Sam Halpern

Interview conducted by

Mark Jones, PhD

August 20, 1997

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Samuel Halpern

Dr. Halpern received his M.D. in 1962 from the University of Louisville, School of Medicine and completed an internal medicine residence in 1968 at the University of Oklahoma. He worked with Hybritech beginning in 1970 as a consultant doing radiopharmaceutical research until 1991. Dr. Samuel Halpern trained in radiochemistry, clinical nuclear medicine and obtained board certification in internal medicine.

THE SAN DIEGO TECHNOLOGY ARCHIVE

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JONES: Were you here in 1977, when Ivor Royston and Howard Birndorf arrived?

HALPERN: Yes, I was here since August of 1970.

JONES: When they arrived, had you heard of monoclonal antibodies before?

HALPERN: I heard of monoclonal antibodies when the paper came out by Kohler and Milstein in, I believe, '75. It made a big splash. The paper was published in Nature, I believe.

JONES: And did you recognize potential applications for what you were doing, or what others were doing?

HALPERN: I recognized that its major benefit would be in radioimmunoassay, which is exactly where its major benefit has been, in my opinion. I also felt that there was some potential for therapeutic things, but I did not see it as a panacea.

JONES: What kind of work were you doing at the time?

HALPERN: Radiopharmaceutical research. In short, I was trying to look at things for tumor imaging. I had worked with renal imaging, I had built a renal imaging agent, I'd built a lung scanning agent, and I was interested in things for cancer, for some personal reasons.

JONES: And were you using antibody-based delivery systems?

HALPERN: No, I was not.

JONES: What kind of stuff were you doing?

HALPERN: I was looking at a variety of metal ions. I had looked at some labeled antibiotics. I had looked at the distribution, and this is important, I believe, the distribution of relatively large molecular weight proteins in tumors, namely albumin, which is 68,000 daltons, about. And so I knew a little bit about the distribution of proteins, large proteins, in tumors. I was working at that time with a model, the buffalo rat, with the 7777 Morris hepatoma, intramuscular.

JONES: Were you involved with the Cancer Center that the university was putting together?

HALPERN: No, I had VA grants, but I've been involved with the Cancer Center, yes.

JONES: Do you recall meeting Ivor Royston when he came down?

HALPERN: Yes, he was up in the hemoc.

JONES: Did you meet him?

HALPERN: Oh yeah, I met him ahead of time. Birndorf was working as his technician at that time.

JONES: Were you aware of what they were doing with monoclonals?

HALPERN: Yeah, he was from Stanford, he was interested in monoclonals, he was trying to look, he was interested in lymphoma, to a considerable extent. He was not interested, at that time, in imaging systems, at all. He built an antibody, a monoclone called T-101, which targeted T-cells, and that antibody was actually the thing, more than anything else, that got Hybritech Incorporated started, T-101. T-101, of course, it turned out, was not worth anything.

JONES: This got their imaging and therapeutic programs started?

HALPERN: Well, this was the time, the late '70s, early '80s, the time of great biotechnical fervor, in that people were looking for places to invest their money, and venture capital was flowing into these areas, and there was a guy up in Northern California by the name of Brook Byers, who I'm sure you know of, and he was once, I was once told that he was the CEO of more corporations than anybody in the state of California. I don't know if that's true or not, but Brooks was, he was a money man,

you know, and that's where he was. He was putting together corporations, gluing them together and getting them started with venture capital.

JONES: Well, what was your perception of this stuff that was going on?

HALPERN: I was very skeptical of its ability, there are some misconceptions. You know, you're going to get a lot of stories when you talk to these people, because I'm going to give you a bunch of names, many of them you probably already know, but many of them you may not, people to chase down with Hybritech. Some of the greatest immunologists you can imagine, and immunochemists, were hired by Hybritech. And they stole them from UCSD and Scripps, and places like that.

JONES: Stole them?

HALPERN: They made them offers they couldn't refuse. That's what they did. And these were PhDs, some of the brightest people I've ever worked with in my life, people like Gary David, Richard Bartholomew, they had truly first-rate minds. And their expertise was in immunochemistry and immunology, but they had no concepts of the pharmacology of these things. And I began with Hybritech, I guess I was either the first consultant or one of the first consultants. They had some trailers, two trailers, up near the Cancer Center, they were renting space in these trailers, and they had a little lab there, and very soon after I joined them, we had these meetings in these trailers, and at the start it was Gary David and myself, a chemist that I had, Phil Hagan, a radiopharmacist, who else was in those meetings? I guess Bartholomew was already there. They hadn't hired Frincke yet. They hired Frincke very shortly, I'd been working with them for a couple of months before Frincke came.

JONES: Was Tom Adams involved?

HALPERN: They hired Tom Adams, I was there before Tom Adams, they hired Tom Adams about two or three weeks after I started with them, maybe a month after I started with them.

JONES: How did your initial connection with the company get established?

HALPERN: Through Royston. Royston came to me and said that this monoclonal antibody, which I knew about, was going to be a wondrous thing, and that if they shot it in, that it was going to accumulate in the tumor. His concept was it's all going to accumulate in the tumor, and the tumor is going to glow like a beacon in the

night, and we're going to be able to detect cancer all over the place, and hopefully, if we can get enough in these tumors, we're going to be able to treat it. And, what I'm going to tell you now is hearsay, but I was told that it was Birndorf who pushed to take this T-101 and make a company, to get the venture capital. That's what I was told. I don't know if it's true. Anyway, I kept refusing because I was into my own stuff, and I told them, 'Look, I've injected proteins, high molecular weight proteins, into these things, and I know a considerable amount of tumor physiology, because I had to read it for my own work, you know, and I was well aware of the work of Intaglietta [M], and Guilino [PM], and Grantham [FH].

JONES: I'm not familiar with those names.

HALPERN: These were tumor physiologists, angiologists, tumor angiologists, and I knew how difficult it was to get a tumor to acquire a radiopharmaceutical, even a very small one. When you're trying to move something the size of an IgG antibody, you know, that's 150,000 daltons, into this damned tumor, and I kept trying to explain that the tumor capillaries, to begin with, there were too few capillaries in the tumor rather than too many, unlike what most people thought, that as tumors grew, the blood supply dropped like a rock, that was all the work of Gullino and Grantham, and those people. And there were massive shunts, so what even did get into the tumor, 50% of it swished back out without ever going through the tumor, AV shunts were just all over the place.

JONES: So, the problem was not so much the antibody finding the tumor, but…

HALPERN: Getting into it. You had a lousy blood flow to begin with in the tumor, then it had to get out of the tumor capillary into the interstitial fluid space, then it had to go through the interstitial fluid space to find the tumor. Along the way, it was facing shunting of blood, as much as 50%, was shunted straight into a vein. So, the lousy blood flow, 50% of what's presented is disappearing, it doesn't even get into the tumor, then you had to go through the capillary, then you had to swim, literally, that's how large molecular weight proteins, or any large molecular substance, once it gets through the capillary, it does not work on the basis of diffusion, it works on convection currents, OK? So, I kept telling Ivor, 'This will fail. This will fail. This will fail.' So, he prevailed on me to do a study with some iodinated antibody, and we did the study with the iodinated antibody, and as I predicted, the amount in the tumor

was low, very low. But, the amount in the tumor was higher than the stuff that I was fooling with. Under those circumstances, it became a better mousetrap for me.

JONES: So, the tumor did light up and it was also specific…

HALPERN: No, the word specificity, specificity is one of the most overrated terms in the world. To begin with, there is nothing specific. There's just more or less specific. Indeed, the term avidity, which many people don't even know exists, is probably more important in tumor imaging.

JONES: Is that binding strength?

HALPERN: It's overall binding strength based upon, not just the affinity, which is the interaction of the hypervariable region with the antigen, but the general binding on the basis of weak forces, hydrophilic bonds, van der Waals forces, those kinds of things, which work at very close apposition [?]. This is probably just as important, or maybe more important than the specific area, as a matter of fact, when I ran this experiment, I took antibody, specific antibody, and I labeled it and I took a non-specific antibody, hung a different label on it, injected both from the same syringe at the same time, then I quantitated how much more of the specific got into the tumor than the non-specific. It was just higher by a factor of three, specific over non-specific, so, specificity, it's important, yes. But a long way from being the only factor. So, anyway, once I saw that there was a slightly better mousetrap, then I decided to join.

JONES: Had Royston just talked to you about serving as a consultant to the company, or had he tried to recruit you?

HALPERN: Well, I was offered money. Yes, I was offered money. I was offered a thousand shares of stock. All of the consultants, as far as I know, and I knew quite a few of the consultants, were offered this thousand shares of stock. It cost, I believe, $37.50, something like that. But I was doing research with these people. I wasn't just an occasional consult. I was actually sitting there and working with them day by day, we used to hold research meetings in this office. We had two research meetings a week, one here and one there, and I was spending as much as four hours a week in meetings with them, early on. This drifted to two hours per week later. Hagan was is on the same things. These were marathon sessions frequently. And so, I turned down the money. Everybody thought I was crazy, but the problem was that I was too close,

and it was more than just a conflict of interest. I mean, I've taken consulting fees from other companies, but those I wasn't working with on a daily basis. And so, I was worried about. That stock, they tell me, is now worth about $80,000 because it was exchanged for Eli Lilly stock, and that stock has gone up, and so I'm out eighty grand, but what you don't have, you don't miss. So, I've never worried about it. I'd turn it down again. It was just too close. Anyway, we got started and the biggest problem that I had was to convince my brilliant colleagues, I mean, I had all the respect in the world for them, I still do, really extraordinary minds, but they were immunologists, much more so than biologists. I mean, things worked at the level of a gene with these people, or with some other organelle of the cell. They never thought about anything that was systemic. And they had absolutely no, there wasn't a physician over there until Bruce Merchant came on, and Bruce Merchant had spent some much time in regulatory affairs that his knowledge of medicine had dimmed. He hadn't kept up. And so, to convince them of what was happening in the rest of the body, the animal's body, was difficult. Also, they knew nothing about nuclear medicine. Absolutely nothing. So, I had to go into that with them. And their problem was to educate me in immunology, because frankly, I was weak in immunology, very weak. When I was a resident, I got out of medical school in 1962. I finished my internal medicine residency, where I had my last formal immunology, in 1968.

JONES: Where did you do these things, by the way?

HALPERN: I went to medical school at the University of Louisville, and my internship, and then my internal medicine residency was at the University of Oklahoma, and then I did a year of radiochemistry, I did a year of clinical nuclear medicine at the University of Oklahoma, then I did a year of radiochemisty with Manny Tubas [?], he's now deceased, at the Wadsworth VA, Manny was one of the grand old men of nuclear medicine. Anyway, I didn't know any immunology. I was in terrible shape. I got books and just started reading like mad. You can imagine how much I had to read, because I didn't know anything. I had to be able to speak these people's languages, and it was like they were talking Greek sometimes. But six months later, between what I garnered sitting around talking to them, and what I got out of textbooks. I was just reading textbooks. I wasn't reading articles. I was just trying to get basic knowledge, that's what I was getting.

JONES: That's pretty much what I'm doing, but I'm trying to read the literature, too.

HALPERN: Well, when you don't know anything at all about something, you go to where the stuff is concentrated and where the proven stuff is laid down, and that's what I did. And then, after that, I started reading the literature and understanding what was going on, but it was a crash course, self-taught, and taught by them. In immunology then, they decided that they wanted me to begin doing studies over here. I had Phil Hagan here, who's a superb radiopharmacist. I had a chemist that, well, I'll leave that out.

JONES: Well, Gary David told me that one of the chemistries that you tried didn't work.

HALPERN: Well, it worked for one antibody and then it blew, you know, it just chewed up the antibodies. It was [?]. I knew that iodine came off the antibody. I was certain of it because of other work that I had done, and because it made intellectual sense, in that the body is loaded with dehalogenase enzymes, and iodine is basically a hydrophilic ion, and once it splits from anything that's binding it, it will, if it's free, it's going to go out in the urine, you know, very quickly, and so the signal would leave the target and we didn't have very much there to begin with. As a matter of fact, I sat down and wrote a paper for a throwaway journal called Diagnostic Imaging. It was basically a theoretical paper, in which I took our own data and I took the natural physiology of the mouse and computed a poor man's guess, which I'm sure was accurate within a factor of two or three, how much, if you presented a thousand molecules to the tumor, OK, the percent that was captured and kept. And it came out to something like one out of a thousand, which means, you know, it's a disaster, and so that paper, it's turned out that that paper was really very accurate. It's one of the most accurate predictions I've ever made, and so based on that, the fact that I knew the iodine would come off the signal and tumor, I began pushing Hybritech very hard to use indium, and for a therapeutic ion, if they wanted to make one, to use yttrium-90.

JONES: And why did you think that these would be better isotopes?

HALPERN: Because I knew that when yttrium came off, if you chewed up the antibody, that yttrium and indium would end up, probably, in the lysis zones of the cytoplasm, which are in the cytoplasm of the tumor. And therefore, they would remain in the tumor. They would also remain, to a higher degree, in the background. All of those things came to be.

JONES: Were other people at the time starting to use these?

HALPERN: No, the ideas, the whole thing with the yttrium and the indium actually came from work that we did, from arguments that took place at Hybritech. I was the guy who pushed the indium and yttrium like mad. I never stopped talking. I pushed it and pushed it and pushed it, until finally, I think, they made a decision just to get me to shut the hell up. So, to this day, I think it's a better system for detection than iodine, and yttrium may, be certain may is in there, may be a better system for therapy than iodine, although I'm no longer so sure of that.

JONES: For what reasons?

HALPERN: Well, the good part of the yttrium is that it's a pure beta emitter, very high energy. So, the only thing that comes off the patient is breaking radiation, which is known as bremsstrahlung. It's a German word that means breaking, because the beta particle swings around the nucleus in a crack the whip thing. And as it cracks the whip, it starts to exceed the speed of light. It can't exceed the speed of light because Brother Einstein said that it couldn't, and it can't, but if it gives off energy, it will slow down, and so it gives off the energy, the breaking radiation. It slams on the breaks and off goes this photon. But that's low energy stuff, so you can treat the patient on an out-patient basis. And today, it's a big damned deal, because if you hospitalize somebody, especially if they're in an isolation room, you're looking at a couple thousand bucks a day. It pushes the cost way up.

JONES: Is this true or not for iodine?

HALPERN: No, iodine, you're going to have to keep them hospitalized because it has a huge gamma component. There are five or six photons that come boiling off of iodine, some of which are very high energy, they can go all the way to up to 700 keV or better, and there's a significant percentage. Even the principal photon, 82% comes off at 364 keV, and so you've got well over 90% coming off at 364 or greater, so you're going to shower everyone around you. And people don't like that. And it's got an eight day half-life, so you're going to shower a long time. So, you're going to hospitalize them, or else you're going to have to use very small doses. So, yttrium has got a half-life of around 70 hours, and it's pure beta, and you can shoot 'em up and ship 'em out. That's one thing going for it. Going against it, unfortunately, is the bone marrow effect. The iodine circulates around, it goes into the tissues, once it gets into the tissues, it starts dehalogenating like mad. This comes out and it's kicked out in

the urine. In the case of yttrium, the stuff stays in the body, and the stuff is swishing through the bone marrow, and the bone marrow becomes the critical organ. And your platelets sag to zip, and your granulocytes drop like a rock, your lymphocyte count goes way down, and you hope they go back up.

JONES: Are these effects that you were aware of when you started thinking about using yttrium?

HALPERN: Yes, I knew this, but when you, what is it Shakespeare said, "Dread diseases" or "Dread therapies make," something to that nature, one of his characters said that. I knew that, you know, but I knew that what I was poisoning them with probably wasn't as poisonous as some the things the oncologists poison them with. Oncologists shoot stuff into people that, you know, unbelievable. I mean, some of that stuff that they shoot into people is more poisonous than arsenic by far, multiple times that. So, mine wasn't anywhere near as draconian as some of that, so I thought, 'What the hell, it's a dread disease. Dread therapy? Go for it.' We didn't have anything else. So, that decision was made and from that point onward, we designed these experiments, one after another. We even held retreats, bed retreats. There's a guy named Dennis Carlo, who was the head of therapeutics over there, a bright guy, owns his own company, Immune Response, over here, he and Jonas Salk started Immune Response. They got him, I believe, from Merck. Anyway, Dennis is a good man. He was willing to gamble on things. He's willing to make a decision. One of the hardest things to find in a corporation, anywhere in a corporation, is a person who will make a decision, and then stand by it. Dennis Carlo is that kind of person. He may be wrong, but he'll make the damned decision. You walked into Dennis Carlo's office, and you walked out with a decision. I had some hellacious fights with Carlo. He and I became very close friends.

JONES: What kinds of things did you have disputes over?

HALPERN: Oh, God. The disputes over science were never real disputes. Intellectual arguments used to take place over there, it was a real intellectual ferment. Honestly, there were times when the intellectual ferment over there was better than at any university that you've ever been at. Everybody stood up and spoke their minds, everybody. And at these retreats, you sat there and people would blast away, but it was never personal. It was always the science, which I really loved, you know. And there were times when it was obvious, you know, when they were right and I was

wrong, you know, I never had any problems with that, never…the disputes that I had, there were times when corporate decisions were made about some things that I'd put in huge amounts of work on, and I'd been promised, and then they'd been reneged.

JONES: This is, for instance, pursuing a path of research?

HALPERN: Yes, and I would have been promised this. It happened three or four times.

JONES: Do you recall what projects those were?

HALPERN: I do. I remember one. I was promised, and Gary David sat and heard it, this didn't involve Dennis Carlo, it was before Carlo. I was promised that I would be the first person to use the antibodies in a radioimmunotherapy way. I already knew that I was going to be the first to do radioimmunodiagnosis with them. But I was promised that I would get the radioimmunotherapy.

JONES: To do a human clinical trial?

HALPERN: A human clinical trial of radioimmunotherapy. A man by the name of Stanley Order was at Johns Hopkins, and Stanley was a guy who, he could mesmerize you, he could. He should have been a United States senator or something like that, because when you sat and listened to Stanley, he blew you away. He just blew you away. And he was bright, but let's say that he was less direct with his data than I was.

JONES: So, he painted a rosier picture about the prospects for what he was doing?

HALPERN: He was less direct with his data than I was. And anyway, the decision was made that I wouldn't get to do the therapy. It was given to Stanley Order.

JONES: Who made that decision?

HALPERN: Tom Adams.

JONES: Originally, they were using polyclonals with him, but that didn't matter to you, you just cared about the labeling, basically?

HALPERN: They were using my ideas, man, they were using the yttrium. That was my idea. Now, don't get me wrong, I mean, if I thought that Stanley Order could have done it a lot better than I could have done it, was better at it and knew more than I knew, and that patients' lives hung in the balance, I would have stood aside. I didn't think that. I thought I was right. I thought I knew more than Stanley Order did. I still do. But, Stanley had an operation going, and Stanley put on, Stanley was doing therapy of hepatoma with iodinated polyclonal antibodies. He'd done quite a few cases, and he was reporting extraordinary results, extraordinary results. Turn off the tape recorder...[tape stops]

JONES: Well, when you're faced with the realities of financing these unproven technologies, nobody knows whether they're going to work, they're big technical challenges, and to make some of these things work, maybe you need people like that. People talk about Ted Greene the same way, they say that he can generate excitement.

HALPERN: You know Ted?

JONES: No, I haven't met him yet, but this is what people say about him, and that's the way these biotech companies have been able to amass millions of dollars to fund research.

HALPERN: Let me tell you something about this company over here, Hybritech. I don't know all these other companies, but I knew Hybritech. I didn't know the people doing the in vitro work. I knew some of them, but not well. But I knew the people in therapeutics, and that was as fine a group of scientists as was ever accumulated for a biological project. I mean, these people could do science. The possibilities of the company back in those days were almost limitless, if they could just push the money out there and keep it going. I don't know what we'd have come up with, but we'd have come up with a lot of stuff. I mean, they had the likes of David and Bartholomew and Lallo and Martinis. These people just knew so much, they were just so good. It was such a joy to work with them, when the corporation was kept off our backs and we could just do science. As a matter of fact, eventually, they put Gary David out working on what they called the 'Blue Skies' project, which basically meant that he could do anything he wanted to.

JONES: Was this before or after Lilly bought the company?

HALPERN: I think he went Blue Skies actually before Lilly, but it was about the same time. But anyway, you know now, about the thing where I lost the right to do that, so there was a great to-do. Carlo was there by that time, and you know, I told you we had some monumental fights. That was one of the things we had a monumental fight about, and then there were a couple of other things. I don't remember exactly what they were. I quit two or three times, and then he and I would always get together and hammer things out.

JONES: Do you keep in touch with him?

HALPERN: Well, I got a Christmas card from him, my wife and I used to be friends with he and his wife. I understand he's had some marital problems. I don't want to go into that, but anyway, he kind of…I haven't seen Dennis personally for years, but he's right up the street at Immune Response. But I like him a lot. We used to go fishing together he and I, long-range deep sea fishing together.

JONES: Where did you go?

HALPERN: Oh, we'd catch a sport fisher out of Point Loma, the Polaris Spring is one I think we used to ride on, and we'd go down after the big yellowfin and wahoo and big yellowtail, stuff like that. Dennis is an enormous man. He dwarfs me, and his physical prowess is well known. Anyway, we had a few conflicts like that, but basically, working with Dennis, when he ran a project he would make a decision and that was delightful. They funded me to do research. I was in on setting up all the research. Some things they wanted, they'd do, some things that I wanted, I'd do, you know. I'm still publishing stuff out of that. I've probably killed between ten and twenty thousand mice from 1980 to the early 1990s. There were weeks in which we'd do experiments with a hundred and fifty mice. It looked like a slaughterhouse upstairs.

JONES: So, at some point, you made a decision that you would focus all of your energies on monoclonals and on this chemistry?

HALPERN: From 1980 to 1991, everything I did in research, I mean bench research, I did a few clinical things here. I worked with the shrinks on brain blood flow, I wrote up some clinical stuff, case report stuff, things like that, but really the most significant research I did in my whole life was the research I did with them. I actually felt, at times, that I was part of the corporation. And I was treated very well, very

respectfully. They respected me as a scientist and as a human being, and then Eli Lilly came along. And they destroyed the company.

JONES: Well, when Lilly bought the company, Hybritech was generating revenues with the diagnostic kits, but people have told me that initially they were interested in the imaging, rather than therapy, I mean, they would vacillate between their commitments.

HALPERN: Well a lot of the vacillation in the company concerning imaging and therapy was based on the science. The science is going to drive you one way or another. I mean, you're not going to make a decision to do something that flies in the face of the science. If the science says you can't go there, then you don't go there, and when something else comes up that looks good in the other direction, some technique or something that might help it, that might change things, I mean, then you vacillate back the other way, you know. And it's true there was some vacillation, but the vacillation was driven by the science, mostly. But also to some extent by the marketplace. I was aware of that, and I was aware of that all along. I mean, I don't expect corporations to act simply like a university and to do pure research and not keep the bottom line in mind. They'd be fools to do that. If I ran a corporation, I wouldn't do that, and I don't think you would, either. You've got to make a living. And you've got stockholders, employees, people whose lives are at stake. But what Eli Lilly did, and what I'm telling you now is my gestalt of it. To begin with, I started being excluded from the meetings. There was a dramatic change. I began to get the feeling that things weren't being said at meetings that I was at. I got the feeling, and once more, I can't prove this, but I got the feeling that some meetings were much more covert. Once I smelled that, I wanted out. You know, I was either in or out. And I was aware, even before Lilly came on, that there were things in the corporation that they didn't want me to know, and I understood that. But it didn't involve the science.

JONES: Were there also new faces involved?

HALPERN: New faces showed up, people I didn't know, people I'd be introduced to, but they were all the same, you know, they were just faces. There was nothing, they never spoke at the meetings, they'd just sit. They never spoke. I mean, was this Big Brother, or what, you know? And so, then when Dennis quit, I knew that things had to be going from bad to worse, and my tip off to absolutely limit my time with Hybritech, or to get out as much as possible, was the day that Dennis Carlo told me

that he was quitting. It was at that time that I said to myself that staying around here was stupid. I have a funny story to tell you.

JONES: Please.

HALPERN: As close as I came to being a millionaire. I told you I turned down the thousand shares of stock, which I did. But I went on vacation, and I don't know, I was on vacation for about ten days or two weeks, something like that. I came back and the first thing I did when I came back to work was to call them over there, to find out what was going on, what study was being done that week, and all that kind of stuff. And I got a hold of a new secretary, and she didn't know me from Adam, you know. So I said, I think I asked for Richard Bartholomew first, and she said, 'Well, Richard's not here.' So I said, 'Well, let me talk to Jim Frincke.' She said, 'Frincke's not here.' So I said, 'Well, give me Gary David.' And she said, 'He's not here. They're all in Indianapolis.' All in Indianapolis. Why would all of the chief scientists be in Indianapolis? Then I thought, there is either a hostile takeover that they are trying to deal with, or there is a friendly acquisition going on, and what I need to do is go out and hock the house, get myself a hundred thousand dollars, and buy Hybritech like mad, because if a merger goes through, that's going to be worth a lot of money. I almost did it, but then I decided against it. I don't know why I decided against it. It had nothing to do with principles, because there wasn't any insider trading here, I figured out what was happening. And then, of course, it happened, and then the stock, they sold the company for a certain amount, and then they renegotiated the deal and went up to, I don't know, four hundred million or something, some outrageous figure that they were putting out. The stock was selling for ten dollars a share, and it was then exchanged for Eli Lilly stock which then ran up to about eighty dollars a share. I have no idea what Lilly's trading at now, but that's how close I came to becoming very rich. But anyway, I didn't do it.

JONES: Well, backing up a few years, I'd like to hear about Jim Frincke coming on, and about the chelation technology, I guess the name is Krajcarek.

HALPERN: Gary Krajcarek, yeah. Hagan knows Krajcarek. Gary had been around nuclear medicine quite a while, and he came up with this, there was no great chemistry involved, it was pretty straightforward. All he did was form an anhydride of DTPA, and react with the anhyride with a lysine group on the antibody, and that left you with, you know, you dehydrated one of the five carboxyls, so you had four

carboxyls out there to chelate. It's straightforward chelation chemistry. What you wanted to do was limit the number of side chains that you added, because as you kept adding more and more side chains, you'd change the distribution in the body. So, they looked at that, and Frincke had come on, we were still in the trailers, I believe, when Frincke began, and he went to work on this technique, and he did a lot with it, he did a huge amount with it. He was responsible, in my opinion, for making, for cleaning up, I mean, the concept of bifunctional chelation was not Jim's, but taking it and raising it to a high level, that was Jim's thinking. And the chelation chemistry involving the yttrium was Jim's and the cleaning up of the yttrium was Jim's. He had a whole process over there for cleaning up the yttrium, and he did a lot for the company. He fell into disfavor after I left. The reason I really don't know, but after the acquisition by Lilly, a man named Jacques Chiller came on as the overall scientific head, I guess. I think everybody reported to Jacques, although I'm not certain of that. Certainly everybody in therapeutics answered to Jack. And he was extremely bright, and I was told, and I don't know if this is true, but Jim somehow got crosswise with Jacques, and Jacques made his life miserable until he quit. That's what I was told.

JONES: Do you have any idea where he is now? He's one of the people I haven't been able to locate.

HALPERN: Jacques Chiller?

JONES: No, Jim Frincke.

HALPERN: He went up to Northern California with a small company, a very small start-up company, and I was publishing a paper, and he'd done a lot of work on this damned paper, and I wanted him to review the paper. It was important that he review the paper. So, I called his secretary and Jim would never call me back, which surprises me, because I never had any trouble with Jim Frincke at all. I never had, oh, we had cross words one time, but he later on apologized for it, otherwise I had no problems with Jim Frincke. He joined this little corporation, he never did review the paper. I kept trying and trying, and finally the data was growing cold. I just published it. I had to take his name off, because I would be publishing something without his final review, and I wasn't about to do that. I could get into a lot of trouble with the university for doing that. So, I published it. Then I heard that he had a lot of marital

problems. His marriage fell apart, apparently, and the kids moved with his wife down here, and then I lost all track of him. Have you seen Bartholomew?

JONES: No.

HALPERN: He's up at Immune Response, he and Charlie Lollo both, they're with Dennis up there. You can talk to Dennis, if he'll talk to you. Do you have Roberto Fagnani? I may have his number, let me see where it is. Tell him Sam sent you. Yeah, I've got his home phone number and his fax is the same. It's (619) 455-9176. The last time I saw Roberto was about a year ago. He and his dad were here. His dad was visiting from Italy. F-A-G-N-A-N-I.

JONES: Do you have any idea what he's doing these days?

HALPERN: Consulting work, I think.

JONES: Well, you were working pretty closely with Dennis Carlo, and he was involved with all of the strategic discussions.

HALPERN: Oh yeah, but Dennis traveled an enormous amount. That stock that they sold when they went public, Dennis Carlo is as responsible as any man for getting that stock sold. He spent half of his time away from here. He lived on an airplane, selling that stock. And it sold. I think Drexel Burnham was handling the stock deal for them.

JONES: I've heard stories that he didn't particularly care for reporting to Tom Adams. Were you aware of anything like that?

HALPERN: Tom Adams was a difficult man. That's not to say that he was a bad person, it's just that there was only one way to do things, and that was Tom's way. I saw that also, and I'm sure that he was like that with everybody. He was a good friend of Ted Greene's. The problems, direct problems, between Carlo and Adams, I don't know. I wasn't really privy to what took place. Dennis was very close-mouthed about it. But I know there were problems. But he's not the only one who had problems with Tom. I had some minor clashes with Adams, but it didn't take me long to understand that they owned the baseball, and if I was going to play in the game, I had to use their baseball, so as long as I could make my interests coincide with their interests, I stayed with them. And I pretty much managed to do that whole thing. There were a couple of things that I was asked to do that I refused. I refused to work with monkeys. I was

asked one time to do that, and I had worked with macaques, way, way back, in the early '70s. I was causing strokes in these poor animals, and then it hit me one day when I walked into the facility upstairs, the animal resource facility upstairs, back into the primate area, these macaques would see me and freak. They'd go absolutely nuts. They recognized that I was Dr. Death, and as soon as I realized that there was some cognition in these animals, I refused to do any further work with primates, and I have not to this day. I prefer to work with mice and rats, rodents, mice, rats, rabbits, that kind of thing. They don't know what's coming off, you know. Even there I sometimes get some guilt feelings.

JONES: Were you actually growing hybridomas here?

HALPERN: No, I was not. The hybridoma technology was all over at Hybritech.

JONES: So they would send antibodies over?

HALPERN: The antibodies came over. I had a huge source of antibodies. I shot nineteen different antibodies into human beings. I probably shot more different kinds of antibodies into human beings than any other guy alive. I shot in IgMs, I shot in IgGs, G1s, G2As, I shot them in as intact antibody, as FAB2s and FAB' [primes], as FABs, labeled with indium, labeled with yttrium, labeled with technetium.

JONES: What's your appraisal of technetium for this purpose?

HALPERN: All right. In the case of the technetium, the only reason you're seeing it is because of the enormous photon flux of technetium. Technetium's got a six hour half-life. You can inject 30 millicuries into somebody. The most you're going to inject of indium is 5 millicuries, so you get six times as much in. You can use low-energy, ultra-high resolution collimation, you don't have to worry about rad dose to the patient. If it was worthwhile, you could go even much higher than that without harming the patient. And so, the technetium is going to show you a lot based upon photon flux. On the other hand, given the clearance of the compound from the vascular compartment, the background is going to remain relatively high, so there's going to be whole areas of the body denied to you. Anything overlying a blood vessel, that sort of stuff, you're going to be at its mercy, so I believe that the technetium will have a problem. When you take out a piece of the technetium labeled compound and you look at it, you get even less in the [?] injected dose per gram in the tumor than

you do with the indium, because the indium is floating around longer, it takes a longer time to acquire.

JONES: But it might be preferable for certain indications?

HALPERN: Yeah, it would be, if you were trying to label something where you were getting the isotope into fast, like trying to image cholesterol plaque, or something like that. I'm involved with a project of that nature now, with the lipid research group here. We're using technetium.

JONES: Well, through all of your work with Hybritech, was Ivor Royston involved in any of that?

HALPERN: With the company?

JONES: With the research that you were doing. I know that he was sitting on the board of directors, but…

HALPERN: OK, marginally. His scientific input into what I was doing was zero. His scientific input into what Hybritech was doing was zero. He had a lot of conflict, I was told, I don't know this, with Tom Adams, and just stopped his interaction. So, he was very marginally involved with anything to do with the science.

JONES: When they started Hybritech, and when the stock in the company started to have some value, what was the atmosphere like around here? Were a lot of people upset that Ivor Royston was…

HALPERN: Yeah, there was a lot of jealousy. A lot of jealousy. Ivor's not the first academic who ever made money. I don't begrudge Ivor having become a millionaire. That's no skin off my nose. I don't care. More power to him, you know. He didn't take anything away from that Cancer Center down there. He didn't take anything away from this VA, or from this university. These were petty jealousies. And in this case, I fault the university, not that Ivor was all that easy and reasonable to deal with, because he wasn't. And there were conflicts that occurred between he and the university, flashpoints that didn't have to occur, but Ivor didn't do anything to keep it from happening, and you could see what they were going to be. Like the war that took place between he and the head of the Cancer Center.

JONES: I don't know much about that. This is what precipitated his starting of the…

HALPERN: He had already left, but he had problems with the head of the Cancer Center before that. And, we started the radioimmunotherapy stuff, and I was with Ivor, you know, we were shooting in yttrium labeled antibody, and once more, he sat in on the research meetings, but as far as making the intellectual decisions, no, he didn't. He would put his two cents in, but generally his two cents weren't worth that much.

JONES: He wasn't involved on a day to day basis?

HALPERN: No, not on a day to day basis, but he would attend the research we would have for the radioimmunotherapy work that was being done with IDEC, which was a different corporation.

JONES: Were you involved with IDEC?

HALPERN: Yeah, I was involved with IDEC, with the original stuff that they were doing. It was kind of combined thing between IDEC and Hybritech. This was in lymphoma. IDEC's still working with it, successfully, there are some success stories coming out of there.

JONES: Well, they've almost got final approval for a product but it's...

HALPERN: It's a non-labeled product, right? But I was involved only with the labeled ones, and they're doing studies with the labeled ones, and I've only seen a couple of patients, but I'm a consultant to them, and the boys over at Sharp have been working with it, and I've spent a lot of time around antibodies, and they hired me as a consultant, and so I've seen some very good stuff from them, very good.

JONES: But now, in 1991, you stopped working with Hybritech?

HALPERN: Basically. I didn't do much with them after 1991, almost nothing. I don't remember exactly when I quit working with them. I think '91.

JONES: What prompted that decision?

HALPERN: Well, the guys at Eli Lilly. The atmosphere wasn't good, the intellectual ferment was gone. The excitement was gone. I saw the corporation going from what I thought, what I considered to be a great potential, to nothing. Lilly never knew what it was doing. I swear to goodness. I don't see how Eli Lilly has become such a mover

and shaker because I saw nothing but what I consider rank amateurism come out, just amateurism. They took that little company, with all of its potential, and destroyed it, in my opinion.

JONES: When they closed the in vivo division, the FDA had actually approved an imaging product. What's your take on that?

HALPERN: It was the best product on the market. ZCE025 is the best damned antibody for imaging I've ever seen.

JONES: And this is an antibody that Hybritech developed?

HALPERN: It was the one that developed and the one that they were going to use. They got it from Jean-Pierre Mach, I did a sabbatical with Jean-Pierre, he's a close friend of mine.

JONES: Where at?

HALPERN: Lusanne, Switzerland. They got it from Jean-Pierre, and it was superb. But they pulled the plug on it. It would have been really a wonderful product. Well, really, there's no such thing as a wonderful product in this kind of stuff, OK? Everything has to be qualified. There are limits to what you can see with nuclear medicine techniques. There are limits to what you can see with any technique. What's happening, just conceive of this. If I had something the size of a grapefruit, and I shot in radiolabeled mud, the odds are, I'd still see it, right? Just on a mass basis alone. If I had something the size of an egg, I might still radioactive mud. Now, if I dropped that to the size of a golf ball, I may have to have a better radiopharmaceutical than radioactive mud. I might start to have to have decent lesion to background ratios based on something other than volume. If I drop it to two centimeters in size, then I have to start getting good, because the background surrounding it will beat you. If I drop it to half of that, one centimeter in size, then I start getting into problems of resolution with my equipment.

JONES: And that's where Hybritech was with this product, right?

HALPERN: About a centimeter in size, that's right. If I drop it to about a half centimeter in size, then you have to really, really be good. But do you realize how many cells there are in something that is a half centimeter in size? Billions and billions of cells. If I drop it to the size of a pencil point, a couple millimeters in size,

there's no technique known to man that will pick it up. We just can't do it. But if your patient has colorectal carcinoma, and there are three or four two millimeter mets around, he's a dead man, OK? So, what good is it to diagnose something that's one centimeter in size. Well, you might say you can berry pick it, you can go in and remove it. But almost invariably, there will be others around. Where there's one, there's more. And therein lie the problems of cancer detection. And they are enormous, because you can't get down, theoretically, a single cell can kill you, and it's true, because if you look at the leukemia data, if as much as a single cell remains alive, the leuk's going to come back, and it's going to get you. So, it's an all or none thing.

JONES: Do you see anything on the horizon, prospects for solving these problems?

HALPERN: Well, I think much of the…we're going to learn a lot from molecular genetics and molecular biology. We're already learning a lot. I mean, for example, you can see people, high risk people, that sort of thing. Ashkenazi Jewish women, for example, they have an enormous percent chance of getting cancer of the breast because they're BRCA 1 and BRCA 2 positive. People who have the thyroid carcinoma gene, forty percent of them are going to get thyroid cancer. If you can identify that gene, then you can do something about it. The last time I looked, there were sixty-eight oncogenes that have been identified in colorectal carcinoma. Now, what do these genes mean? What does it mean when, on chromosome #10 of a thyroid cancer, you have a pericentric inversion of a gene that puts a promoter, promoting a kinase, promoter kinase right next to a promoter gene? Cancer is a genetic disease. It's gene driven. How those genes are driving it, I don't know, but that appears to be the case. Not all of these oncogenes are making something. Some are, some aren't. What are they making? What is what they're making doing? As more and more data comes in, when the Human Genome Project is over, you'll have a huge amount of data laying there. And then, I think, you're going to start being able to identify spin-offs from that as to what is occurring at certain areas of the gene, and the ability to plug all of this stuff into computers and crunch numbers and find out where everybody's at, that might help to identify a lot of things. Then, the question is can you intervene with vectors, that sort of stuff. I don't know, but I've got a feeling that if cancer really is a genetic disease, and we know so much about the genome that eventually we're going to be able to intervene. But for right now, how long it will take, I don't know. But I can tell you this much, you've got to pour the money into these things. There are a lot of smart scientists out there, there are a lot of Gary Davids walking around, you

know, guys who have got a billion of ideas. The majority of them won't work. In science, if one out of ten of your ideas is correct, you're golden. One out of ten. Ninety percent of all the experiments I ever used were abject failures.

JONES: There's no way beforehand, though, to...

HALPERN: That's right. You can't predict these things. If you can't live with failure, don't do science. Mother Nature treats us all the same. Like dogs.

JONES: Well, in terms of detecting cancer, though, in terms of getting down to those levels...

HALPERN: OK, where we're going to go down to, of course, is first going to be in vitro. What does it mean to be able to pick up the genetic material from BRCA 1 or BRCA 2 in serum? If you pick it up in a woman who has no known breast tumor, do you remove both breasts before the fact? Do you do this?

JONES: I read an article in the New York Times where someone had it done.

HALPERN: Well, there are times. I mean, if you have this gene and all the women in your family by the time they were forty years old, had breast cancer, then you better start thinking very seriously about having a bi-lateral mastectomy. If you don't, it might cost you your life. We don't know where that stuff is going to go yet, but, there are a lot of things that we can do before that. I mean, do you realize that in the United States, right now, if you look at the deaths, if you take the forty-eight nations, industrialized, for lack of a better word, nations, we rank, I believe among deaths from cancer, twenty-seventh out of forty-eight among men, and eighth out of forty-eight among women. The reason that women are dying from cancer at this enormous rate is not the breast CA, which is a plague, no question, but from lung. The reason they're dying from lung is Virginia Slims, you know, the damned cigarettes, not just Virginia Slims, of course, but cigarettes in general.

JONES: Well, men smoke, too.

HALPERN: I know that. That's true, but in the incidence of cancer in women used to be about what it is in the men, and the women started smoking like mad. It used to be that carcinoma of the lung in women was way, way down. Now, it's way, way up and tobacco is the thing that's wasting them, along with God knows what else. It could be a lot of other things.

JONES: Well, what's your overall assessment of the legacy of Hybritech and the research that was done there?

HALPERN: Well, PSA has done a great deal of good. The in vitro kits have done a lot of good. In the '8os, it was an absolutely wonderful company. In my opinion, Eli Lilly destroyed it. I will believe that till the day I die, and I don't care what they think about it, you can write that if you want to. Because, in my opinion, they did not know what they were doing, they had preconceived opinions of what antibodies were all about, what you could do with them, what you couldn't do with them.

JONES: Did you hear any talk about them perhaps using these as delivery systems for their own cancer cocktails?

HALPERN: No, I don't know. I have no idea. But what they did was stop the intellectual ferment, the way that it was going, and everything became the Lilly way. I used to hear those guys comment about it, they would say, 'Why don't we do things like Hybritech used to do things? Let's do it the old Hybritech way.' And of course, they could only do that so much before they got in trouble.

JONES: Well, there are a lot of these small biotech companies around. Do you think these are places where, in a lot of cases, really good science gets done, perhaps with better resources than in universities?

HALPERN: Well, let's talk first about biomedical. Looking for product, OK? Not just a diagnostic product that's a kit, or something like that, that's going to be in vitro. Let's talk about in vivo things. I think the vast majority of them are going to fail.

JONES: And why?

HALPERN: To begin with, the work's just damned hard. Science is hard. The science is just very hard, it's very hard. So, you're going to have some hits in this thing, but the vast majority, nine out of ten, are going to fail, and I think the thing that's done, I think in order to…I'm not saying that they go out and give bad information in order to get funded, but I think they tell…they accentuate the positive, let me put it that way.

JONES: Well, it could hardly be otherwise, if they're going to have these companies and try these things.

HALPERN: Right, I think it's a high risk business, very high risk. But I think, yes, you can do good science in them, you can. I think they probably work best when they're allied with university.

JONES: When there's close interactions, for instance the kind of association you had with Hybritech?

HALPERN: Very close interaction, yeah. I think that it's best for the university to limit the amount of money that's coming to an individual for doing the work, not research money, but the private money. And I sit on committees, oversight committees, what we call conflict of interest committees, and I always give a good hard look because, by definition, there is a conflict of interest, if a scientist is working with a corporation and they're a university employee. There's conflict unless you have certain criteria, you know. The university has a mission, education, obviously, public welfare, and that sort of stuff, and I support looking at that, committees such as the ones I sit on.

JONES: But there's no inherent conflict. There may be cases where there are real conflicts of interests between associations with industry and the mission of the university, but not necessarily.

HALPERN: Not necessarily, no. But anytime somebody is allied with the corporation, doing research for the corporation, you have to say, OK, we're going to have an oversight committee, and OK, we're going to call this a conflict of interest with oversight. And if there's oversight, intellectually honest oversight, and you see that this supports the university's mission, I have no problem with it. I do this myself, you know. I worked for Hybritech for many years. I had tremendous sums of money coming in. One year, between public and private money, I must have had half a million dollars coming in that year. I was grinding out research like mad. But, it has to be watched, and you have to remember, and this is important, you have to remember that what you're doing is applied research. This is all applied research. It's not really basic research. Basic research is where somebody gets an idea that has virtually no economic value and pursues it.

JONES: No obvious economic value?

HALPERN: No obvious economic value, and pursues it as an area of interest, and then publishes the research. I mean, my hero up there [Albert Einstein], he sat there

in the patent office bored silly and came up with the theory of special relativity, right? If they had found out what he was doing, they would have probably fired his ass. But, I can imagine that Albert must have been spending most of his time on the theory of relativity and very little on those damned patents. But, the sensitive area of industry and the universities, we must never ever stop publicly funding research. We must always have basic university research funded through the NIH, NSF, whatever. Public money.

JONES: Now, would your argument for that be sort of the knowledge for its own sake argument, or the argument science produces things spontaneously?

HALPERN: You're working there without the constraints of what a corporation might want. A corporation must be sensitive to its stockholders and sensitive to the bottom line. And so, what you're going to do is goal-directed research. The vast majority of research is goal- directed research. That doesn't make it bad, not by any stretch of the imagination, some of the best research that has been done is goal-directed research. On the other hand, you need somebody out there doing blue skies, like Gary David. And you'll spend half of your life failing, ninety percent of your life failing. But every now and then, you'll come up with a concept. If you come up with something, the spin off on that can be enormous. I mean, let me see if I can give you an example. Fleming, Alexander Fleming, screwing around with mold, you know, and the world of antibiotics was born from these molds. And even today, I guess, the vast majority of antibiotics probably come from molds. You know, he came up with this, and through history, you see the same kinds of things. You have this one little breakthrough, and from it will bloom everything else. Monoclonal antibodies, you know, you've got these guys slogging away over in England, and they immortalize the cell, and from that has come a hug spin off of all sorts of things. Magnetic recording research, all of your computers and everything, come from initial work in magnetic recording research. So, you have to have somebody getting that basic data, and one of the problems in the United States, see, the public, unfortunately, doesn't truly understand, and most of this is the fault of the scientists, I really believe that, that we don't explain to the public what the real virtue, what the real usefulness of pure, unapplied basic research is, so let us fail and fail and fail, throw money into it and let us fail and fail and fail. Because sooner or later, something is going to trigger. When that thing triggers, most of those experiments are not going to fail, and it's going to bring the public back a huge amount. The war on cancer, in 1965, Lyndon Johnson launches the war on cancer. By 1975 and 1980, you're reading that the war on cancer

has failed, miserably. By the 1980s, they're cursing Lyndon Johnson. In the 1990s, for the first time this year, is falling rapidly.

JONES: Is it?

HALPERN: Yes. Better treatments is one thing. Better knowledge, some of the clinical studies coming out of the war on cancer showing that the direct correlation of smoking and cancer, the chemotherapeutic agents that we've come up with, the understanding of the cell that we've come up, it goes all the way back to the time Lyndon Johnson, in 1965, found some loose money laying around, loose change, and pumped it in and said we're going to have a war on cancer. That war is bearing fruit now. We're beginning to win that war. But that's 1965, that's thirty-two years. Lyndon's finally beginning to win his war.

JONES: Well, there are probably a lot of people who are still not convinced, when you think of all the money....

HALPERN: But we haven't really communicated enough to the American public about what really happens with this, about how hard this really is, and how important it is to run some of these studies that people have said are idiotic. It may seem idiotic, but there's a lot of gold, sometimes, at the end of the rainbow, but the end of the rainbow is way the hell out there, you know. So, we must never stop the public funding of research. We need the non-goal directed research funded heavily by our nation, and when you look at the money that we throw at different things, the NIH budget, and the NSF budget, it's just, the percentage of the tax money that comes in is so small it's absurd, you know. But I fault the scientific community. Too many of us walk around with our holier than thou attitude and don't explain to people what's going on, and the American people, you know, there are a lot of smart people out there who aren't scientists, you know, and just because somebody has got just a high school education doesn't mean they're stupid, it just means they didn't go on to college. They might be smart as hell. And if you tell these people what the facts really are, really level with them, I think we can go a long way. We've done a few things, programs like NOVA, kids watch NOVA, and the kids are going to become adults, you know, and the old folks are going to go the way of all flesh. So, I have an abiding faith in the American people, I really do. A lot more faith in them than I do in Eli Lilly.

JONES: And in science, too?

HALPERN: Yeah, anyway, I don't know how much more I can tell you. You know all of the names that I've ticked off.

JONES: Well, let me ask you one question. What was Richard Bartholomew's particular contribution to the research that you were doing?

HALPERN: He was an immunochemist. Richard Bartholomew is absolutely brilliant. He learns at an incredible rate. The only problem that Richard has is that his mind works so fast that the rest of us can't keep up with, and he takes on too much. That's always Richard's problem. He gets overloaded. Always he's overloaded. But he's a wonderful guy. I love little Richard. And Lollo's an excellent scientist.

JONES: Also an immunochemist?

HALPERN: Yeah. Fagnani's a pharmacologist. I don't what happened to Martinis, I don't know where she's at.

JONES: She's up in Seattle, teaching school. She lives on one of the San Juan Islands, and she has a primary school science education program, teaching science.

HALPERN: Really? I'll be damned. She was a really hard-working woman, and Dennis, I don't know if Dennis will talk to you or not, he may not. Like I say, I exchange Christmas cards with him, but I haven't seen Dennis in years.

END INTERVIEW

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The San Diego Technology Archive (SDTA), UC San Diego Library, La Jolla, CA.

The San Diego Technology Archive (SDTA), an initiative of the UC San Diego Library**,** documents the history, formation, and evolution of the companies that formed the San Diego region's high-tech cluster, beginning in 1965. The SDTA captures the vision, strategic thinking, and recollections of key technology and business founders, entrepreneurs, academics, venture capitalists, early employees, and service providers, many of whom figured prominently in the development of San Diego's dynamic technology cluster. As these individuals articulate and comment on their contributions, innovations, and entrepreneurial trajectories, a rich living history emerges about the extraordinarily synergistic academic and commercial collaborations that distinguish the San Diego technology community.