The American Association of Immunologists
Oral History Project

Transcript

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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

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

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

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 T cl s]TJ0.00226Td ( )Tj 0.0 /P <<

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-

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 ad a do end of t s, andk(r)3(o t)-2(,)-20(ye)4(l)-22.03(-2(s)-1(, but)-)2(nd)-1 yTd [(s.71-2(r)3(r)

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 he ulbould(ou p)-2iusu2(he)4(s)-13( )-10(g)1( )-1(

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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

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

And in the early to mid-nineties, we showed that in mice, everything I said. So

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."

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

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

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

Irving L. Weissman,

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'ywcomboutiasij3.e auT-1(i)5(e)-6(r)0(no g)10(ove)secoms(e)-6(s)-1(, t)-28(ni)-2(ed, s)am7]TJ e(r)3(ne)4(d)-10(a)4(dTJ T* [(r))-4(m)-6(e5h[e)4earnedJtihepiah-1(i)-(r)3(ne)4(d[e)4(be)4(du 3TJ 0 Tcok 0 Tw(ah[e)4euT-19.97(en)-14(g)6(e o)-14(r)-1(d)1014(i)-6(d27.)3((e)-6(s)-1(, t)-28