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Breaking down barriers to clinical translation: an interview with Laurie Glimcher

Laurie Glimcher is a physician-scientist with a true passion for research. In this interview, she discusses her early career, key issues in successful clinical translation and her move to become Dean of Weill Cornell Medical College in Manhattan.

Laurie Glimcher has made countless contributions to many areas of biomedical research. Among these are the identification of several factors relevant to human health and disease, such as T-bet, a transcription factor required for the differentiation of T helper 1 (Th1) cells, XBP-1, a transcription factor involved in cellular stress responses, and Schnurri-3, an important regulator of postnatal bone mass. Laurie Glimcher is also an outstanding mentor to trainees, a respected role model for women in science and a visionary leader with a commitment to translational medicine. On January 1st, 2012, she will take up the position of Dean at Weill Cornell Medical College and Provost of Medical Affairs at Cornell University, where she will aim to integrate a multidisciplinary team of scientists in an expanding research and clinical programme, as well as continue to lead her own laboratory.

How did you become interested in science and medicine?

My father [Melvin Glimcher] was an orthopaedic surgeon, and I used to love to go with him to his lab [at Massachusetts General Hospital (MGH)]. I always loved learning about science and thinking about science, and my father was an excellent role model.

Where and with whom did you train?

I've spent nearly my entire career in the Boston area, except for 3 years when I was a postdoc at the NIH. Briefly, I did an undergraduate degree at Radcliffe College, and then went on to Harvard Medical School. Near the end of medical school, I spent some time in Harvey Cantor's lab, where I got hooked on research. I then did a residency in medicine at MGH – but only for 2 years, because after being in Harvey's lab I was certain that I wanted to do research. So, I then went to do a postdoc at the NIH, which was a really amazing and collaborative work environment. I was primarily supervised by Bill Paul, but during my time there I also collaborated with many other investigators, including Ethan Shevach, Al Singer, Ron Schwartz, Ira Green and others. It was a very fruitful time.

After 3 years at the NIH, I came back to Boston and started a full-time Clinical Fellowship in Rheumatology at MGH, and at the same time started up a lab with my first R01 grant, which I'd written during the time I was a postdoc. This was a very tough time: as well as several clinics each week, I had the challenges of starting up a lab, teaching medical students, and I also had two very young children at home. My first husband, Hugh Auchincloss, was at that time a surgical resident and was incredibly busy. What saved me during those years was help from my parents. My Mom and Dad would come by several times a week and help out with the kids in the evenings, and on weekends when my husband was on call I would pretty much move in with my parents so that I had extra help.

Credit: John Abbot.

But you persevered, and you've been extremely successful. What has been the most exciting discovery of your career?

I think I would have to say it was our identification of T-bet, a transcription factor driving Th1 cell differentiation. That discovery was truly an "Aha!" moment. I still remember the day that my postdoctoral fellow Susanne Szabo came into my office with the data – she had isolated a cluster of yeast cell clones containing genes that suppressed IL-2 [interleukin-2] expression. (We were using a region of the IL-2 promoter as bait, as little was known about other Th1 cytokine promoters at the time.) In any case, we were confused by this finding, as we thought we were looking for a factor that induced, rather than suppressed, IL-2. But, we followed it up, using retroviral transduction technology that had just been developed. And, again, I remember so clearly when Susanne came into my office with the flow cytometry plots showing that T cells that were transduced with this gene – the gene encoding T-bet – produced truckloads of interferon-γ [the primary Th1 cytokine]. And that discovery was a gift that has kept on giving over the years. We later discovered that T-bet is involved not only in Th1 cell

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differentiation, but is also important in innate immunity and many other aspects of immune function that have substantial impacts on outcomes of human disease. For example, in collaboration with a genetics group, we discovered a polymorphism in the gene encoding T-bet that is associated with childhood asthma.

If time and money were no object, what research questions would you tackle?

That's actually a question I've had to consider carefully lately, as I'm downsizing my lab when I move in January to become the Dean at Weill Cornell. I've had several postdocs in my lab that have done tremendous work on T-bet and will continue to work in that area, now in their own independent groups. So, I feel that will be very well looked after, and I'll focus on other research questions in my group – in three main areas. First, my lab will continue to explore the role of the ER stress response in innate immunity and also in cancer. Second, we've become interested in the immune response to HIV/AIDS as part of my connection with the Ragon Institute and will continue those projects. Third, we are excited to continue our studies in skeletal biology, an area that I think is really understudied and underpopulated. Diseases such as osteoporosis and osteoarthritis affect a huge proportion of the population – as many as 50% of postmenopausal women suffer from osteoporosis, for example – yet there are very few therapies available for either of these diseases and little knowledge about the mechanisms underlying their pathogenesis. We made a very serendipitous discovery several years ago of an adaptor protein now known as Schnurri-3, which controls adult bone mass. We were initially disappointed to find that decreased expression of this factor led only to a very mild immune phenotype, but we later realised that mutant mice lacking Scnhurri-3 display a very striking bone phenotype of extremely elevated bone mass. After we published this finding, we were contacted by several companies and decided to work with Merck on finding compounds that would inhibit Schnurri-3, with the potential to be developed into a treatment for osteoporosis. Most available therapeutics for osteoporosis target the osteoclast (the bone-resorbing cell), but in fact the compound we are looking for would inhibit Schnurri-3 in osteoblasts (the bone-forming cell), and would thereby preserve or promote bone deposition. Our interaction with Merck was wonderful: our lab had almost daily contact with their scientists, and it was a true collaboration. These types of academic-industry collaborations are on the increase, and they can be very successful as long as everything is completely transparent. Transparency in working with industry is crucial. I like to quote an old saying when it comes to this issue: "Sunshine is the best disinfectant" – as long as everything is out in the open, things can move forward in a productive way.

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In addition to transparency, what else is important in facilitating clinical translation?

I think that academic institutes need to become better centres for clinical research. And I think that we should try to remove the divide between what we refer to as basic scientists and translational scientists – they should be one and the same. Basic scientists have a responsibility to translate, because the focus of basic research should ultimately be on the patient. And a key to this is having different types of scientists working together and communicating every day. We should have structural biologists and chemical biologists and molecular biologists and computer scientists and clinicians working together. And new trainees should learn about, or at a minimum be exposed to, all of these different fields. This will help to encourage more multidisciplinary working environments, which are key to successful translation.

These are the kinds of things I want to prioritise in my new position as Dean at Weill Cornell. There is a big expansion planned – in fact there's a new research building going up as we speak. It will be called the Belfer Research Building, owing to generous support from Robert and Renee Belfer. It is scheduled to open in 2014, and in the interim I am going to invest a lot of time in recruiting many outstanding scientists and clinicians. I am excited about this position not only because Weill Cornell is an excellent medical college and clinical centre but also because of its president, David Skorton. He is an outstanding and transformative president of Cornell University and a wonderful person, and we've already established a great working relationship. I'm really looking forward to working with him. I am also thrilled to be working with Sandy Weill, Chair of the Board of Overseers of Weill Cornell Medical College, whose enormous generosity and devotion to this institution are legendary.

What will be the focus of the expanded research program at Weill Cornell?

The Belfer Research Building will be a multi-disciplinary institute, but Weill Cornell is not a huge college, so we must focus in specific areas. One subject area that we will specialise in is neurodegeneration, in part thanks to generous support from Robert and Helen Appel that enabled establishment of the Appel Center for Alzheimer's Research. This is a really crucial area of research at the moment: I don't have to tell you that diseases like Parkinson's and Alzheimer's are putting a huge strain on our healthcare systems – a huge proportion of the elderly population is affected by neurodegenerative diseases. In fact, I would say this is an area of medical emergency in a world where the percentage of elderly people is rapidly increasing. Another area that the institute will specialise in is cancer research. Like neurodegenerative diseases, cancer is a disease that primarily affects the aging population. In general, I think a main research focus should be on how to promote healthy aging and longevity by treating age-related diseases, which also include osteoporosis and diabetes.

How about your clinical work – will you be able to continue that when you take up the new position at Weill Cornell?

I would definitely like to continue working with patients. As a trained physician, that is really my identity – I'm a physician first, and then a scientist. At the moment, I work as an attending rheumatologist at Brigham and Womens' Hospital, and I would like to continue doing some clinical work when I move to Weill Cornell. I won't take that on until I get settled, of course, but in anticipation I'm now applying for my medical license to practice in the state of New York. At the same time, though, I want very much to reserve some time for my lab. Scientific discovery and the chance to mentor young scientists have been such a rewarding part of my career that I couldn't bear to abandon the lab.

You're known for having a great work-life balance. What's your secret?
There's no secret! It's been a challenge, and I've always worked very hard. My advice to young scientists is that unless you really have a passion for science, unless you *really* love your research and thinking about experiments, then don't become a scientist. It's a tough career. Particularly for women – although I like to think that we can change that. I'm involved in some initiatives that are trying to introduce ways for women to take on a career in science without being 'penalized' for taking time off to have a family, because this is often what taking time out for children amounts to. I came back to work within days of having each of my three children, because that was the right choice for me, but not all women want or are able to do that. In particular, we're trying to come up with ways to support women at the transition from Assistant to Associate Professor, as this is when women in science usually encounter the most difficulties in juggling family and work. For example, the idea of two women sharing a single lab has never been explored. Imagine if two women wanting to work part time could co-head a lab and have equal responsibility and get equal credit for the lab's findings and funding? This is possible in other professions, such as clinical medicine, law and teaching – why not science?

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You're incredibly driven – what keeps you going?
I really have a passion for science, and I always have. Also, mentoring is one of the most rewarding parts of my career. Of the awards I've received, the Excellence in Mentoring Award I received from the American Association of Immunologists is the one that has made me most happy. It's our responsibility as scientists to train the next generation.

What would our readers be surprised to know about you?
I have three terrific children that could tell you plenty of stories that would surprise you! When one of my sons was about 12 years old, he came with me when I received an award [the American Society of Clinical Investigation's Distinguished Investigator Award]. He didn't really understand what I did professionally, but at this awards ceremony it dawned on him that I was a scientist – not just his laid-back Mom who wandered around the house in flannel pyjamas singing made-up songs to our dogs.

DMM greatly appreciates Laurie Glimcher's willingness to share her unique thoughts and experiences. She was interviewed by Sarah Allan, Scientific Editor for DMM. This piece has been edited and condensed with approval from the interviewee.