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News

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JCI: What led you to study infectious diseases?

Crowe: During my time as an undergraduate, I developed an interest in service and global issues. As I went to medical school, my plan was actually to be a medical missionary in Sub-Saharan Africa. I worked in West Africa and in East Africa, and when you see infectious diseases occurring close up in those settings, it changes your mind and your heart. I really wanted to have an impact on the things that were affecting people there in low-resource settings, and especially children, because I was going to train as a pediatrician.

Figure 1. James E. Crowe Jr. will be honored with the 2017 ASCI/Stanley J. Korsmeyer Award for his work uncovering B cell responses to viral infections.

I met my wife in medical school, and she had similar interests. But we decided that, for the most part, many of these settings need public health intervention, water, and security. Our plans did not coalesce on providing medical care in that setting, but it led us to think about what we could do with our background skills and training that would affect these settings in a larger way.

That led me to thinking about tropical medicine and infectious diseases, and so I went to NIH to work on vaccines. Robert Chanock, who ran the lab and had trained with Albert Sabin, had been involved in a lot of vaccine work and had made the first association between respiratory syncytial virus (RSV) and respiratory disease in children. By the time I was in residency, RSV was well-known as the most common cause of hospitalization in children throughout the world. My vision was to go work with Dr. Chanock to make a vaccine for the most common cause of respiratory disease in children.

JCI: Can you describe the extension of your work from basic research on immune responses to the development of vaccine candidates for clinical trials?

Crowe: For me, it actually happened backwards. My postdoctoral fellowship was really applied. I was taking RSV and randomly mutating WT virus strains to find attenuated mutants, and then I was doing preclinical testing in small animals and nonhuman primates, to down-select large panels of virus vaccine candidates for clinical trials. We did clinical trials with at least five of the viruses that I made. But in my mind, I was always thinking, "How does the immune system work? And what is it we're actually trying to accomplish with these vaccines? And are these vaccines going to trigger the type of responses we want?"

After my postdoctoral studies, I decided I wanted to understand mechanisms of immunity relevant to vaccine work. I had to self-train as a human immunologist, because my postdoctoral training was in vaccine development and virology, but my interest was in immune responses. The first five years of my faculty life, we didn't generate any data at all; I was just training myself in human immunology and developing new techniques that didn't exist to study human B cells.

At the time I started, scientists in the field were able to make mouse monoclonal antibodies, but if you looked at the efficiency of those processes, they were in the realm of recovering between 1 in 100,000 to 1 in a million cells — it was incredibly inefficient. In a mouse, you can hyperimmunize and you can harvest their whole body if you need to, but you can't do that in a human being. This led us to develop single B cell techniques in the early '90s, when people just couldn't imagine it. But I knew it was what we needed, and it actu-

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ally was fun; it was kind of an engineering project, almost like tinkering with toys.

It was really exciting when we finally started to be able to make human monoclonal antibodies from single cells. From that time on, I tasked every person that came into my lab with bringing a new method into the group — either a method that existed in the field that we didn't know how to do or something we wanted to know how to do and no one knew how to do it, but we developed it. The beginning of the training of almost every student and postdoc in my lab has to do with some kind of methods development; I'm trying to give other people the experience that I had.

JCI: What propelled you to expand your work into a broader range of infectious diseases?

Crowe: I was interacting with a company as a consultant on RSV, and one of the other scientific advisory board members was Harry Greenberg, from Stanford. He spent most of his career working on rotavirus, and he said, "Well, if you've got these B cell techniques worked out, you should look at rotavirus." For me, this was not that far a leap, because rotavirus was the most common cause of diarrhea in children, and it seemed attractive because then I would be covering the two major causes of acute illness in infants. It was congruent with my personal mission, but that step took me away from my comfort zone of my postdoctoral training in RSV.

After that time, I made a decision that changed the course of our studies. In the late '90s, there was a movement between the Soviet Union and the United States to autoclave all of the smallpox stocks to eradicate the virus because it was no longer circulating, and it was only supposedly in two countries. However, scientists in the virology community raised the concern that we actually didn't know that much about pox viruses. We didn't even know the sequence of their whole genomes.

President Clinton put about $50 million into pox virus research and suspended the plan to autoclave the stocks temporarily. We were awarded a grant to study B cell responses to pox viruses, and at that point, I was no longer working with RNA viruses but, instead, DNA viruses. I went to meetings about smallpox and realized that there was an entire world of emerging infectious diseases and bioterror issues that are poorly addressed. Most researchers in 1998 had no interest in this field. That was a stepping stone. We went from RSV to rotavirus, which is a pediatric pathogen, to smallpox. And at that point, anything became fair game.

Now, we're working on over 50 targets, and we were well-positioned to work on Ebola before it happened. We were working on Zika before it happened, all sorts of unusual bird flus, chikungunya — we have antibodies that are now in development for clinical trials for all of these programs.

That curiosity about emerging infections turned in to a full-time activity of finding human monoclonal antibodies for diverse targets. We're now at the point where, instead of reacting to a government's call for funding proposals or reacting to an outbreak, we're trying to anticipate the next outbreak and get ahead of that. Of course, at some level, that's impossible, but if we have a list of 50 targets, we can guess that one or more of these that is already circulating has the potential to become pandemic.

JCI: Can you tell us more about how your group was able to so quickly identify antibodies to neutralize Zika virus infection?

We were highly involved in research on dengue virus, which infects 400 million people per year and is a major vaccine target. We started thinking about other Flaviviruses that cause human disease or could potentially cause a disease as widespread as dengue. We started working on West Nile virus, Japanese encephalitis virus, and the yellow fever virus. Then you start going down the list of related viruses, and you find things that are more esoteric. But we started some low-level activity on these others because there was no intellectual reason to think that they didn't have the potential to cause an outbreak.

Zika was on that list, so we started working on Zika in May 2015. We collected some human specimens around that time because I read a case report of a sexual transmission, and it was clear from the report that the people were in the United States. We tracked them down, and they were gracious enough to give us samples. We already had Zika immune B cells in 2015, so when the outbreak occurred, we were in position to expand our work. And our experience with dengue was very important because we understood a very similar virus, so we knew how to screen properly, which got us going very quickly.

JCI: The Korsmeyer Award also recognizes your role as a mentor. In what ways did your postdoctoral years shape your outlook, and what do you see as important in mentoring in your own lab?

Crowe: I think the common approach in university settings now is to spend a lot a time talking about mentoring and mentoring programs. But in my experience at NIH, basically we just worked one-on-one with our mentor. There was more talk about the work and less talk about career development — the career development happened naturally. I think sometimes people overcomplicate the idea of mentoring.

In my own mentoring, I've taken on a commitment to training for diversity in a much more deliberate way. Institutions and mentors always give some commitment and lip service to doing this, but I've been trying to seek out the broadest diversity of individuals that I can because our work is focused on international global health issues. I want to train people from all over the world and from different backgrounds. During the recruiting process, we are very intentional about that, and if you look at our group, it's very, very diverse. And we benefit from that. I think in a mentoring relationship, you develop a close personal bond, but it's through the work. You can have people from very different backgrounds with cultural norms that might otherwise be divisive, but in the context of a very focused work environment, we can celebrate our differences and benefit from them.

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