# People & Ideas

## Irving Weissman: Working for regenerative medicine

A force behind both the science and politics of stem cell biology, Weissman now strives to translate his successes to the clinic.

The thriving field of adult stem cells and its burgeoning therapeutic promise owe a big tip of the hat to Irv Weissman, who in the late '80s isolated the first class of these pluripotent cells—the mouse hematopoeitic stem cell (1). Not long afterwards, he identified its human counterpart (2) and then began determining the environmental cells in the bone marrow (3, 4) and thymus (5, 6) that are necessary to support developing blood cell lineages. Stem cell and cell lineage research is a critical component of his Stanford and Hopkins Marine Station laboratories as well as several companies he has helped found.

Not surprisingly, Weissman has been far from silent in political debates in this arena. After the Bush administration's ban on NIH funding for research using newly derived human embryonic stem cell lines, Weissman was instrumental in the writing and passage of California's Proposition 71, which protected the research as a state right and allocated three billion dollars in funding over 10 years. Weissman recently took time to discuss his past and future influence in the field.

### MONTANA TRANSPLANTATION

***Where did you grow up?***

I grew up in Great Falls, Montana, and I still get back there a lot. I started in a laboratory when I was 16 with Ernst Eichwald, a pathologist who was editor of the journal *Transplantation*. His laboratory now includes five PIs and is called the McLaughlin Research Institute. I'm head of the scientific advisory board, so I spend a fair amount of time going back and forth.

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***How did you get interested in working in the laboratory so young?***

When I was 10, I read a book called *Microbe Hunters* about the life of scientists. I went and talked to Ernst because I heard he had mice that I might be able to take care of. After the first week, he gave me a paper to read that was totally impossible. It was about "histocompatibility genes." If it had said "tissue transplantation genes," it would have been easy to understand. Of course, now I know that people write and speak like this all the time to make our field obscure and difficult to teach and learn.

***When did you become fascinated by stem cells?***

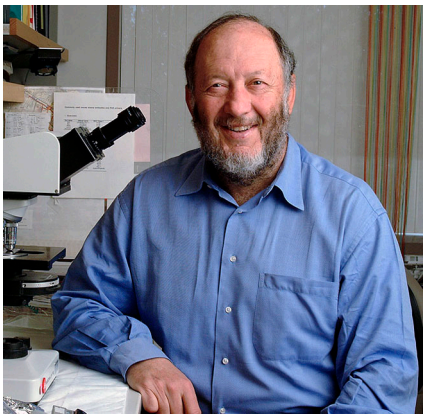
I was fascinated from the very beginning by a paper from Billingham, Brent, and Medawar, who induced transplantation tolerance in fetal mice. That meant to me that the immune system was maturing during a mouse's fetal or early neonatal life, and I wanted to better find out when.

When I was in medical school, Jacques Miller showed that if you removed the thymus from newborn mice, they couldn't reject grafts, so I began tapping into cellular lineages in the thymus. I wanted to know if there really was such a thing as a common lymphocyte progenitor.

***How did you succeed in identifying the first stem cell population?***

I had found that a cell that had a B cell surface marker couldn't make a clone of T cells, not surprisingly. But it couldn't make a clone of B cells either. That meant that the precursor for a B lymphocyte didn't have a B cell marker on its surface. It struck me that it also wouldn't have a T cell, macrophage, or red blood cell marker—they would all be absent from a cell that could make at least B and T cells.

I remember at that moment thinking, "I'm not working on lymphocyte development; I'm working on stem cells." Then very rapidly, we isolated the mouse blood–forming stem cells. But I didn't set out to do it.



STANFORD UNIVERSITY SCHOOL OF MEDICINE

**Irv Weissman**

### THE HISTORY OF HISTOCOMPATIBILITY

***What's the focus in your Hopkins Marine Station laboratory?***

There, we found the most primitive chordate that can make an immune response. It's called *Botryllus schlosseri*, an ocean creature that metamorphoses during development into an invertebrate by losing all of its chordate characteristics.

When two individuals or colonies abut in the ocean, they send blood vessels into the other and they either fuse or undergo an immune rejection. We showed that this choice was determined by a single gene locus with over 100 alleles. Generally, only siblings share the right alleles to fuse.

This gene has four homologues in humans, one of which is an activating ligand for receptors on natural killer cells. So this probably was the beginning of the natural killer cell system, which recognizes self and kills anything that's not self.

And some of them are markers that we now know are on stem cells. So I think we're looking at the evolution of stem cell systems, caught mid-phylogeny in this animal that's a vertebrate during fetal life and an invertebrate for the rest of its life.

***What else has this primitive organism taught you about the immune system?***

This animal uses a budding process to build new bodies. We showed in the '90s that the cells of a developing body could come from both the budding animal and a fused sibling. But germ line cells were competing ruthlessly; they all come from

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only one of the fused colonies. We isolated the stem cell subset and showed that those from a winner colony beat out those from another when they're both injected into the bloodstream of a host.

Almost certainly then, the immune rejection mechanism is a way to limit germ line stem cell competition and parasitism to your sibling. You might end up being the loser, but at least half of your genes will be carried to the next generation, because your sibling has half of your genes.

## RIGHT TO RESEARCH

***As a force behind Proposition 71, how did you convince politicians of the importance of embryonic stem cell research?***

I simply explained that if you have a genetic disease, you might be able to capture that disease in a cell line that can make every cell type in the body, and those cell types can be tested for their function in an immune-deficient mouse. The technique then proven by the Jaenisch laboratory was via nuclear transfer of a body cell nucleus to an egg, and later isolating the inner cell mass of a developing blastocyst to make the cell line. I convinced my panel that if you go forward with the research, oversee it, fund it well, make sure nobody's doing anything crazy, this could open up a whole new era in understanding human diseases like multiple sclerosis and Lou Gehrig's Disease. It's a powerful argument. And as long as you don't use words like "histocompatibility" and "polymorphism," most people will understand it.

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***How are you dealing with the NIH's recent announcement of a ban on funding nuclear transfer–derived stem cell lines?***

When President Obama announced that he was lifting Bush's ban, I was there for the speech in the White House and later at the NIH. I was ecstatic. It was one of the greatest speeches of all time. So you can imagine how surprised I was when the NIH made their announcement that nuclear transfer research would not be supported.

There's no scientific reason not to push for nuclear transfer as a method. The only arguments against nuclear transfer are religious or political, or are based on a personal moral code.

I'm president of the International Society for Stem Cell Research, and we jointly decided to weigh in to say, "This is wrong; you should permit funding so long as it is done ethically and efficiently." It's falling on deaf ears right now, but it's a start. It takes a while.

***What are the biggest nonpolitical hurdles to this type of research?***

The first, of course, is creating the lines with just a few eggs. Nobody is going to be happy if it takes 200 eggs to make a single cell line, because eggs come from people, by an invasive procedure. The most important technical breakthrough will be doing efficient nuclear transfer with a few primate eggs to make stem cell lines. Or you could produce eggs from already developed embryonic stem cell lines. There are some people doing that, and it looks promising.

The real barriers will come as therapies emerge, when we have to fund clinical trials and companies that know what they're doing. Many barriers will come up, but the biggest will be the financial ones.

***How are your own efforts in this area coming along?***

We've shown that, at least in mice, you can induce permanent transplantation tolerance by irradiating them and transplanting them with blood-forming stem cells from a donor. Then, whether the same day or a year later, you can transplant, for instance, a heart, or skin, or insulin-producing islets from the same donor. So we think that if we can establish that it's safe and effective to transplant stem cells into people, and that the method induces tolerance, that it sets the stage for, 10 or 20 years from now, using ES-derived liver precursors or blood forming stem cells, or whatever, for treating diseases. That's truly regenerative medicine.

**A *Botryllus* colony has a primitive immune system that Weissman's marine laboratory studies to understand the evolution of immunity.**

***What types of disease are you working on?***

At our institute, almost every one that's a degenerative disease, where stem cells can regenerate the tissue. First we're going for genetic defects of the blood-forming system, and then eventually for other ones.

Nine years ago, we isolated the human brain–forming stem cell. We know that in mice they can make virtually all of the brain cell types that are necessary for the therapies we're doing. A company I started, called StemCells Inc., has already done phase I trials in children with an otherwise lethal neurodegenerative disease called Batten disease. Eventually it would be best to have the stem cells from the same donor, so that you wouldn't have to immunosuppress the kids while you're treating them.

At some point, stem cell transplantation could be used to treat autoimmune diseases and to get transplantation tolerance to grafts with no continuing immunosuppression. And because stem cells self-renew, it's a one-time treatment.

But in my own laboratory, I'd say the major emphasis right now is on finding cancer-initiating cells from primary human cancer samples and testing antibodies—which are made in mice bearing these cancer stem cell transplants—for their ability to ablate the tumor.

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