Memorial Sloan Kettering Cancer Center. How do you manage to maintain a lab together with the different puzzles that come along with a job as enormous as that?

Thompson: It's an exciting time right now in cancer biology, with success in targeted therapeutics, epigenetics, and immunotherapy. My secret is to work with really smart and dedicated people who all want to take responsibility for what they do. And that is easy to do at Memorial Sloan Kettering. We all know why we're coming to work. Everybody's very proud and very responsible in their jobs. It's more about delegation and making sure we're aligned in the correct way.

I've also been very fortunate to work for over 25 years with my wife Tullia Lindsten, who is better trained than I am. She is an MD PhD from the Karolinska Institute, trained in both tumor biology and immunology.

JCI: Would you ever counsel any of your mentees to try and emulate your path?

Thompson: I always argue that if my trainees try and emulate my path, I will be a failure as a mentor. By the time graduate students come to us, and certainly by the time postdocs come in, they're fully formed adults with their own ideas. We tend to think of them as not fully formed. That's not true. They have to forge their own path. They need to figure out how to exploit their best strengths, how to be effective, and what I did will never be an effective way for them to be successful.

JCI: When you were a kid, what did you think you were going to grow up to be?

Thompson: I was pretty sure I was going to be a lawyer. I have no idea why, other than there was nobody in the family that did that, so it seemed like an open field. I took one pre-law course in college and realized that was the stupidest idea I'd ever had.

JCI: So then, a related question: if you couldn't be a physician or a scientist, what other career path do you think you could've excelled at?

Thompson: The only other path that I explored, which was actually what I thought I would do until I got into medical school, was getting my teaching certificate. I would've tried to be a high school science teacher and sports coach.

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