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Oral History Project

Transcript

Irving L. Weissman, M.D.
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Williams: This is an interview with Dr. Irving Weissman for The American Association of Immunologists Centennial Oral History Project. Dr. Weissman is professor of pathology and developmental biology at the Stanford University School of Medicine and professor of biology at the School of Humanities and Sciences at Stanford University. He is also director of both the Stanford Institute for Stem Cell Biology and Regenerative Medicine and the Stanford Ludwig Center for Stem Cell Research. Dr. Weissman was president of the American Association of Immunologists from '94 to '95 and served as an AAI Council member from 1989 to '94. We are in Dr. Weissman's office at Stanford University. Today is Monday, January 21 [2013], and I'm Brien Williams.

Well, before we get to that distinguished career, let's start a little bit with your background, Dr. Weissman. Tell me a little bit about your family and how they came to Montana.

Weissman: So as with most Jews, both of my grandfathers who lived in the area between Romania and Moldavia and Russia, by the time they were in their young teens it was Russia, and the czar would draft Jews at about age thirteen and put them in the front lines of the army. So I think that's the main reason that the Jews left Russia beginning at that time. You ask anybody my age, roughly, and that will be the story if they're Jewish.

Williams: You say, "at that time," so what are we talking about?

Weissman: So we're talking around the early 1900s, maybe 1905 to 1917, that is till the revolution.

At least on my father's side, my grandfather got to New York, and he and his brother, for one reason or another, decided they wanted to homestead, and at that point at that time there were homesteads offerings. So they, I think, pretty much walked and traveled by the gifts of others to get first to Chicago, where they met the Shvonetsky [phonetic] sisters and married them somehow, almost right away.

My grandfather had his first homestead in South Dakota, and my father was born there, but they failed at that, and they moved to another one outside of my hometown of Great Falls in a place called Floweree. They failed at that, and my grandfather became a merchant. He became a junkman, became a fur trader. So eventually he built up that business, which my father and my uncle went into and others in the family. But that's how we got to Montana on my father's side. It turns out that both of grandfathers were born in the same town in Russia, Suroki [phonetic], but they didn't know each other until the marriage.

My mother's family went to Butte, Montana, where they had the mines, and so there was lot of jobs, the copper mines. My mother's mother, at a very young age, they were living in what was called the Austro-Hungarian Empire but is Poland now. They couldn't afford for her to have schooling beyond high school.

Father was a butcher, and her older brother was already accepted in Vienna Law School. So she was sent out to the family in New York, and they knew a cousin in Montana who had a friend who offered to pay her way. She didn't realize that meant for her to meet and marry him. So she was married by sixteen, had my mom by seventeen.

In the meantime, the family in Austria, Hungary, Poland, of course, were coming up to the Second World War, and by that time, although she hadn't quite realized it, her older brother had become a Zionist after he finished law school and was involved in the Jewish College Students of Europe Association, where he actually met Einstein and others, and he became a lawyer in Palestine and, just to scoot forward, was the first appointed mayor of Jerusalem in 1947 and then '48 after the revolution, or the war and revolution, he was elected mayor.

A lot of this we didn't know about because they had lost track of each other, my grandmother and her brother, because of the war. All the rest of the family except a couple brothers in New York were killed in the Holocaust. Uncle Daniel, Daniel Louster [phonetic], somehow got a hold of my grandmother and he came out. He was, in 1952, the representative to the U.N.'s Geneva site. I guess it was the old League of Nations. So he came to Montana.

But other than that, we had no expectations of higher education. My father took one year of college. My mother was a gifted pianist, and so she was a scholarship student at Juilliard, but the [Great] Depression was way too much. So they married and settled down. He joined my grandfather as a fur trader, a junkman, eventually steel supply, plumbing supply, hardware, and developed stores all over Montana and Wyoming.

So that's the background. I've got to say that in around 1976 I was giving a talk at Harvard College, actually looking at a job there, and Matt Meselson asked me where I was from, and I said Great Falls, Montana.

He said, "Let me tell you a story of your family." So Matt Meselson, sometime earlier, I think it was the early to mid-fifties, was at a meeting with Selman Waksman, Byron Waksman's father, and Selman asked Matt where he was from. He said Denver, Colorado. And he said, "Let me tell you the story about your family."

So that's the constant story of Jews who ended up being in the West. Many of them, my grandfather's brother included, they thought they had consumption and that fit with the idea you should go West, but I think it was more than just that. So that's that. That's pretty much the family.

Williams: So describe your own early family life growing up in this family.

Weissman: Well, I grew up in Great Falls, Montana, which was about thirty to forty thousand people. I was a good but really undistinguished student, but when I was ten years old I read a book called *Microbe Hunters* by Paul de Kruif. This was the story of the lives of scientists who discovered microbes, Pasteur, Robert Koch, and on and on. That was absolutely thrilling to me, and I realized even at that young age that's what I wanted to do.

The most important event actually probably of my life was I found out from a friend that a pathologist was doing research at the local hospital called the Montana Deaconess Hospital. I was just between fifteen and sixteen, and I went and asked for a job for the coming summer, which was between my junior year and senior year of high school. I said many things. He was partially deaf, had a thick German accent. His name was Ernst Eichwald, and it turned out that he was interested that I even asked him for a job, but I couldn't tell what was going on until I told him I'd work for nothing. Then he said okay. He actually paid me twenty-five bucks a month.

I started as a mouse caretaker, but very rapidly he would show me papers and I would try to read them, primary papers, mostly about histocompatibility, tissue compatibility. The year before I started working with him, he had discovered in that remote non-university hospital what's called the H-Y antigen, the first gene encoded by the Y chromosome known, and this encoded a transplantation antigen.

So amongst these important things while I was in the first couple of weeks with him, he described transplantation genetics to me, and I got it right away. Genetics is actually pretty easy for me. Then he said, "We had a problem when we were trying to transplant skin." He wanted to use skin transplants in mice to determine the number of genes that encoded transplantation antigens between two strains of mice. George Snell had done it with tumor transplants, but because we knew there were not only strong differences between strains of mice or individual humans that would have rapid rejection times, there were others that were very weak, and a growing tumor could overcome it.

So he said he wanted to repeat it with skin grafts, and the general method—I'm going to give you a little science now—is that between two pure strains of mice that are inbred, you make an F1, and the F1 expresses all of the codominant genes of both strains. When Snell transplanted tumors from strain A or strain B to each other, A to B, B to A, they were rejected. Transplanted them to the F1, they were accepted because the F1 had all of the genes that encoded transplant antigens. So the emerging field of tolerance in self and non-self would dictate that they would be accepted. F1 back to parent, AB to A, AB to B, is rejected because of the foreign antigen. That's what he told me. He said, "But in our inbred strain of C57 black mice, we got about a quarter rejections. Can you explain it?" So he didn't tell me what it was. He made me explain it.

And I thought about it for a minute and I said, "It must be male to female." Because the Y chromosome was the only difference in an inbred strain. And he said yes. I realized then that you could actually think about a problem intellectually and then do an experiment to test whether it was right. So that really hooked me. Now at that time—I was in high school—I was also his autopsy assistant. This was the time of Billingham, Brent, and Medawar.

And I should say one more thing. Eichwald was not just a pathologist in a private hospital; he was the founding editor of the journal *Transplantation Bulletin*, which became *Transplantation*, which is still the leading journal in the field. When I was just starting my first year of college, I was a founding member of the Transplantation Society.

So Billingham, Brent, and Medawar had just published that they could transplant spleen or bone marrow cells from an adult strain-A mouse into a sixteen-day fetal mouse, and when that mouse of a different strain CBA grew up, instead of rejecting A-strain skin grafts like they should, they tolerated them, and they did not tolerate third-party grafts, say, from C57 black or some other strain. So they had the concept that Burnet had predicted and others eventually tried to explain, that the immune system during development somehow takes account of everything that is self and tolerates it, but sometime after birth, anything that is introduced that's foreign would be non-self and rejected.

That captured my attention, and even then while I was in high school, I began doing experiments to try to understand first many things about this H-Y antigen. Was the Y-chromosome antigen the same or different between strains of mice? Was it different between species? And I developed a sensitization assay of adult mice where I could see if the antigen was there, then a skin graft that was put on the back of a female mouse that had been sensitized with cells from the putative H-Y donor, it would have accelerated rejection.

But I was really interested in trying to induce transplant tolerance, and as I was doing it, I realized—and don't ask me where it came from—that sometime during embryonic and fetal development, which I barely knew, that the immune system had to develop and that if you studied the cells that were developing in the mechanism of development, you would get at some really interesting stuff. I was naïve as that.

I do remember, though, that in reading the papers by Billingham, Brent, and Medawar, when they did the A to CBA, they described that many of the animals were growing up runted, smaller. And as the controls to mice male to female, I had done transplants across generations, I mean S species, and I saw the same thing.

One of the most interesting things, though, at the time was that was the time that irradiation and bone marrow transplants for radiation—this is the fifties now—

was starting to take hold, and I was seeing if I did male to fetal female or male bone marrow to adult irradiated females, could I induce the specific tolerance in the adults by replacing the female immune system with the male's bone marrow.

In reading the papers, I got interested in that runting, so I wrote a letter—I still have it somewhere—to John Trentin, J.J. Trentin, who was then, I think, at the either National Institutes of Health or Baylor, and I said, "Is it possible that the immune cells of the donor were attacking the host to cause the runting?" And he sent me back a very nice letter saying that he had just discovered that. So, again, I realized that by reading, you could have ideas and you could do experiments.

Now, when I said that I was not a distinguished student, I want to really emphasize that in case anybody who's in high school ever reads this. I graduated 41st out of a class of 360 at this very competitive high school in Great Falls, Montana. I did score extremely well on the SATs, and I was a National Merit Scholar, but I had no evidence that I could do well in school. A lot of people say, oh, you must have been bored. No, it was hard. I mean, reading a lot, doing physics, all of that, that was hard for me. Now, I could argue that maybe they weren't great teachers, because now when physicists tell me things, I can understand it. But what I learned very quickly, and especially in the field of biology, that what you learn from didactics had very little to do with how information was gained by experiment. So I didn't care too much.

I went away to Dartmouth College. I was accepted to Harvard, Johns Hopkins, and Dartmouth, and a lot of people, including Eichwald, convinced me that it would be better for a small-town boy to go to a small place like Dartmouth. But Dartmouth, I found, in my second year when you got to zoology and biology, was ancient. I knew more about recent biology and genetics than the professors who were teaching it, at least in my field. I also hated the idea that as a Jew from the West, I was being classified as a Jew, and there was a lot of anti-Semitism at the time from the East, people who grew up, and there was a lot of way-over pro-Semitism by the Jews, so I was not socially in either of those groups.

Williams: What was the attitude towards Jews in Montana?

Weissman: Oh, we were so rare, we convinced everybody what Jews were, except for people who were recent immigrants from Europe. Then there was anti-Semitism.

Williams: But you and your family were not subject to that?

Weissman: Very little. Very little. I would say the main thing was I hated it when I'm school at Christmastime they would be singing Christmas songs, and I wasn't going to say the word "Jesus" for anybody. And we didn't have that in the Pledge to Allegiance then, so we're fine. So pretty much I was in a place without prejudice where they took you for who you were.

Williams: Were you practicing Jews?

Weissman: Well, it was hard to practice. There weren't that many families. But we had an air force base, a military air force base, and they provided a traveling rabbi or a student rabbi to them about once a month, so we would go out and we would do things for the high holy holidays, and when I was thirteen, I had a bar mitzvah because the local guy who ran the cosmetics store and was Jewish taught me by memorizing how to make my speech. But, really, other than that, I didn't grow up as a practicing Jew. I knew what it was, I respected it, but I wasn't going to be involved in all of those kinds of things.

So I left Dartmouth after two years, went to Montana State College, where I met some of the most remarkable professors and teaching that I could imagine. It was amazing at the time. So this was right at the time of *Zen and the Art of Motorcycle Maintenance*, and that guy and his school of philosophy were teaching it from Bozeman, Montana.

There was a fantastic geneticist named Palmer David Skaar, S-k-a-a-r, who had learned his genetics at Indiana from Sonneborn and from Lederberg and decided Montana's where he wanted to live, and he could do his research there. So in my junior year of college, which was actually my last year of college, I took one undergraduate and five graduate-level courses in genetics and evolution from him, and this was spectacular.

So between that and the fact that I was going back every summer to do research in that lab in Great Falls, Montana, and although I was the first student, Eichwald said it was a good thing, so began the tradition that every year a junior high school student would come in the lab, one from the public high school, one from the Catholic high school. Easy to tell them apart. The Catholic high school kids were well behaved, and it was tough for them to learn by experiment. Well, I could get into it, but I'll just say that the nuns were very strict and they required you to memorize and behave, and none of that was going on in the high school, the public high school.

Williams: So the public high schools made better scientists at this point.

Weissman: Yes, oh, by far, no question about it. And because he put me in charge to teach them what the field was, I was teaching from the beginning. Now, I barely knew the scientific jargon of the field, so I taught in plain English, and I've always taught in plain English since then. I don't see any reason that we should invent Greek and Latin terms for what we discover, because that just makes a language barrier between us and other people, including the nearby sciences. So I spent probably too much time on that.

But when I applied to medical school early out of Bozeman, Montana, my junior year, I only applied to Stanford. I only applied to Stanford because it was a

required five-year medical school instead of four. The basic sciences that normally take two years and you do that from eight to six every day, now the basic sciences were spread over three years. That meant every day we had a half a day free.

I quickly began to do research. I spent fall quarter of my first year working in the laboratory of Len and Lee Herzenberg. I did that, actually, because the very first day that I arrived at Stanford, I decided in the evening that I would look at the building, and I was walking. I went down the stairs in the basement, and I bump into a guy with a plaid shirt and slippers, and we started talking. It turned out he was Av Mitchison, and I knew his name because he had worked with Medawar, and I knew that he had defined immunological tolerance and reactivity by showing that lymph nodes of a naïve animal transplanted into an immunologically tolerant animal could be stimulated by antigen and reject the graft. So that said, it wasn't the cells that processed the antigen; it had to be the central cells in the immune response.

So, anyway, I knew his experiments, and he was on sabbatical at Stanford to test the clonal selection hypothesis that Burnet had proposed. Lederberg was the head of the Department of Genetics. He had proposed a mechanistic version how tolerance might happen. It was all incredibly exciting.

At the same time, Gus Nossal, who later became head of the Walter and Eliza Hall Institute, was there as an assistant professor, again, also in a postdoctoral fellowship. Mel Cohn was in biochemistry, a fantastic-thinking biochemist and later immunologist. We would have seminars once a week at the Herzenberg house to go over papers and cut them apart.

By the end of my fall year at Stanford, I noticed that I was learning in biochemistry that the lac operon, if lactose came in, that the way that it turned on the enzyme that degraded it, that Manod and Jacob had found, was by eliminating a natural repressor. So at Christmastime my first year, I wrote a paper back in Great Falls comparing the switch from seeing everything that's self to be tolerant to seeing everything that was not self as being immune after you went through the switch, and proposed that there had to be cells that were negative regulators of the immune response, and probably what antigen did in postnatal life was to get rid of the negative regulators so the response could go on, but if they stimulated the negative regulatory cells during fetal life, it kept them alive. It was just another explanation. But you could call those regulatory T cells now, and in the early seventies, my friend Dick Gershon called them suppressor T cells. But I got it published in the *Transplantation Bulletin*. I think it was '61, maybe '62.

I remember when I presented the idea in the sessions we were having at Stanford the following quarter, both Nossal and Mitchison said that was exciting, I should keep going, and Len Herzenberg says ideas were a dime a dozen.

So I switched from Herzenberg's lab, because he thought my ideas were a dime a dozen, and went to work with the famous radiologist Henry Kaplan, who also had dabbled in immunology and done some really beautiful experiments. He gave me a lab in the Department of Radiology. He even gave me a half-time technician that I shared with an assistant professor at the time, Saul Rosenberg, who later became the most prominent oncologist in the world but he was an assistant professor then, and he was so disinterested in the experiments, I had a full-time assistant by January of my freshman year of medical school. By junior year, I had recruited a couple of medical students to work with me, and we worked out a lot about immunological tolerance.

In 1962, my sophomore year—it could have been '61 or '62—Eichwald and I had written a paper that was going to be in the meeting of the annals of the New York Academy of Sciences. So the New York Academy of Sciences put on the most important immunology meeting each year during those times, and I went to the meeting, took some time off from school. I think it was September of the next year. So, anyway, met Don Thomas there, visited his lab. He later invented the field of bone marrow transplant. We visited his dog lab in the Mary Imogene Bassett Hospital in New York. But the most striking thing is Jacques Miller showed for sure that if you removed the thymus from a newborn mouse, it was immune deficient throughout life. Carlos Martinez, working with Robert Good, reported similar things.

But the most exciting to me is Jim Gowans of Oxford described his experiments of looking at lymphocytes as a physiological system, and he knew the hypotheses about immunity intolerance in clonal selection, and he had identified, by the most spectacular and precise experiments in rats, that small lymphocytes that went from the tissues into the thoracic duct and then back into the blood system through the tissues back through the thoracic duct, recirculating small lymphocytes were the central cells in the immune response. They were responsible for the first part of the immune response, they carried immunological memory. In immunological tolerance, they had lost the activity, but they had all those cells. So, obviously, they were losing those few cells that had receptors for antigen that was self, leaving behind all of the cells to see everything else, and the experiments was so clear and precise and physiological.

So he would take thoracic duct lymphocytes from a rat, normal and living, purify them away from the large lymphocytes, let's say, the small ones, rapidly, and reinfuse them back into those rats or other rats that had their thoracic ducts drained of all lymphocytes at the physiological rate into the blood system, the venous system, where they would go normally to show all of the things that he did.

So I had been considering going to work with Mitchison at Mill Hill, but I switched at that point and asked Gowans if I could work with him. So between my fourth and fifth year of medical school, we had a nine-month gap, and I went

to Oxford to work with Jim Gowans. At that time, Sam Strober, who's here now, was in the lab as a medical student from Harvard from the transplant labs. William E. Ford, was a graduate student from Edinburgh. Peter McCullagh was a Rhodes scholar from Australia. And me. We were the students, and it was spectacular.

I showed by direct experiment that the thymus, instead of producing hormones that caused precursors of the immune system to develop at a distance, actually made cells in the thymus that migrated out. And in true Gowans style, I did it in a very carefully controlled physiological system. Now, three months into my stay there, of the eight or nine months I was there, Gowans went to work with Jonathan Uhr to look for the carriage of memory by small lymphocytes, so I was left with our group, and I finished all the experiments.

I met Gowans in New York on the way back, and I described the experiments, and he said, "Well, you have to write those up." It took me a long time, because I had to finish medical school, but I wrote up, I think, a really important paper called "Thymus Cell Migration." It was done at the same time that Gus Nossal was doing the same sort of thing in guinea pigs, but I did it way more carefully, just to be honest.

I knew that if I wanted to mark the cells in one place of the body to see where they would go, and this was the first ever marker experiment to see where cells would go, where they were born, and how they developed, that the label I used, tritiated thymidine that goes into DNA or tritiated adenosine that goes into RNA, that the label could leak out. Then if I saw something at a distance, it could be that there was a cell that picked up just the label as it was dividing or was making RNA. So I infused cold thymidine intravenously while I put hot thymidine into the thymus with a micro needle infusing at a very low rate. The same with hot and cold adenosine, and then I also labeled cells in the bone marrow. I've never published that part of it.

So I published the thymus cell migration and did see that the bone marrow very rarely sent a cell out to the thymus to give rise to T lymphocytes. So I think those experiments pretty much abolished the idea that thymus was a gland that had hormones, but, in fact, was a place where it made T cells.

Just to skip forward in a very brief way, once I knew that the thymus was the place that made T cells that I could mark them, that I decided I wasn't going to do an internship and residency. Six months after I was in Gowans' lab, I was back. I was a full-time research associate because [Henry] Kaplan allowed me to do that. Everybody, including Saul Rosenberg, got on my case. They said, "You're never going to be anything if you don't do your internship."

So, okay. So I kept doing experiments, and I eventually published a whole bunch of them, but by then it was clear that since the thymus generated lymphocytes and

it looked like bone marrow could give rise to it, that I could begin looking at the origins of the immune system. So, ’65.

In ’67 and ’68, Jacques Miller, in a brilliant set of experiments—remember, he’s the guy who showed the thymus is responsible for the development of the immune system. Gowans at the same time said the lymphocytes were the central cells in the immune system. ‘67, ’68, Miller showed that there were two kinds of lymphocytes, one that came from the thymus, T cells, and the other that came from the bone marrow, B cells. Noel Warner, in the Robert Good school, thought that B cells came from the bursa of Fabricius, including Max Cooper.

But what was clear then is that somehow a place like the bone marrow was generating the cells of the immune system, T and B. So over several years I worked out the order of cell production in the thymus and where they went, switched to looking at the order of B cell production of the bone marrow, where they went. Along the way, I had to develop methods to see those cells. I made antibodies that saw T cells that were clean before monoclonal, so they had to be absorbed to specificity, and B cells.

Actually, this happened even in ’64 when I was visiting Gowans, we stained lymph nodes. No, pardon me. It was ’65. We stained lymph nodes, and with the antibodies that saw the thymus and the T cell migrants, it lit up a part of the lymph node which we now know as the T cell region. Then with the antibody to B cells, there was another region called the follicle, a B cell region. And in ’68, ’69, ’70, I showed that both purified B cells and purified thymus-derived T cells migrated through the same blood vessel to get into a lymph node, and there were similar things in the spleen and the liver Peyer’s patch. The T cells knew how to go to the T cell region, and the B cells knew how to go there.

So I added to looking at the development and the purity of the cells, and the fact that now we had invented this method of staining lymph nodes, by the way. The classical method that people used to stain any tissue and see where antigens were began with classical formaldehyde fixation, and I showed very quickly that destroyed all the markers in the antibodies we saw.

So my student and I, George Gutman worked out that you could slice thin a lymph node, put it on a slide, and dip it into acetone for fifteen seconds, wave it dry, and it fixed the tissues good enough so you could see them. It fixed the tissue to the slide so it wouldn’t fall off, and it left all of the antigens unperturbed. So we were the first to ever use antibodies to see cell membrane antigens in a tissue section, and we worked that up as well.

Williams: Why did you settle on acetone so quickly?

Weissman: Oh, we went through everything.

Williams: You went through everything.

Weissman: We went through paraformaldehyde, nitrogen monomeric paraformaldehyde, glutaraldehyde, alcohol. So we were systematic. We just hit the right one.

Williams: Now, are you saying that the Ts and Bs are separately generated?

Weissman: Yes.

Williams: Or that there is now a relationship?

Weissman: Yes, they are both separately generated and that when they went in by this vessel that Gowans had discovered, the postcapillary venule, they somehow knew to go to the different regions. So that got me very interested in how they homed, how they knew to get to that particular vessel, and then how did they know to go to the different regions. And because I could stain that lymph node and see T and B cells, we would immunize with all kinds of antigens, and we'd see each day what happened in the T cells and what happened in the B cells. And we discovered the T cells that were activated in the T cell region migrated to the B cell region and helped form germinal centers. So we got into what germinal centers were and so on.

But that led me many years later to discover the homing receptors that took both B and T cells either to the lymph node that was one set of molecule called L-selectin and now or CD62L, and the other one that took them to the intestinal lymphoid tissue, the Peyer's patches, and that was an integrin, integrin alpha-4/beta-7. We discovered both chains. We showed by antibodies specific to them that they would stop the ability of cells to home to those regions, and I think that began the field of looking at how cells migrate.

I had two students, fellows, working with me as postdocs, Eugene Butcher and Mike Gallatin, and I think between us we were describing how you would approach homing by blocking it with very specific, by then, monoclonal antibodies. Of course, I was looking at exactly the same time at how did B cells mature compared to the thymus. Since I knew by then that the bone marrow gave rise to both of them, I wondered if there was a common lymphocyte progenitor, so that you became a lymphocyte progenitor first and then you decided you'd be a T cell or a B cell, or if they were always independent lineages.

So all of that was cooking at the same time, and we were working out assays from the bone marrow cells that went to the thymus. Was it a single cell? Could it make a clone? Could you follow the daughters of the clones in the thymus, and did they give rise to only one kind of T cells, because it was becoming clear there were killer and helper T cells. We showed that the progeny of a single clone, Sophie Ezine and I, could give rise to all the varieties of phenotypic mark or functionally different T lymphocytes in the thymus. But it also became an assay

for the cells that could form a clone in the thymus, I realized it could be a quantitative assay.

While we were developing our studies on the B cell system, I had a stroke of luck that Cheryl Whitlock, who had worked with a friend of mine named Jim Watson and done a postdoc—not the Jim Watson in Cold Spring Harbor but the one who was then at Irvine. She had done a postdoctoral fellowship with my first M.D./Ph.D. trainee, Owen Witte, who was at UCLA, and she wanted to go to medical school. She got into Stanford. He said, "You'd better take her."

So I said, "Let's try to develop an assay how the bone marrow makes B cells." At that time, it was reasonable to begin looking for the stromal cells in bone marrow that taught early bone marrow precursors to become B cells. So she had made one of those stroma. It was called the Whitlock/Witte stroma. And I said, "Boy, those look interesting," because we would make the stromal cultures, wash away any non-adherent cells, pour on bone marrow, and there would be little tiny foci in one condition, which means you have to have cortisone and some other stuff there, that would make a colony of B cells. And we went on to show that was derived from a single cell. And if you didn't have the other stuff there, they made mainly myeloid and erythroid cells like Till and McCulloch had shown in the spleen colony assay in vivo. This is all happening all in this same time.

So we cloned the stromal cell that supported B cell maturation, and we poured bone marrow on, and 1 in 2,000 cells in the bone marrow could form a colony, and the colony went through an early burst of myeloid and erythroid and then B lymphoid. I said, oh, my god, we not only have a quantitative assay for B cells here and with the thymus home for T cells, but now we know the cell that can make B cells can also make myeloid and erythroid.

So we began the search for what was the cell in the bone marrow that could make B lineage and T lineage. And I remember Christa Muller-Sieburg, who had been in Basel with Klaus Rajewsky and Shin-Ichi Nishikawa, came to my lab for a postdoctoral fellowship, and we began looking at antibodies. My postdoc from a few years before, Bob Coffman, and I had made a bunch of antibodies to B cells and also to some of the myeloid cells, so we began fractionating the cells in the bone marrow and asked what was the surface marker phenotype of the cell that could make the B cell in the Whitlock/Witte clonal stromal culture, and what was the phenotype of the cell that could make a T cell.

So the very first antibody we tried was an antibody Coffman and I made called B220. It's CD45R-something nowadays. The B220 positive cells couldn't make a B cell colony, but the B220 negative could. I said, if a cell that's committed to making B cells doesn't make a—it's already too late to make a B cell colony, then the cell we're looking for that can also make myeloid and erythroid cells might be a blood-forming stem cell.

So we added simultaneous assay of the cells that we were separating, the thymic assay and the bone marrow assay, and very rapidly Christa and I found both the earliest B cell progenitor and a partially purified stem cell we published in *Cell*. We realized at that time that one other lab was also looking with other markers for the cell that could also make a spleen colony-forming cell.

Jerry Spangrude joined my lab then. I met Jerry Spangrude in Montana. I was hiking with my family in Glacier Park, and we were going over what's called Logan Pass going to the Sun Highway, and this guy shouts out to me, "I know you. You're Irv Weissman." He introduced himself, he was from Missoula, and he was just in graduate school at Utah. By then Eichwald had moved from Montana to Utah, and so he knew a lot about me, and he says, "I want to work in your lab." So he told me what he was doing there on Logan Pass, and I said, "Sure." So he came to my lab.

I've got to say, just as an aside, Logan Pass in Glacier Park was named after an early prominent Montanan, maybe governor when it was a territory, whose granddaughter, Valerie Logan, was and is the wife of my very close friend Leroy Hood, who you'd better interview, because we grew up in Montana together. Anyway, that's a separate story.

So Jerry came to my lab, and at that moment, I remember, Jan Klein, somebody I had known also from the beginning, had published that he could find pre-T cells in the bone marrow with a particular marker which he said marked pre-T cells. Now, he didn't actually see if they were pre-T cells, but they had a marker that was on T cells which he thought was Thy-1. So he sent me this whole set of antibodies because I asked him for it, and one of them which was on a cell that had Thy-1 on it but at very low levels, not the high levels T cells have, one of them pulled out a cell that was very highly enriched for making the bone marrow and the thymic colonies. We call that Stem Cell Antigen number one or SCA1. When we added that to the antibodies Christa Muller-Sieburg and I had worked out for the B cell progenitor, we got the first purification of hematopoietic stem cells, and that opened up lots and lots of doors.

Williams: When was this term "stem cell" first being referenced?

Weissman: Well, the first reference was way before in the nineteenth century. The embryologist at that time and the plant biologist at that time recognized that there might be cell or cells that were at the earliest stage. Nobody until Till and McCulloch had come to the conclusion that there might be a cell, a single cell that could give rise to many different fates of a particular cell lineage like the blood-forming lineage.

Till and McCulloch, beginning with their experiments in '61 and going right up through '68, showed that they could put bone marrow into a mouse that had been lethally irradiated, and if they don't give enough bone marrow for the transplant

to take and save the animal, right around eight, nine, ten days, the animals that were starting to get sick had bumps in their spleen. And instead of throwing the mice away, they examined each bump, and each bump had cells of the monocyte-macrophage lineage, the granulocyte lineage, and the erythroid lineage. Sometimes there were even some megakaryocytes that make platelets. No lymphocytes, but they thought to themselves, how could each bump have all those different cell types? Were they derived from a single cell that could make all those types, or did all those cells home together to that place?

Then in probably still, I think, the most brilliant experiment in that whole field, I think it was Becker, Till, McCullough, maybe Siminovitch was on the paper, they pre-irradiated the donor bone marrow, and they knew that it would kill a lot of cells, but some of the surviving cells had a double-strand break in the DNA. And if the double-strand break was sensed as lethal, the cell died. But if it translocated and fixed that cut end of the DNA, now we know, the cell could survive. And because radiation is random, it created translocations or deletions in the chromosomes that were random.

So they pre-irradiated the bone marrow. They found the dose of irradiated bone marrow that would give spleen colonies. They took out the day eight, nine, and ten spleen colonies. And all of the dividing cells in one bump had exactly the same chromosomal marker, and all the dividing cells in the next bump had a different one, yet both of them had myeloid and erythroid cells. They coined the term "stem cells" from that, a single cell that could give rise to multiple lineages.

They showed some but not all of the bumps contained cells that could make more colony-forming cells. They called it self-renewal. So they had the intellectual beginnings of what stem cells were. So a lot of people in retrospect say, "No, I did it because I said the word 'stem,'" or, "I said the word 'stem.'" It's all baloney. They did it. They saw what it was.

Actually, back in the early seventies before I did the stem cell isolation, I went back to Oxford for my first sabbatical, after just barely getting tenure, and I'll tell you why in a minute. And Gowans was there, but I wanted to work not only with Gowans, but across the street with Richard Gardner and his postdoc at the time, Virginia Papaioannou, because they had developed tools to begin looking at early embryos, and they were interested in the first steps of differentiation from fertilized egg that outside of the uterus made what's called the blastocyst that would implant in the uterus to make the embryo. And they wanted to know were the cells inside the middle of that truly able to make a whole embryo. Were they pluripotent? They were way ahead of the embryonic stem cell field, but they were helping found it. I realized if they could do that, maybe they could help me look for the first place that blood formation began and the second and the third, because I was interested in following the full development of the blood forming in the immune system.

So while I was with them, I did the experiments where I would take the earliest place you would see blood, the yolk sac blood islands, separate the cells, and I transplanted them from that early-phase mouse between embryo and fetus, day eight, into the yolk sac cavity of a same age but genetically different host embryo fetus. Then I let them grow up and asked did I have cells of the blood-forming system from that original embryo fetus?

Now, lucky for me, I became friends with a guy named H.S. Micklem, or "Spedding" Micklem, who had been at Oxford and was actually still around there at the radiation labs, and he had done a lot of beautiful experiments, but one of the things he did on the spleen colony-forming assay of Till and McCulloch would show that if you pre-immunize the mouse into whom you're going to inject bone marrow, whose spleen was going to get the spleen colony if a cell landed, single cell—this is all '74—he showed that pre-immunization, that the immune system that was there would reject the incoming bone marrow cells.

So I made a leap. I immunized an adult mouse against the transplantation antigens of the intermediate animal that weren't present in the original donor, so that when that animal grew up after having cells go into the yolk sac, then we could just take his bone marrow, put it into the pre-immunized animal, and it should have been that all of the spleen colonies came from the donor, because you would reject those. And it was.

I teased them apart and showed it and showed that the beginnings of the blood-forming system were there in the yolk sac. Now, much later, people tried to transplant yolk sac blood island cells to save adults, and some people say they can, but many more people say they can't. And that's led many people to say you make yolk sac blood island cells only for the embryonic stage, and then somewhere in the body you make a second round for the adult.

Even now, I have to, at meetings of stem cells like Thursday of this past week, I get up and show my slides, and I say, "It is incontrovertible that normal yolk sac blood island cells at the eighth day of gestation, before there's any cells inside the fetus, can grow up in the yolk sac blood islands and then spread to the rest of the body to give rise to spleen colony-forming cells." And I had also shown, with that thymic assay, T cells. Still controversial. I did the experiments in '74. What is it, twenty-eight years later, and they're still puzzling. But nobody does the experiments like Gowans would do it to say what really goes on in vivo, in vivo veritas. So I don't know. That's sort of aside.

But I guess what I'm saying is what I picked up from Ernst Eichwald was use genetics to find out what's the truth, because genetics doesn't lie. What I picked up from Henry Kaplan, about whom I haven't talked about very much, was translate your discoveries to medicine. He was not only a great diagnostic radiologist, he was the person who, with physicists here at Stanford, invented the linear accelerator to do radiation to cancers in the body, not just on the skin. He

was the person who, in looking at the lymphoid system, noticed that Hodgkin's disease spread from one lymph node to the next one in the lymph node chain, so he irradiated not only the lymph nodes that were involved with the Hodgkin's, but the next one up the chain, and really in one clinical experiment changed Hodgkin's disease from an always lethal disease to one where he could cure 85 percent just with that.

Williams: Incredible.

Weissman: So, I mean, in many ways, I only published maybe one or two papers with him in all the time he was there. All the rest were single-author papers. By the way, Gowans also told me both times he didn't need to be on the papers. I had done it, really, using his lab, but he didn't tell me what to do.

So, Eichwald, genetics. Kaplan, translate your discoveries. Gowans, in vivo veritas, and work with as pure a population of cells as you can. That's what my lab offers in many, many different fields.

I barely got tenure in 1974. I went to Gowans' lab and Gardner and Papiano in '74, '75—'75, actually. 1976, I'd published enough papers, they asked me to go on the immunobiology study section, a review group of NIH for immunobiology. As I walked in the room the first time, I wondered how they let me in with all those famous people, because there was not a weak person on the study section. Noel Warner, Max Cooper in the basic science. Everybody in that room were leaders in the field.

During the four years we had the study section, and especially in the senior years, I brought them to Montana twice for a study section, because I could show it was cheaper. We went once to Glacier Park and once on the edge of the Bob Marshall Wilderness. The bureaucrats at NIH finally quashed it, because even though it was cheaper than going to Bethesda [Maryland], they couldn't stand it that we were in a beautiful surrounding. It was amazing.

The reason I'm saying that is because when I went on the study section, I saw who they were. But if you now fast-forward to around 1989, 1990 when I first got on the Council of AAI and then became the president, I started the practice of looking at the study sections and who were on the study sections, and they were no longer the top people in the field. So, first on my own, and then with Herman Eisen and then with Herman and Mark Greene, for five or six years we sent the names of the top immunologists in the country who agreed to go back and work on study sections, to the seven immunology-related study sections that met three times a year.

At the end of the year—you can see this if you read the AAI newsletters at the time, and I think you should. You'll see what happened. In all of that time, the study section secretaries never asked a single one of our people to come on the

study section. Nobody was asked in those years. And this wasn't 2012 or 2013; this was 1989 to 1994, when I was president. So that made me curious how and why that happens, and I'll get back to it.

But I wrote the results of that, that discovery, in my President's Address in one of the newsletters. As you will notice in those newsletters, I used every one to address a topic that I thought was important to scientists. I did that because I thought that being president of AAI was okay, it was interesting, and I had to, on the first day I took office, make the decision about who would be the administrative head of AAI, and I found out not such pleasing things about the then current head, and I had to fly to Washington, and with Michael Jackson of FASEB [Federation of American Societies for Experimental Biology] I had to fire this person, then set up a search in which I hired the current head, Brigid. But I have to say in the late sixties—

Williams: Not Brigid. Michele [Hogan].

Weissman: I mean Michele. There's a Brigid Hogan that I always say. Right, Michele.

In the late sixties and early seventies, we were in the Vietnam War, and campuses like Stanford were being torn apart. I was morally opposed to the war—not religiously; morally—and so I was amongst the activists. In '65, after I graduated medical school, I gathered a group of people and we signed a petition that we put in *The New York Times* and *The Washington Post* that said we could not—these are all physicians—we could not be physicians in the military by what was defined in the military code, because your job in the military, contrary to the Hippocratic Oath, was to keep the fighting force healthy. So if given the choice of saving somebody with a minor injury or a life-threatening injury, you were supposed to take care of the minor injury first. It's in the Military Handbook.

Second thing is, if you had two people of equal injury or one with more and one less, one was the enemy, one was yours, you take care of yours first, no matter what the severity of the injury. So I said I'd be happy to do volunteer service or go to the NIH, and I was saying that with tongue-in-cheek, because I'd already arranged to go to the NIH and I had two labs that had accepted me.

After we published in *The New York Times*, two things happened simultaneously. One, I got my draft notice early, and, two, when I called to go to the NIH, they said, "You've been blackballed." Lloyd Law and John Fahey. So I couldn't go to NIH. So I understood politics pretty well and I understood political activism. It turned out that I got appointed to the Stanford faculty soon enough that I didn't end up being in the military. Well, it was a very close call.

I was the head of the Life Science Caucus of the April Third Movement during the bombing of Laos and Cambodia. Now, whereas other people would sit-in a

building, I couldn't go that far, so I'd teach a class on life sciences to the people who were revolting against the war, and ethics in the life sciences out on the lawn.

So by the time I became the president of AAI many, many years later, I had many, many years of political activism, and I knew what you could and couldn't do, and I knew that if you were quiet, the bureaucracy would still grind on. So in one of the newsletters, I described the fact that the cost of mice was way more than the real cost of taking care of mice, and that the veterinary centers around the country were a monopoly that were setting the prices not on the cost of mice alone, but the cost of their whole veterinary services, and I demanded here at Stanford a cost accounting. They said no.

By that time it was the eighties. I had started a company that had an AAALAC [Association for Assessment and Accreditation of Laboratory Animal Care International] and NCI [National Cancer Institute]- approved mouse colony. I called them up, I said, "Do you mind if I have my Stanford mice at that company?"

They said, "So long as it's ALAC-approved."

So I moved my mice over. I think Condoleezza Rice was our provost at the time. And they agreed to have a cost accounting. I knew right then after the cost accounting, I brought my mice back, that we dropped the cost of mice back in the early to mid-1990s from the direct cost of 95 cents a cage down to the direct cost of 30 cents a cage. And in that laboratory I started with Eichwald, which still persists today as the McLaughlin Institute, and I was a trustee, it was 15 cents a cage.

So it turns out that by veterinary centers being able to amalgamate all of their costs not on a species-specific basis, they could pay veterinarians on the staff, but for mouse breeding there was no reason to have a veterinarian come walk in the room. It would be like you're in a hotel, here, right, that every day a doc would check up on you. "You okay? Okay. Move on."

So we accomplished that. I think we're the only place that ever accomplished that, and as it drifts forward, you know, it's different. But if you go now to any immunologist who uses mice for their experiments, and you say what is the greatest barrier to you doing your research efficiently, they'll say the cost of mice, because nobody else ever did it. I would say two-thirds of the amount of money I have on grants for mouse research are simply to pay for mouse costs, and we are still lower than others. So that's crazy. And if it's unnecessary, it shouldn't happen. So I was mad. I did that.

I did the one on the study sections, and I proposed then and I propose now what I learned from the study section I had been on before. After a while, we realized for anybody who'd been in science for more than seven years, it didn't matter

what detail they put about how they were going to do the experiments. The only thing that had enduring value for picking great people was what was their recent track record published on experiments in the field, that a lot of people can write experiments that look great, but within a year, usually, somebody else or your own observation makes that original set of experiments stupid to do the way you were going to do it. And the real person you should support is the person who in that setting understands what they just saw and that they've got to change what they're doing, or in the setting of some new advance technically that somebody else made, you've got to change things. So I said then and say now that the only thing a study section need do is to understand who had the best track records leading up to that grant in the funding in the area of which they were experts. That means the composition of the study section should be experts, not as they were then.

Now, one more thing. For people who are young, I said you should set aside a pot of money that they compete with each other only. It's no fair for them to be with experts who have a track record. But I said you've got to have some way of evaluating them that's different than track record, because you don't know, when they write the grant, did they just come out of a great lab, whether they participated in that or not. So I suggested, I think, a reverse site visit, something like that.

And I've been on many panels of the National Academies and NIH, and every time I bring it up, the opposition say, "Oh, you're going to make it into an old-boys' network if only experts get to judge, and if they do it on track record, that's not fair." So now we're in a time of very low NIH funding, and we would survive as a science funded by NIH, whose goal is to advance science for the health of Americans. We would survive that if and only if we have the best experiments funded, the best people funded, but we don't have that.

As a member of the National Academy of Sciences about eight or ten years ago on a committee I was on called the Committee on Science, Engineering, and Public Policy, I brought in people who were expert in review of scientists and the things they do. So we had the former head of Bell Labs, the former head of research at IBM, the NSF [Nation Science Foundation], the Agriculture, the Hughes, the NRC.

Everybody but the NIH at that time judged the person on their track record, not on the application they wrote. NIH judged on whether the application you write would work, and, as I said, even later on when I did it when Zerhouni was head of the NIH and I made the same statement, I said, "It's broken. It can't work this way, because it doesn't evaluate what's best in science." It evaluates what my cousin Richard Lerner [phonetic] says are best seconds. The grant looks good because they can write a great grant on the discoveries of others. Okay, so anyway I wrote that one.

I did say that you should have experts on peer review, and I was countered by the person from NIH saying, "No, we believe peer review means peer top to bottom." So somewhere in there is a very democratic, egalitarian, populist but confused way to judge science going forward, and I think it's still horrible, even though I wrote about it in '94.

Williams: So your campaign then did not result in what you'd hoped for.

Weissman: Then or now. It's the same right now. It's exactly the same. The politics of NIH are difficult, and I'll just leave it at that so I don't get a libel suit if you keep this in.

The other thing that I did write one about I remember was the Bayh-Dole Act had been passed, and that gave the patent authority, of course, to the institutions where the discoveries were made. We at Stanford, for example, sell all of our patents to the university for a dollar, although I don't think I ever got a dollar even for them. But that's not the problem. Bayh-Dole said in order to encourage American industry, the university would not have to share the royalties with the NIH, so the university would be incented to get it out to the right industries in order to allow these advancements in science.

I said, "That's crazy. I think the university should share their royalty with NIH. It should be set up in a fund to fund even, for example, training or postdocs or whatever." You can go back and read it. Within a day of the publication of that newsletter, our head of the Office of Technology Licensing [OTL], Kathy Ku, called me up and she said, "All of the people at the OTLs around the country are screaming at me for not controlling you, and their main thing is they're saying, 'What is he smoking?'" Right?

And my answer is the same still, that if you don't take care of having that loop of fund flow go back to the innovators, it won't work.

I'm going to do a little science and politics now. You asked me what's the definition of stem cell, because out there if you ask the public, they say, well, a stem cell can make everything. As it came down to it, the only such stem cell that exists are the cells from that pre-implantation blastocyst, the inner cell mass, that are falsely brought into culture so they self-renew. The definition of a stem cell is that it can self-renew to make more daughter cells of exactly the same stage of development and daughter cells that are more mature of the tissues they could do.

Embryonic stem cell culture lines that are not physiologically growing and self-renewing at the single-cell level can give rise to all cells in the body. It's the only cell that does it. Once it implants in the uterus, in a day or two, as Janet Rossant and Richard Gardner showed while I was in Oxford that one time, the cells, even a day later, can't go back into the blastocyst and participate. You can't transplant them back into the blastocyst to participate in all stages. Whereas if you take the

cells from one blastocyst and put it into another one, they can participate, and you grow them out as embryonic stem cell lines. And we make hay, even now, by color-marking an embryonic stem cell when it gets in the blastocyst and look at all the tissues of that color.

But Till and McCulloch's definition was for the blood-forming system. In the late 1990s and 2000, with the advance that Jamie Thomson made on being able to make embryonic stem cell cultures from primates and then humans, which really followed on the very important work of Martin Evans making the first mouse embryonic stem cell, and Gail Martin all around the work at that time of Richard Gardner and Bea Mintz and others, the embryonic stem cells came from what the Catholic Church and the right, far-right people called embryos, and so there was a political problem about embryonic stem cell research.

I was asked by Bruce Alberts, then head of the National Academy of Sciences, to head up a panel on cloning; that is, taking a cell from the body like John Gurdon did in '65, Briggs and Kings in the fifties, and Ian Wilmut famously in 1997 or so, put it into an egg to reprogram it back to that early stage, and then either to clone the animal as Ian did, or what I thought was way more interesting, make an embryonic stem cell line or pluripotent stem cell line if it had reprogrammed itself sufficiently.

Now, this is pre-Yamanaka and the genes to do it. So I headed up that panel, and we showed by reading the literature that 99.2 percent of the blastocysts derived by nuclear transfer into the egg in cows, mice, all the animals, that 99.2 percent of them died after implantation. Many of them didn't die like people have miscarriages. They could sustain into the middle of gestation. I was head of the panel. And they were large enough to cause the death of the mother carrying them. So I could say biomedically and ethically, without religion, that human reproductive cloning wasn't there. So long as the animal counterparts, the fetus died and the mother often died, this was an experiment that the Nuremberg Code said was not allowed.

But while I was on the panel, Rudolf Jaenisch and Konrad Hochedlinger had published an experiment—you'll see where I'm going—where they could take the cells from a lymph node and put that nucleus into an egg and make a blastocyst, and once in a while, when the blastocyst actually survived, give rise to an animal derived from either a T cell or a B cell.

And I realized that if you could capture the immunoglobulin rearrangement of a B cell in a pluripotent stem cell line or the T cell receptor rearrangement in an animal, you could capture the genes of any person. So I advised my panel that the real reason to do nuclear transfer to create pluripotent stem cell line was you had the first chance to make not a mouse genetic model of a disease, but a cell line from humans that had all of the genes that caused that disease.

And I wrote an editorial also in the *New England Journal of Medicine*, and all of this was before anybody showed proof of principle, that that's why we do it. And if you look at the letters afterwards about me in the *New England Journal of Medicine*, they thought that I was lousy as an ethicist, lousy as a philosopher, and that, you know, the ban should go on. So what is today the most important thing we learned by even the Yamanaka factor reprogramming? That we can capture human diseases in a dish, not that we're cloning cells from ourselves to make tissue stem cells for ourselves.

So all of this was going on 1999, 2000, so on, and suddenly there were papers coming out—Helen Blau here, Eva Mezey, Peggy Goodell, saying that a blood-forming stem cell is only a blood-forming stem cell when it's in the bone marrow. If it travels to the liver, it's a liver stem cell. If it goes to the muscle, it's a muscle stem cell. If it goes to the brain, it's a brain-forming stem cell. And they got their papers published in journals that at the same time rejected the paper by Nobuko Uchida, Ann Tsukamoto, Rusty Gage, and me with the first isolation of the human brain-forming stem cell, prospectively by antibodies, made cultures and, by the way, now are in at least fifteen people with spinal cord injury, with failure to make oligodendrocytes [unclear] and in lysosomal storage disease and showing some efficacy at least in all of them.

But this was a moment when the definition of the stem cell was being challenged, so we tested in every model possible, and we showed that the blood-forming stem cell makes blood and only blood. It doesn't make brain cells to regenerate the brain. It doesn't make muscle cells for muscular dystrophy. It doesn't make pancreatic for insulin. It doesn't make heart muscle in a very famous paper we countered in *Nature*.

And, believe me, getting those papers published was almost impossible. Now, here it's really amazing. In *Science* magazine in the year 2000, they published the Mezey and the Blau paper, even though I now know all of the reviewers, all of them rejected that paper. But it was sexy. And they rejected our paper on the authentic isolation of human neural stem cells, which when we put in the brains of mice were *fantastic*, and we showed even in the first experiment where stem cells self-renew, a year later the human stem cells in the mouse brain are self-renewing. Where mouse-derivative stem cells migrate long distance to give rise to neurons, astrocytes, and oligodendrocytes, the human cells were doing that. And the cells they turned into at those distant sites were site-appropriate. An amazing, amazing experiment rejected in favor of phony science, and that phony science then is fraudulent clinical practices now.

So you may know that a few years ago before I was president of the International Society of Stem Cell Research, just the year before, I called those practices of clinics that say, "We can treat you with your own stem cells and cure every disease you have, genetic and otherwise." So I went after it, and we set up a panel and we came down with the simple proposition that we, as the International Stem

Cell Society, would have a website that would say to people and their caregivers, "When you are contemplating having your incurable condition cured by stem cells by somebody, find out when they were in their experimental phase in a hospital or a clinic, the name of the institutional review board that oversaw the safety of those experiments in humans. It's all recorded, so you could find it. Then if you're paying for it, for its efficacy, find out in that country the FDA or FDA equivalent that independently looked at it and said it's not only safe, it's effective."

So we simply put up a website for those two things, and a lawyer in Chicago wrote a letter to the Society and said, "By what authority are you sending people to ask those questions of us?" And the International Stem Cell Society backed down and pulled the website. This is politics. This is the same sort of politics. Now, it happened that there was science, bad science published in great journals that gave them license to say, "Hey, we're just extrapolating from those experiments."

So when we came out with our report in 2001, 2002, I already knew that pluripotent stem cells, so that's that old report, could be made by nuclear transfer, that the best use would be this, and that tissue-specific stem cells of one phase didn't turn into another. So the only time you could get those cells is from that early egg to blastocyst stage, which the church would never accept.

In that crucial period, we had not only isolated blood-forming stem cells and then human brain-forming stem cells—and by the way, we isolated the mouse blood-forming stem cell in 1988, the same year Mike McCune and I made a mouse called the SCID-hu where we combined immune deficiency that had human fetal bone, human fetal liver, human fetal spleen, human fetal thymus implanted into it.

We showed two things while we were forming a company. One, that you could inject authentic HIV into it and that those human cells would be infected and later, we showed, lose their CD4 T cells. The second thing we showed is that we could inject into a sub-lethally irradiated mouse with a human blood-forming system bone marrow and candidate bone marrow stem cells from an HLA different human, and we used that to discover the human hematopoietic stem cell. And the company, Systemics, began isolating human blood-forming stem cells and doing AIDS research, founded in 1988.

At that time I did the experiment again that I did in high school in Great Falls, Montana. Instead of using whole bone marrow to induce immunological tolerance in the newborn or the fetus or the irradiated host, I used stem cells. And now when I used stem cells, I could not only regenerate the blood-forming system or participate in the blood-forming system, but it induced permanent donor-specific transplant tolerance of any other organ or tissue from that donor. And, second, that because there were no preformed T cells in the graft, whereas

everybody getting a bone marrow immobilized peripheral blood or cord blood transplant has preformed T cells in it, there was no graft-versus-host disease.

Now, I go on transplant rounds once a year ever since then, 1988, and I go into the transplant rounds and there are two kinds of patients that are being treated. One is called autologous transplant, where they take their own mobilized blood out, they then give them a lethal dose of chemotherapy or radiation or both to try to kill the last cancer cell in the body because you've upped the dose, and then save them with their mobilized blood. Or allogeneic transplant donor to host usually HLA-matched where now you transplant the whole thing in order to regenerate them because they might have a defective system like sickle cell, severe combined immunodeficiency, Thalassemia, and so on. Lots of reasons.

So I do those rounds 1988 and today. I would not do any of the transplants the way they're doing. So we showed in the early 1990s of that company that we could by purifying stem cells with their multiple antibodies in the bottle or the test tube. You only had stem cells, no T cells. And from a cancer patient with cancer in their bone marrow and blood, no cancer cells. It was those two ways that we wanted to modify the practice of hematopoietic cell transplants.

So we transplanted fifteen women at Stanford with metastatic breast cancer. Of course, I couldn't be on the clinical side. And Stanford also transplanted at the same time seventy-eight women with the standard of care, the whole mobilized blood. We knew that about 50 percent of the mobilized bloods had large numbers of breast cancer cells in them. We transplanted them into the women after they received essentially a lethal dose of combination chemotherapy. We thawed the purified stem cells or the mobilized blood that had been stored, and it went back to the patients.

Fifteen years later, one-third of the women that got cancer-free stem cells with metastatic cancer are alive. Of the seventy-eight women who got back the whole transplant, 6 percent are alive. But fifteen years later, 27 percent, that is 85 percent of the thirty-three, have no disease. One woman has gotten back maybe a secondary breast cancer. The seventy-eight that got the mobilized back, even in the 6 percent they had recurrence of disease. Now, if that was a pill, that would be a product.

Now, we did that in 1996 to 1998. I wanted to be able to have autologous cancer-free stem cells to do that treatment in that and non-Hodgkin's lymphoma and multiple myeloma, the major people who still get those transplants. And I wanted to be able to transplant healthy stem cells from a donor to a host to have an allogeneic transplant that induces permanent tolerance from a genetic donor that doesn't have the disease the host has to get rid of the blood disease, and because of the tolerance, you would be able to transplant—if the mouse studies held—any organ or tissue or tissue-specific stem cell from the blood-forming stem cell donor, and it would be tolerated.

And in the early to mid-nineties, we showed that in mice, everything I said. So we could induce permanent transplant tolerance with pure stem cells. There was no graft-versus-host disease across these barriers in mice. Then if we transplanted stem cells from a mouse that was resistant to Type 1 diabetes into NOD mice about to get Type 1 diabetes, we permanently cured them. They never got the autoimmune diabetes. If they already had lost their islets and were surviving on insulin, if we give a co-transplant of stem cell and islets from the same donor, it cured them. Okay? We did the same thing with lupus, and Judy Shizuru has done the same with a model of multiple sclerosis, all of that back before 2000.

But my company was bought by a large pharmaceutical company. The antecedent of that large pharmaceutical company was a company called Sandoz that was in the market of immunosuppression, and they knew from our studies on being able to induce tolerance with cells once would cut into that market, and so the smart people in that company, Max Link, Victor Bischoff, engineered that they would own 60 percent of our company, but they knew, very wise, that if they tried to take control over our company, they would screw us up, that their business style and their management would do that.

So I was happy when they bought 60 percent of the company, made us a lot of money, but you have to believe me that wasn't my motivation. I've given away all of that money since, to the McLaughlin, to Stanford, and so on. The most important thing to me was getting these products into people for these serious diseases, immunological tolerance, blockade of autoimmunity, cancer-free stem cell transplants.

When Ciba and Sandoz merged to form Novartis, there were a whole bunch of different people who owned us, and they did a buyout of the rest of the stock. It was hostile. I tried like mad to stop them. They kept me on as an advisor, and within a year they had screwed up every one of the things.

He's looking at me with a questioning eye.

The reason that I've learned over the years is that they have huge money, whether it is big venture-capital firms or hedge funds or banks or pharmaceutical companies. They have the desire to look to the future and control the market. They have none of the vision that led to these discoveries. They're all from the culture of random screening of lots of small molecules, and you hope in the right assay it works. Their idea of self-renewal is every day you remember to take your pills, which I do and you do, too, I'll bet.

Stem cell biology can change medicine because the cells, if they're site-appropriate and they're the right stem cells and they're healthy stem cells, they self-renew for life. It was for those women with metastatic cancer who survived,

the last time they got treated for cancer, they're alive, productive, teachers, journalists. I mean, this is amazing.

So you would have thought that this would be big news, but I found out when I went back to try to do it again, to start to form another company, and I gave a talk at the American Society of Clinical Oncologists, and I said to them, "Giving back cancer-contaminated stem cells, mobilized blood, is not the same as purifying and having cancer-free stem cells." I even said to them, "The first thing you're going to say to me after my lecture is that stem cells have been tried in breast cancer, and they don't work."

Gina Kolata from *The New York Times* hammered that point home, that the bone marrow transplanters had committed fraud on the American public and taken money from them. Well, Gina understands fraud, and there was certainly more hope and hype when you gave back mobilized blood, but she doesn't understand science, I don't care what she says.

Purified stem cells that don't have cancer do better. Purified stem cells that don't have T cells don't cause graft-versus-host disease. We've wasted the time from those trials '96 to 2000, let's say, when they accrued, and now.

So back when I was asked to look at different kinds of stem cells for the National Academy of Sciences and reprogramming, I was very clear that I thought that if ever we could make tissue-specific blood-forming stem cells, tissue-specific brain-forming stem cells, liver, and so on, that the future would be the donors wouldn't be the rare people who match with you, but they would be the cell lines.

I immediately started getting two kinds of responses from the right wing, of course, and the [George W.] Bush administration, very negative, and from parents of diabetics especially. They would say, "You mean that Bush's ban means that we can't have this kind of a transplant to cure this immunological disease?"

I said, "Yep, that's what it means."

So a movement began in California, first with the parents of diabetics, to get a proposition before the state to not only codify, oversee, and allow stem cell research, including embryonic stem cell research, but to fund it. That became Prop[osition] 71. We were, to be honest, a group of people who were politically naïve, although my politics was on the other side. And it wasn't until Peter Van Etten, the president of the Juvenile Diabetes Foundation, said to us at one meeting in Hollywood, I remember, "You need Robert Klein to come here and help you. He's been a dynamo for the Juvenile Diabetes Foundation, and he has a kid with diabetes and a mother with Alzheimer's."

He joined up with us, and we jointly wrote Prop 71 which, by the way, I included expert review only track record, and that everybody who's reviewing had to be

from outside of California, with no financial ties with those from California who would write the grants. And it passed very well, even in a hard time. It was 51-49, so landslide. Three billion dollars, when the state was poor, to do this kind of stem cell-related biomedical research.

When they had their first meeting of that organization, they said, "Okay, what do we call stem cells that could be researched?" Well, the first, of course, was embryonic stem cells or reprogrammed stem cells, because the federal government wouldn't pay for that. So that was the highest priority. But behind that was finding and validating tissue- and organ-specific stem cells beyond the ones that were known. And the third one coming from research that I was doing and Mike Clarke was doing was every cancer we proposed, since it came from our tissues, like leukemia, could still have cells that have self-renewal and daughter cells that don't self-renew. And if you think about it, the only cells dangerous in a cancer would be the self-renewing ones.

So in the year 2000 we purified to homogeneity the acute myelogenous leukemia stem cell, and it was at a stage of blood formation one step removed from the real stem cell, so a cell that normally wouldn't self-renew when it was part of a leukemia did. If you fast-forward now, we have published that every genetic step going from a normal blood-forming stem cell to finally the emergence of this leukemia stem cell was in a clone of stem cells that got the hits one at a time. And there may be as many as twenty mutations or what they call epigenetic changes, inherited changes in the expression of genes that allow the cell to do something. Okay? And we said if you could purify cancer stem cells, which may be as few as 5 percent or 1 percent of the cells in the cancer, it's their gene expression that's relevant to their behavior, not the whole tumor. So they included cancer stem cells, and it's very important.

Okay. So now you have this juggernaut, $3 billion to be funded. One-quarter of the money for this building we're in came from our competitive grant to CIRM, the California Institute of Regenerative Medicine, funded by the passage of Prop 71. Everybody in this building probably has a grant from CIRM to follow their particular pursuit.

When I was looking at those blood-forming stem cells from humans and mice that we discovered in 1998 and 2000, for an overexpressed gene, a name popped up called CD47. CD stands for cluster differentiation. They're applied to proteins or glycoproteins on the surface of cells against which you have antibodies so you can describe them.

After a few years and a lot of cheerleading from me, finally I got somebody in the lab to take up this molecule CD47. I must say that the reason that it finally got taken up—and all this brings me back to immunology, that's what I'm saying—was that a group in Sweden, Oldenborg and Lindberg, had discovered if they had done a gene knockout for CD47 in mice, their red blood cells disappeared faster

than they should, and they showed that CD47 was an age stamp on red blood cells, high levels on young.

As it faded away, they got removed, and they went on to show they were removed by macrophages that used other receptors to test them, right? They'd bind to them, and if CD47 was there, it delivered a "don't eat me" signal. And the macrophage had a receptor called SIRP, signal-induced receptor pathway, very generic, and actually closer to my plain English that I was trying to say before, "don't eat me," and that delivers a signal to the macrophage it can't eat a cell that's got CD47.

And I said to people in the lab, I said, "Look, it's a 'don't eat me' signal for red cells, and every mouse leukemia and now every human leukemia expresses it. Don't you think that maybe there's something there?"

Sidd Jaiswal, a graduate student in my lab, picked it up, and we showed very rapidly it was in all human leukemias, that normal blood-forming stem cells when they're sitting in the bone marrow have very low levels of that "don't eat me" signal, because they're hiding away in a very special niche that macrophages don't penetrate.

But in the year 2000, Amy Wagers and I and Doug Wright showed that every once in a while a normal stem cell goes into the bloodstream and then it rapidly homes very specifically—we know the receptors—to another bone marrow niche that had lost its stem cell. So it's a way for stem cells to be able to refill all the stem cell niches continually through life, and so if a cell dies, we don't die also.

So when this cell is ready to go in the bloodstream—and this is what mobilization is, by the way, it's the cytokine you give to a human that induces stem cells that are resting, all to divide and then all to go in the bloodstream. You get the mobilized peripheral blood that's enriched for stem cells, and we used to purify the stem cells from it. So, anyway, Sidd and I showed that just before they went in the bloodstream, they up-regulated CD47. They went in the bloodstream. They homed directly to another bone.

Now, in the bone marrow are blood vessels that have the addresses to which their homing receptor is specific. They stop there. They roll. They detect a signal from in the bone marrow, a chemokine called SDF1 or CXCL12, to tell them to come in and directionally move, just like that old problem of T cells and B cells homing to the lymph node and going directly to the right place. It's exactly the same. Then they shut off CD47 when they got to the new niche. So we said, this is neat. The normal physiological function of the "don't eat me" signal is to allow the cells to go from one place to another, pass through fields of macrophages, which are just behind that blood vessel, and get to their home. And the cancers during the process of becoming cancers, to be a successful cancer to grow and

spread, they just have to flick on this gene that was there all the time, the "don't eat me" signal.

So we have shown that every cancer in humans not only has to defeat programmed cell death, which is induced by suicide when an aberrant gene turns on, but also programmed cell removal. Now, the programmed cell removal, loss of the "eat me" signal, we thought, is there in the dying cell before it dies so that when it pops open, it doesn't cause inflammation where it is. So it pops open inside a macrophage if it lacks the "don't eat me" signal. So it said there has to be an "eat me" signal. So we found many of the "eat me" signals, including the one that's on all leukemias called calreticulin. That's not important.

What's important is that we developed an antibody which blocks the "don't eat me" signal, and when we tested leukemias and normal bone marrow, it caused the leukemias to be eaten by human macrophages. Human leukemias, human macrophages, so it's part of the innate immune system. So the human leukemias eat, are eaten, if and only if we block CD47, and the antibody we use could be replaced by the receptor itself, the SIRP-alpha receptor, taken out, made much higher affinity, and you could do that.

So it's not an action of the antibody; it's blocking the "don't eat me" signal. And that reveals in leukemia and cancer cells the "eat me" signals, but not in normal cells. So when we take that antibody and humanize it and we put it into immune-deficient mice that are carrying human primary breast cancer in their breasts, or human primary glioblastoma in their brain, or colon cancer or melanoma or leiomyosarcoma or bladder cancer or ovarian cancer, every human cancer, our antibody leads to the phagocytic removal of it.

So, just like when we formed Systemics, all of us working together, company and big pharma, to move forward, and then big pharma decided it wasn't going to make enough money soon enough. They shut it down. Even though we've grown up in this wonderful capitalist country that's so successful and entrepreneurial, I found out that the money doesn't know the vision. All right.

So the third thing that I wrote into Prop 71 was that they should be able to fund any stem cell science, not just on discovery and preclinical proof of principle, but to fund the clinical trials themselves, so that you wouldn't have to offer anything out to industry until you took the risk away.

So, today I'm flying to London. I'm flying to London because we have formed a clinical trial consortium between England—Oxford really—and Stanford. We're going there to give the final discussions to their FDA equivalent and to their funding bodies, the MRC and the Cancer Research UK. They have assembled a team of superb clinical trialists because they have a single payer, the government, for health insurance, and you only negotiate to do a clinical trial with a single payer.

If I were to do, let's say, the acute myelogenous leukemia just at Stanford, within a year I might be lucky that they had thirty new leukemias eligible for the trial, and I'd be fighting Genentech and Novartis and all those other companies, because I can't pay even that as much as they get. In England, they unified so everybody in the country who gets acute myelogenous leukemia is offered the chance to be in a trial. So when Paresh Vyas and Alan Burnett said, "We'd like to work with you, do the trial also in England," I said, "Well, why should we?"

They said, "Well, we get a hundred patients every week. Which week do you want?"

And that is an enduring and an important political principle. Here in the U.S. in this last presidential election, keeping even "ObamaCare" was considered to be like Communism. But that means that we aren't going to be the people who get the first and most promising treatments, and we won't have the best clinical trialists who know how to do this, because they do it with very large cohorts of people. We do it and we have good clinical trialists, but we build huge, expensive bureaucracy, and the costs of clinical trials is way more.

So I know that seems it's pretty far away, but we have gone to CIRM to fund the humanization of the antibody to "don't eat me." We're about 10 million in toward 20 million grant. We've already shown that it's effective against every human cancer, whereas when we started, we thought it was only against leukemia. It works through a mechanism that's an immune mechanism. We know that the receptor for the "don't eat me" signal that's on macrophages is also on the dendritic cells that will present the antigens to the T cells in the immune system, and we've got to work it out if that really works also. But we're going to do a clinical trial within a year because we've shown that the antibody as we've humanized it is effective and barely toxic, easily overcome in cynomolgus monkeys that have the same CD47 molecule and the same tissue distribution as we have.

So it's a good chance that this is going to work, and I assume if I'm alive and still pushing it, that we will use this antibody to treat cancer. I have negotiated from the big company that bought Systemics the rights to the antibodies that we made at that company to isolate human stem cells. We're setting up a clinic here for pure stem cell transplants. We will do the rest of the breast cancer trial with much larger numbers. We'll do myeloma. We'll do lymphoma. Those are the big three of autologous transplants that need cancer-free stem cells.

We have another grant, which is also from CIRM, that Judy Shizuru, the person who did all this tolerance in diabetes studies with me when she was a medical student, now she's an associate professor of bone marrow transplant. We are going to transplant T cell-free stem cells from a sibling or a mother into a child with severe combined immunodeficiency. It's the only way to cure them, is a

transplant, and the transplants they get up to now cause graft-versus-host disease. You don't know the persistent immune defect that they have, whether it's due to the graft-versus-host disease, which have T cells that have homing receptors that take them to lymph nodes, Peyer's patch, spleen, and thymus, and they destroy first the immune organs, right? So I think I know why the immunodeficiency is there. But we'll do the clinical trial with that. It'll be the first time on Earth that we transplant cancer-free stem cells.

So what I've said is that beginning with an experiment I did in high school because of the wonderful work, I've got to say of not only Billingham, Brent, and Medawar, but a really fantastic guy, Ray Owen at Caltech, still alive, who in 1945 published a paper that calves, where you have multiple calves in a same litter in a mother, if male and female calves are born so they're genetically different, they permanently have the blood-forming system of both. He knew that a transfusion would have rejected it, so there must be something in the early time when cells can migrate back and forth and can induce tolerance, and they must be stem cells now retrospectively to last for life.

So it all started back then, '45, '53, '55, '56, when I started experiments. I'm still doing the same experiments. Old habits die hard, as my friend Jim Gowans told me when he visited the lab much later. It went, starting with immunology and transplantation, to stem cell biology writ large, and now it's all coming back to immunology and cancer immunology and transplantation and immune tolerance and blocking autoimmune disease. So I feel fairly comfortable that this is something that will cause a revolution, and I'm happy about it, of course. But nothing makes me happier than every day when the fellows in the lab come in and say, "You know, I've got something and I don't quite understand it," and we start talking about it and then we can put it in context to have an idea.

I think what we've established is to use the knowledge of immunology and stem cells to fix genetic diseases that include immunological diseases, to use stem cells that carry surface markers of a different person to induce tolerance. As I said, though, although I am involved in many organizations at many levels, including companies, to try to make it go forward, the one lesson I've learned about going from discovery to real clinical translation is that we all have to go too early because we were taught that we were supposed to hand things over to the companies; they knew how to do it better than us. And my argument is, no, they don't know how to do it better than us once you get above small molecules. Small molecules they do better than us. Proteins they're getting good at, but we can do the same. We can do antibodies. I don't have a GMP manufacturing here. I contract out manufacturing for our California-sponsored, Stanford-sponsored, Oxford-sponsored clinical trials that we're going to do.

So it's important to recognize that when you make a discovery and you think you see a preclinical objective for it, it's your own responsibility to carry it forward. Nobody else knows it better than you, and if you don't have the courage to do it,

it won't go forward. And when you do have the courage, you're going to go up against every possible "I knew it wouldn't work." You'll have, like I told you, at ASCO—by the way, the people at ASCO a year later stood up and cheered when there was no benefit of mobilized blood for treating breast cancer. Now, I can't imagine why doctors who treat breast cancer patients would be happy that something failed. I just don't understand that. I think that we as humans have to understand the human condition, we have to realize that every disease has a scientific basis, and we are the only ones who can bring it out, that even though it seems traditional to hand over your discovery to the commercial people early on, that is the valley of death. And you hardly ever get through the valley of death, so that governments like the state government of California have to take on the responsibility to fund to and through clinical trials.

Now, I don't think that that's possible to do right now at the NIH, because it's a bureaucracy and its study sections are filled with people who are in the middle of the peers, who, nevertheless, think they understand and who, nevertheless, think they can judge whether an experiment will work. *I* don't even know if my experiment's going to work, so I can't imagine how they could know.

So that's the lesson, that we have to take responsibility for what we do. We have to understand the environment in which we work so that we can do it. And if we have to be political sometime, we have to be political. If we have to take on somebody like, say, the Vatican, which I've done several times, you've got to take on the Vatican. If they're the barrier to what you're doing, you've got to do it, and you have to speak truth to power.

Williams: I've been asking everyone this question. What does a scientist do to have fun? What are your outside pursuits beyond…?

Weissman: Well, I've told you the inside pursuit. The best part of my day is when I talk to people in the lab and we're talking about an observation or planning what we're going to do.

I'm a fly fisherman. I'm a mad fly fisherman. I grew up in Montana fly fishing with my dad. I spend a lot of time fly fishing, still, and I've taught a lot of my friends who are scientists to fly fish, and we do that together. I taught Dave Baltimore how to fly fish. We fly fish two or three times a year, exotic places, and Lee Hood and Dave Baltimore and I have summer homes together on the Bitterroot River where everybody but Lee fly fishes. We can't get him to fly fish. Anyway. So I love it. And it's not like it's relaxing; it's just changing your intensity from this to a focus on that.

One of the guys I love to fly fish with is Bob Tjian, head of the [Howard] Hughes [Medical Institute], probably the most intellectual of the fly fishermen who understands what he's going to do and exactly what he has to do. Another great

one I fly fish with is Harold Varmus. We're going to go to Russia this summer to fly fish in a river.

So I fly fish, and I fly fish with friends, scientists, ones who I've taught or fly fished with. In another week, I'll go join a friend of mine from Montana who could not afford any of these fancy things, but we are going to go bum fishing, we call it, in Argentina, where we go from one river to another, stay in the cheapest place, eat the cheapest food, and try to figure out the river.

Williams: And I imagine a lot of good, interesting conversations go on, or do you have to be very quiet when you fly fish?

Weissman: Well, you don't talk while you're fly fishing, unless you shout to somebody, "Come over here! They're rising here!"

Williams: So it's a quiet sport.

Weissman: It's quiet, but then you're together with those people. You're traveling there, you're eating dinner, drinking, and so a lot of conversations go on.

Williams: Right. What about the interplay of your science life and your family life?

Weissman: Well, anybody in any field where you are doing what you really want to do and you see that the more time you do it, the better you do it, the more you advance, that means that successful scientists, and certainly me and my friends, are doing and thinking their science almost all the time until they shut off for what the family does and needs.

So I did all the soccer stuff and the baseball stuff and the basketball stuff, but they all saw how hard I seemed to be working when I was actually having fun doing it, and so all of them but one decided not to do science as their career. The one who likely will do science is a freshman at Stanford undergraduate now, but when she was working in Ravi Majeti's lab next to mine, discovered the "eat me" signal that the "don't eat me" overcomes. So I know she's got that way of thinking. She's been working in the lab for a couple of years, but now life is going to happen, and we'll see if she does it.

My oldest son, who would do anything but science, went into business and sports management and stuff, is the chairman of the board of an entity called the Accelerator, that takes nascent science to something that could make a company. Carl Weissman, he's head of the Accelerator in Seattle. So he and I can talk science, although at a different level, because I tell him that I would not—we agree there's not going to be any family business, because that old family business, the fur trade and steel supply, it mainly ended up alienating members, or one member of the family with the other, because they couldn't cooperate in a business. So my son and I aren't going to do that.

Williams: It impresses me that you have become very skilled in a business sense as well as in a science sense. Has that been a challenge or did that come easily to you?

Weissman: No. I mean, you had to pay attention, but it was part of taking your vision to a practical end, so I knew I had to learn it. I had to learn about patents. I had to learn about intellectual property, about the finance side, which I hate, and so on and so on. So, yes, I've learned a lot.

I think, as I said to you a few minutes ago, any scientist who makes a discovery that they see the translational root, as far as I'm concerned, has to take responsibility to be the champion of that all the way through to the therapy. And that means anywhere in the world, since there are no government companies, then it's going to be private capital that does it, so you have to do it.

Williams: I know we're leaving a lot unsaid today, but I don't want you to get on the plane and say, "Oh, I wish I'd talked about X, Y, or Z." Are we pretty well—

Weissman: Oh, there's a lot of things we didn't say. That's okay.

Williams: Well, thank you very much for this interview. It's been great.

[End of interview]