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From immunological tolerance to stem cell therapy and back: an interview with Irving Weissman

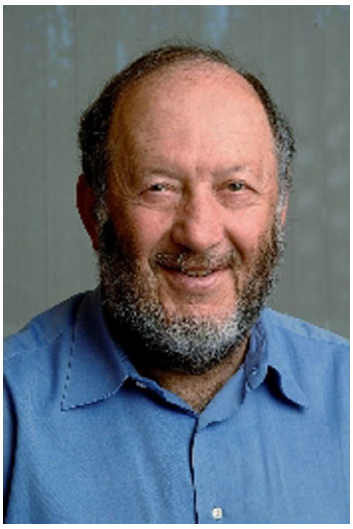
Irv Weissman has pursued many areas of biomedical research throughout his prolific career as a medical doctor and researcher. In this interview, he recalls his early years studying immunology in mice, and discusses the more recent challenges he has faced when attempting to develop stem-cell-based therapies with industry.

Irv Weissman began his career in Great Falls, Montana, studying immunological tolerance in a small research lab. He soon shifted his focus to work on stem cells, and in 1988 was the first person to isolate stem cells of any type to purity. He subsequently characterised several different types of human and mouse stem cells, and developed many valuable mouse models of human disease with which to demonstrate the potential of stem cells as a cellular therapy. He is now Director of the Stanford Institute of Stem Cell Biology and Regenerative Medicine, where his aim is to encourage the translation of new disease treatments in an academic environment.

What drew you into biomedical research? Did you come from a scientific background?

No, I was the first to get an advanced degree once my family arrived in the United States. My grandparents, like many Jews who lived in the area that later became Russia, left to avoid the draft. On coming to the United States, my family homesteaded and became traders in furs, junk, hardware and second-hand auto body parts. When I was 10 years old, I read a book called *Microbe Hunters*, and I knew then that I wanted to do something like that – to be someone that made discoveries relating to microbes and applied them immediately to human health. But I used to wonder not only if I could ever make discoveries like that, but if I would have the will to work as hard as the microbe hunters to make sure those discoveries made a difference. Could I commit myself completely to that life? I later found out that I could – I didn't realise at that time how much your interest in a subject drives you.

When I was 16 years old and in high school, I learned that there was a pathologist in the town where I lived – Great Falls, Montana, which had no university at that time – who had set up a small research laboratory in the hospital. He had formerly been on the faculty at Harvard and in Utah and had become tired of academics. His name was Ernst Eichwald, and he allowed me to work with him. Luckily, he never checked my grades, because I was never better than a B+ student, but for some reason I could think experimentally. Soon after I started working with him I learned that, in an inbred strain of mice, skin grafts were rejected when the donor was male and the recipient was female, implying that the Y chromosome controlled or encoded the transplantation antigen. This was in 1956 or 1957, around the same time that Billingham, Brent and Medawar had just published a fantastic paper on immunological tolerance, and I began repeating their experiments on my own. Even before I went to medical school [at Stanford], I showed that you could get tolerance to Y antigen if you injected haematopoietic cells from male donors into female newborn recipients up until 3 weeks of age. But, if you injected the mice between 3 and 4 weeks of age, this protocol didn't work – instead of



inducing tolerance to Y antigen, the donor haematopoietic cells induced immunity in the recipients.

This was before we knew what the thymus did, and before we knew much about immune development, so this work led me to look into the functions and the cell lineages of the thymus. During medical school, I went to work with Jim Gowans in Oxford for 9 months, which was absolutely fantastic. He had just shown that lymphocytes were the central cells of the immune response, and he had largely explained the clonal selection theory of immunology – that is, that 1 in every 10,000 immunocompetent lymphocytes has a receptor for any given antigen that comes along, and that these cells re-circulate through the tissues, meaning that there will be a lymphocyte specific for a given antigen present just moments after the antigen comes into the body. Jim went on to show many other things, essentially opening up the field of lymphocyte homing. He labelled lymphocytes to follow what they did in vivo, and showed that they went through particular blood vessels – I then

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followed lots of those tracks. For example, I showed in his lab that the thymus works by making T cells that migrate through the same blood vessels that Jim had described. And I went on to determine how to do frozen-section immunohistochemistry without destroying the markers for which we had antibodies, so that we could study the localisation of T cells and B cells in vivo.

That was a very exciting time in the field of immunology. Do you think there's still the same excitement, or has that excitement moved to other fields?

I've moved on a lot from immunology, to work on stem cells, and then on cancer and leukaemia stem cells. But these fields are all connected: all cancer cells must devise a way to prevent the innate immune system from eating them and killing them. Luckily, I came across that realisation at an early stage when studying leukaemia stem cells, which brought me back to studying the functions of the immune system. Right now, I'm looking at the possibility that a tumour essentially surrounds itself with an invisibility cloak – a 'don't-eat-me' signal – to prevent it from attack by the innate immune system. This cloak also might prevent the adaptive immune system from seeing it: it prevents macrophages from eating and killing the tumour, and also might prevent dendritic cells from eating the tumour and from presenting tumour antigens to T cells.

You began your career in academic research and medicine, so when did you start getting involved in industry?

I've been involved in setting up companies and doing clinical trials through companies going back to the 1980s. I was on the founding scientific advisory board of AMGEN and DNAX. I learned very interesting lessons from George Rathman [co-founder of AMGEN], who is probably the greatest CEO in biotech that I've ever met. He demonstrated how you can focus on the things that are important, how you can make a company and keep control. Because the most important thing in having a company is not just to make money, it's to keep control. To keep control by selling off things that are not so important, but keep other things you're going to do all the way, including the clinical trials.

In 1988 I started a company called Systemix with my postdoc Mike McCune, where we isolated pure human haematopoietic stem cells. We wanted to transplant them in two clinical situations: first, we wanted to isolate them from a patient with a metastatic cancer, put the patient through a higher dose of chemotherapy than they normally would have received (a lethal dose, to kill a higher fraction of endogenous tumour cells) and then rescue them with the stem cells we had isolated from them (which, being pure stem cells, had no cancer contamination). We carried out that procedure for patients with breast cancer, myeloma and non-Hodgkin lymphoma. The trials began in 1996, at a time when a company named Sandoz was a partner on many of Systemix's affairs (they owned 60% of the company but were not involved in the science end of things). Ciba and Sandoz then merged to form Novartis and, even though we were in the middle of the clinical trials – too early to have the results – Novartis decided to shut them down. Now, 14 years after that trial began, I've summarised the results of the breast cancer trial: 33% of the patients that received the cancer-free stem cells are alive today, 14 years later. These were stage IV metastatic breast cancer patients. For those patients at the same centre that received mobilised peripheral blood (where at least 40% of the isolates contain massive amounts of cancer cells), only 6% were still alive without disease after 2 years. If this treatment were a pill, it would be how patients with breast cancer were treated today. We had equally good data indicating that the treatment would add years to the lives of patients with non-Hodgkin lymphoma, although I have yet to summarise that trial.

The second kind of stem cell transplants we wanted to do were from a donor to an allogeneic host (MHC-matched) or, in some cases, from a parent to a child (haplo-matched). We had shown in mice that if we did a stem cell transplant in a sublethally irradiated host, the donor stem cells engrafted and the hosts were specifically and life-long tolerant to any organ graft from the same stem cell donor. This was because the donor haematopoietic stem cells passed through the host thymus and bone marrow to give rise to mature T cells and B cells that would not recognise and react to the host's tissues. So, there was no graft-versus-host disease; we had created a setting of specific immunological tolerance. We tested this strategy in animal models of autoimmune disease, including type 1 diabetes, multiple sclerosis and lupus. We found that, in every one of these models, we could completely cure the autoimmune problem by transplanting haematopoietic stem cells from a genetically disease-resistant donor into a diseased host. These proof-of-principle experiments were in fact what got Sandoz interested in purchasing 60% of the company – they'd developed cyclosporine, and were in the field of immunological grafts, and they wanted to follow on in this area.

Later, I formed a company [Stem Cells] with Rusty Gage and David Anderson in which we isolated human brain-forming stem cells. We showed in 2000 that we could transplant them into the brains of immunodeficient mice, and they acted just like mouse brain stem cells. After a lot of work, we were ready to do a clinical trial. We thought that lysosomal storage diseases with a neurodegenerative component might be a good place to start, because the donor-derived normal cells could make and secrete the enzymes that the defective cells could take up into the lysosomes and so on. The first lysosomal storage disease we considered is called Batten disease, which involves the toxic accumulation and aggregation of lipoprotein inside lysosomes. Children with Batten disease are normal until at least 1 year of age, and then, depending on the penetrance of the particular mutation they carry, they start losing their vision and IQ, they become ataxic and they usually die by age 18. When you look at their brains post-mortem, there is evidence of massive neurodegeneration, and there are enlarged ventricles left behind.

The company shopped around for partners to do this clinical trial, and we got into discussions with a centre that seemed ideal: it had the patients, the surgeons, the people who knew how to transplant the cells. But somebody on an internal committee said: "Is this the first time human brain stem cells are being transplanted?" and the company representative said, "Yes, this will be the first time". They said, "Well, you can't do it with children. You have to prove it's functional in adults before you can do it in children". So, the company was delayed. But another university agreed to do it: the University of Oregon treated six advanced-stage cases. There were no adverse effects from the transplant itself, although with such late-stage disease it was difficult to see efficacy. But now they've been approved by the FDA [Food and Drug Administration] to go ahead and work on patients with early-stage disease.

So, the idea is that you provide the proof-of-principle studies in mice, you go to the FDA, you go to the IRBs [institutional review boards] and so on, and then you proceed to the clinical trial. That's how it should have been at Systemix in the case of developing treatments using haematopoietic stem cells. But there are many lessons you learn on the way. You can't know that there will be someone who doesn't want you to put cells into a child to try to treat a childhood fatal disease. You don't realise that even if you have something that really works, the big company that buys you might still make a business decision that your new technology isn't their top priority. And I didn't realise that there is no constancy in the leadership of a company. The one thing that is constant in the function of a company is to make a profit. What's constant in the biomedical research at universities and institutes is to advance medical science without thinking about profit or loss. Venture capitalists have stopped being adventurous – they're risk averse. The timeline has to be to make money in about 3 years. When it comes to small molecules, industry and academia can often join together, but in our case we were dealing with something that wasn't in the business sphere. So, this research on blood-forming stem-cell transplantation belongs in the universities.

To facilitate translation of these types of therapies, academic centres will ideally need to be organised in a certain way. Is this what you had in mind when you became Director of the Stanford Institute of Stem Cell Biology and Regenerative Medicine?

Yes, we decided from the beginning it wouldn't be departmental. To get people to cross disciplines – from engineering to basic science, from basic science to preclinical research, from preclinical to clinical research – departments wouldn't work, because their main concern is protecting themselves and their discipline. So, we decided to step outside of the departmental structure. The investigators in our building have faculty appointments in many other departments, but their slots and their space are determined by the Institute. I'm not there to protect the field of stem cells – I'm there to get the people who can collaborate to make it move forward.

And what about training? How do we go about training the translators – the people who will drive these new technologies to the clinic?

The people who try to be 'translators' but that don't know the basic science are not in a position to do it. The people who will drive translation are basic scientists that have been taught to think about how things might translate from their discoveries. There are not many scientists like this, but there are enough. When you have these types of people working with clinical people in the same lab, with a goal leading to a Phase I trial, you can form a coherent group that has all the elements that you need for translation. But of course you have to consider things like who will do the GMP [good manufacturing practice] manufacturing; you have to find your own regulatory advisors for the FDA, the EMA [European Medicines Agency] the MHRA [Medicines and Healthcare products Regulatory Agency], and so on.

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We should look at the clinical unit that will be eventually delivering these therapies and consider it a model for forming companies. These clinical units include the founder (the scientist with the vision), the experts at doing preclinical validation, the clinical trialists, the regulatory people. And of course, as this unit will carry out its work with a hospital that has a financial structure, it will know everything about the finances and the real cost of goods. The unit will know what's happening each step of the way: no pharmaceutical company will be able to claim that it spent a large amount of money getting a product to Phase I trials and that they have to recover their costs by charging huge amounts for a new drug. So, one outcome from this model, I hope, is that we will be able to come closer to the cost of goods when marketing new technologies. I'm thinking that the next step will be a whole new model of translation and, in turn, a whole new model of establishing companies – at least around the concepts of normal and cancer stem cells, where the cells are really the units of therapy.

If you could go back to the bench and focus on one project, what would it be?

Neurogenesis and neural stem cells, absolutely. Just think: I'm talking to you, and you're listening – how does that work? And how do you remember what I said 10 minutes ago? Nobody really knows. We know that learning requires proliferation of neural stem cells in the dentate gyrus of the hippocampus, and that preventing that proliferation prevents learning. In adult-onset dementia, those cells don't proliferate, and the patients can't learn. They can remember everything that happened to them 10 years ago, but they can't form short-term memories. Perhaps I should have devoted myself and my lab to working on this 10 or 15 years ago, to making neural stem cells from people with genetic disorders, putting them into mice, and really learning about the biology of these cells and these disorders. There's great potential in that area.

Excerpts from this interview can be heard in the podcast associated with DMM Vol. 4, Issue 5 at http://www.biologists.com/DMM/podcasts/index.html. DMM greatly appreciates Irving Weissman's willingness to share his unique thoughts and experiences. He was interviewed by Sarah Allan, Scientific Editor for DMM. This piece has been edited and condensed with approval from the interviewee.