Phil Felgner

Interview conducted by

Mark Jones, PhD

July 22, 1997

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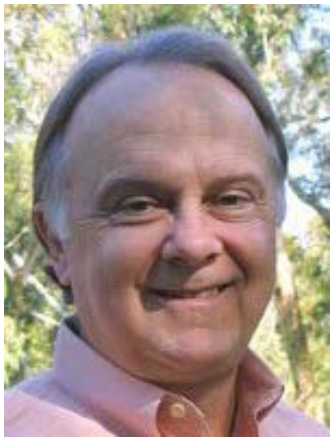

Dr. Felgner received his Ph.D. in Biochemistry/Neuroscience from Michigan State University in 1978 and also completed Postdoctoral training in Biophysics at University of Virginia. He has over 25 years of experience in the biotechnology industry, including senior research positions at Syntex Research where he developed the first cationic lipid reagent for gene transfer. In 1988, Dr. Felgner became Director of Product Development, Chief Scientific Officer and founder of a start-up company, Vical, Inc. With colleagues at Vical and at the University of Wisconsin, Dr. Felgner made a landmark discovery regarding functional reporter gene sequences and demonstrated that potent antiviral immune responses could be generated following intramuscular injection of plasmids encoding viral antigens. These findings have led to development of a new class of infectious disease vaccines referred to as "DNA vaccines". Dr. Felgner has been issued more than 35 patents and published over 100 scientific papers, and for his numerous biotechnology innovations, he received the Southern California 1996 “Inventor of the Year” award. He went on to found Antigen Discovery, Inc. and served as a Professor at the University of California Irvine.

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FELGNER: One of the stories that Ted Greene tells is how he tried to take, basically, the Hybritech story to Syntex for funding, and he likes to yuck it up about how they turned down this multi-million dollar opportunity.

JONES: That was so obvious at the time.

FELGNER: Yeah, so you have that story.

JONES: Yeah, he was calling that Cytex at the time.

FELGNER: Well, when I came over from Syntex, you know, these were the two guys that I met [Ted Greene and Tim Wollaeger], and so they filled me in on all that important history, too. And I think Syntex was considered to be kind of an ideal example of, you know, an idealized example of a successful pharmaceutical business, and guys like Ted Greene, when they were trying to build their models, were modeling them after something like Syntex.

JONES: Because Syntex had been the only new success story in the industry in quite some time?

FELGNER: Right. And at that time, Genentech wasn't mature enough to be considered an example, so they would use Syntex. And he really felt snubbed when he went back there, because, you know, he was sort of idealizing them, and he thought that they would right away embrace what he had, the new things that he had going at Hybritech, and that never came about. So, how would you like to start this?

JONES: Well, I'd like to start by asking you about the very early stages of your career. For instance, how did you originally become interested in science?

FELGNER: Well, personally, I was in college during the late '60s when there was a lot of unrest on campuses and stuff, and I wasn't sure what I wanted to do. I thought I might play guitar, and I went over for a summer to Europe to get guitar instruction from various classical guitarists over there.

JONES: Who did you study with?

FELGNER: Well, actually, most of my study was with a guy in San Francisco named Michael Lorimer. Do you know of him?

JONES: Well, yeah, I mean, he's a famous guy.

FELGNER: Yeah, I have a guitar from him. I bought a guitar from him. I hired a guy here recently who is more gung-ho on guitar even than I was. He's got five guitars and there's a little bit of a classical guitar sort of group here. There's a good guitar builder downtown here.

JONES: Taylor, or a classical guitar builder?

FELGNER: Classical guitar. Anyway, what I decided to do was to go and actually work in a lab as an undergraduate and then see what it was like. I wasn't really that keen on studying in college, but I thought that I'd just go in there and try to work on it. I was always interested in science when I was growing up. The Disney Channel, or...it wasn't the Disney Channel, but Walt Disney was on television every week, and one of the things that he always did was to bring in these scientists, you know, and show all the latest science stuff. And Mr. Wizard was on, and that had a lot of appeal for me, so I was keen on science at that time. But it didn't really connect from studies, that it was that cool, so I just started working in the lab, and went into a guy's lab. His name was John Wilson, and I told him essentially that. You know, I said, 'I'd like to see to what it's like to actually work in a lab,' so I did that.

JONES: Where was this at?

FELGNER: Michigan State. And so, I found that I really liked to do that. I spent all my time doing that, and then just kept on working to get my advanced degrees there, at Michigan State.

JONES: And why did you choose biochemistry in particular? Is that the lab you had happened to wander into?

FELGNER: Yeah, pretty much, that was it. You know, biological sciences were, you know, popular, and that was where people were working, and so I went into a biochemistry lab. I did pretty well in chemistry, so I went into biochemistry, and the biochemistry lab. And then, basically, it just became an apprenticeship as far as I'm concerned. You know, I wasn't really going to school anymore, I was just working from then on. It was all just that.

JONES: You were working with Wolff at the time?

FELGNER: Wilson, John Wilson. OK, so then I went through school, I had some nice papers and things, and I went into a biophysics lab in Charlottesville, Virginia.

JONES: At the university? This was a postdoc position?

FELGNER: The University of Virginia at Charlottesville, a postdoc, right. Well, I guess the graduate student experience is of some note because there was a conflict at that time going on that was unclear to me as I was going through, but there was sort of a conflict between faculty who felt that advanced education should be more an extension of undergraduate school, where you did a lot of coursework, versus sort of a sink or swim mentality, where you would throw people into the real world and have them do original research. So, I was in that side of the thing, and so was my professor. There was a big battle that went on, and I was in the crossfire all the time when I was over there, so it was quite a time. I got kicked out of the program twice, but I got back in and everything, and it all worked out fine, afterwards.

JONES: What were you working on there?

FELGNER: It was on a brain enzyme. An enzyme in the brain. It was a neurochemistry project, and I learned a lot about membranes at the time, or was getting familiar with the problems in understanding the functions of membranes. Membranes are important in the brain, especially because of the kind of nervous conduction that's going on the surface of nerve cells. So, I decided to join Tom Thompson, who was a biophysicist studying the details of membrane structure at a very detailed level, with pure systems, not with complex biological systems. And there, we started working on liposomes. And it became very clear that cells had a charge, a net charge. All cells have a net negative charge, and people began to understand that, and we learned how cell membranes were comprised of these lipid molecules and how they were organized, in their details, you know, what their

properties were. The membranes were real stable structures. It just became more and more clear to me that cells were negatively charged, cells had a net negative charge, and that all the lipid molecules that you have available are either neutral or negatively charged, so there were no positively charged lipids available in nature. And there were actually very few positively charged surfaces in nature at all. One of the few places that you find a positively charged surface is on the surface of a crab cell, and there's something called chitosan that's actually interesting now because they're using it as a transfection reagent. But anyway, everything seems to be negatively charged, and if you're making a liposome, you had all the available components for making liposomes, and all you could make is a negatively charged liposome or a neutral one. So, if trying to use a liposome….have you learned about liposomes at all?

JONES: I know just the basics.

FELGNER: They're little vesicles, and they're made of a very thin bi-layer membrane that's only, you know, five nanometers thick, which is a thousandth of a millimeter and then a thousandth of that yet. It's very, very thin, and you can put things in there, and we did some of these things at Vical. You can put substances inside those vesicles, and they'll stay in there for years on end. They won't leak out, even though that little membrane is so thin. And that's what our cells are made of, these thin membranes. Anyway, you can make these little vesicles, and that's what we were studying in this biophysics lab, how to make them purer and homogeneous in a way that you could understand them better. And then, around 1980, people started getting interested in these things as drug delivery systems.

JONES: Who was doing that?

FELGNER: Well, it started with a guy named Alex Bangham, in 1965, and then there were people like Dmitri Papahadjopoulos, who further developed the practical applications of those things as drug delivery systems. And then, about that time, the venture capital investment climate was very good. Let's see, Hybritech would have come a little bit later, but Genentech would have been about 1976, and they were getting pretty happy with that, so they were looking around for other investments, and liposomes was one of the things that investors were interested in. Three liposome companies, at least, got started. Liposome Company, and then Liposome Technology Incorporated, which changed its name to Sequus recently, and Vestar, which recently merged with another company, and they're now called Nexstar. Those companies

started right around 1980-81, and I was getting interviewed for working at those places.

JONES: Let me ask you, while you were going through, doing the PhD and the postdoc, were you thinking about a traditional academic career path?

FELGNER: Yeah, I think so. I think I was, but I got called from these liposome companies with this biotech opportunity coming up, and then I got a call from Syntex.

JONES: Did these calls come through Thompson?

FELGNER: Yeah, they were looking to take advantage of this potential drug delivery opportunity, and Syntex was interested in having a group work on that. So, I was getting interviewed from those companies. I had an orientation towards patenting things. Thompson was always kind of amused by that. It never crossed his mind to patent anything, to take some discovery and then think about what the potential opportunities would be, and then put that together into a patent. So, I was doing that. It seemed natural to me to do that there.

JONES: You filed some patents at that time? On work you were doing…

FELGNER: In Thompson's lab. And then, the liposome companies. I remember being really amazed because there was this one, this one place I got interviewed, the Liposome Company, by Mark Ostrow. I know Mark, and you may run across Mark Ostrow sometime. I think I've told him this little story, too. I remember feeling like I was naive. I was naive of the pharmaceutical business, and I was naive of this biotech environment. So, I went over to New Jersey and he picked me up at the airport, and started telling me about all these wonderful things they were going to do with liposomes. They were even going to put interferon in a liposome, blow it up a person's nose, and they were going to cure the common cold. And I was so amazed. I thought, 'Boy, I must be stupid. I could never do this.' So, I really felt like I needed to go to a professional pharmaceutical company and learn about how, you know, one goes about this pharmaceutical business. It happened later that I realized that Mark needed that, too. And in fact, the Liposome Company developments were real slow, among the liposome companies, and it got the investors very perturbed because they had to keep making these investments year after year. And what was clear was…well, it seems like what you usually see is these dichotomies played out all the time, you

know, two different groups with different points of view always fighting against each other. So in graduate school, it was the sink or swim pragmatists versus the academics. In this liposome company thing, it was the biophysicists who thought that these pharmaceutical development people were ignorant, and just weren't intelligent enough, and that they were going to be able to develop these things just easily, because of all of the stuff that they knew, and then the pharmaceutical development people probably just thought these other guys were crazy, you know, they didn't know anything about the real practical issues of developing drugs. So, what happened was, when the Liposome Company people, when they would go to meetings, over a period of years, what would be revealed to them were all of these pragmatic drug development issues. And then at the meetings, they would be shown this. You know, they would show like a flow chart of how you should go about developing a drug, which, you know, is Pharmaceutical Sciences 101 for the people who actually get trained in that area. And so, the investors were investing in years and years' worth of training that these people were going through, to just learn these things. But then, you know, on the other hand, what was so hard is that you couldn't take that other technology and put it in the hands of the conventional pharmaceutical development people. They wouldn't do it, either. Well, I was at Syntex, and basically Syntex was an advanced postdoc as far as I was concerned. I was there for six years. I wasn't a postdoc, but that's what it was. It was a beautiful place.

JONES: You had a number of opportunities at the time. Why did you choose Syntex? Was it because this would be like a postdoc and you would have a lot of freedom?

FELGNER: Yeah, I just went there and it's a beautiful campus, and all the people were just like academic people who didn't have to worry about giving lectures, you know. They had weekly seminars, all kinds of people coming through all the time, and they had a beautiful library. And when I went there, I was constantly studying because there would be seminars from people in different disciplines that I didn't know, who I was just listening to, so I'd get this next new one, and I'd be in the library trying to figure out what I had just heard, you know. So, in a very short period of time, what you can do in a company like that, because there are so many disciplines, there are all of your different sort of scientific categories, there's chemistry and pharmacology and physiology and cell biology, and whatever else there is, so those are almost like academic activities going on there, but then there is the pragmatically oriented segment of the company involved in actually characterizing drug candidates, metabolism and toxicology labs, and then all the people who are actually trying to,

once they've identified a drug candidate, they're trying to make sure that that can be put into a vial and then offered as a stable product, you know. So, you have a lot of physical chemists who are making sure that those things are stable. So, it was basically a six year education as far as I was concerned.

JONES: But the work was somewhat more focused than it would be in an academic setting, certainly?

FELGNER: Well, obviously, everything was focused towards drug development, yeah.

JONES: And this was 1982?

FELGNER: Six years I was there, until '88.

JONES: Can you recall your thought processes, did you perceive any kind of risk in doing this as opposed to following the academic track? Did you think, for instance, that if you got into this and found that you didn't like it, you know it's not for me, that you could go back?

FELGNER: No, actually, at that time, what I was thinking…it didn't take long before I was thinking that I was going to be a lifer, that I was going to be a Syntex employee and that was going to be it. I got married and had kids and then I thought, that's probably going to be it, and it was fine. I thought that everything is going to be just fine, there's no problem here. Then my wife, who was working at Syntex, went to Genentech, and then we got exposed to the biotech atmosphere, which was really cool. So that was one thing that was going on. The other thing that was going on was the science at Syntex, which was related to this issue that I mentioned earlier about positively charged liposomes not being available, and all cell surfaces having a negative charge. I felt that there would be a good opportunity, they had a lot of good chemists there, and I thought that maybe they could make a positively charged lipid.

JONES: So you could send it to…

FELGNER: Send it to cells, and they would just merge with cells right away. It would be a real good delivery system. So the chemists made those compounds and we patented those, a whole series of compounds. Then I set out to test their utility in a whole bunch of different applications, and one was to see whether or not we could deliver DNA into cells with these things. And there, the first thing was, we had good molecular biology there, so we could get good plasmids. And I had Hardy Chan make

up some plasmid for me, and then mixed up these liposomes with the DNA. The first thing that was really unusual about that was that when I combined them, what I thought was going to happen was that everything would aggregate and agglutinate, like sometimes you see with antibodies and antigens, when you mix them up, you just get a an aggregation in there. And what was surprising, and it probably doesn't seem that earthshaking today, but it didn't aggregate. You know, it formed a nice suspension. It maybe made a little side event, something going on, and then it just sort of cleared up. And I thought, 'My God! Are they not interacting? How could this be? They must be interacting,' because the DNA is so highly negatively charged and these things are so much positively charged, they must be interacting, and so, we ran a little experiment and showed, 'Yeah, OK, they're interacting.' But what happened was, they got together in a very organized way, not just a disorganized gammish in there. They formed new entities, so now the DNA was wrapped up in this lipid and it had a nice little…maybe something like a virus-like structure. So, that was real exciting, but that was before we found out anything about there being any kind of gene delivery activity, and I brought in an intern, a summer intern, an undergraduate intern, and she knew how to run some of the enzymatic assays that we needed to use to look for gene delivery activity, and she did the first experiment, and right away it worked, so we could deliver genes into cells.

JONES: What year was this?

FELGNER: That was around 1984. So we patented all this at Syntex, and then published on it. And these guys got wind of that result, Karl Hostetler, and Dennis Carson, and Doug Richman, and they had their own ideas about what they wanted to do for Vical, to do this nucleotide anti-viral project with liposomes.

JONES: Did you get in contact with them early on?

FELGNER: Well, I went to a meeting, I went to one of these Gordon conferences, and it was on something like, I don't know, smectic mesophases and crystalline structures, or something, and I go to the meeting and here is this MD, Karl Hostetler, over there, and what's he doing at a bizarre conference like this? I sat next to him and he said, 'Why don't we go out and play golf,' so I went out to play golf with him, and he tells me that he's interested in setting up a company down here in San Diego, and that they had these ideas to do. And I told him he's crazy, you know, to set up a company, he doesn't know what he's getting into, that this deal sounds just like Mark

Ostrow all over again. You know, drug development you should leave to the big pharmaceutical companies. I don't know, we kept on talking, I guess, that week, and got together a couple of other times, and I think that the people that founded it figured that I could do this drug development project, and they also thought on the backburner, this gene delivery stuff might be able to come along. Well, at the same time at Syntex, I felt that Syntex, that it would be well for Syntex to invest in the gene delivery opportunity, and they felt that they wanted to show that they were glad about what I was doing at Syntex, and they were working on trying to figure out how to come up with some kind of promotion, and the promotion they wound up doing was offering me was to, basically, I was going to stop doing everything that I did before and I was going to now become really valuable to the company…

JONES: As an administrator?

FELGNER: Yeah, I was going to go into the pharmaceutical development area. And the people that were working with me were going to have to change what they were doing, and they weren't really keen on that either, and so they offered me the job, and then they said, 'We're going to find you a new home,' and here's what it is. The next day I went home and talked to my wife about this job down here, and we agreed to come down and take the job here, and so the next day, I went up to the, actually, I guess it was the President of the company, John Freed, and I said, 'Well, I found that new home, and it's in San Diego,' and so, I just came down and we started to set up the labs down here.

JONES: Had Syntex devoted resources to developing the gene delivery, or were they just basically looking at the liposome technology for drugs?

FELGNER: They felt that the gene delivery technology, a number of people expressed the opinion, who had some authority, that gene therapy was for the year 2050, and it wasn't something that Syntex was going to be developing.

JONES: And that was a big part of your decision, that you wanted to pursue that and they weren't going to?

FELGNER: Yeah, and I felt that the gene delivery was something that needed time to develop, and I thought that 1995 was probably the right time. And I thought that Vical could be a good incubator for that technology, so I went to the Board and asked them for, Tim Wollaeger, for money and support for that thing to go on as a

backburner project. They agreed, and we funded the Jon Wolff lab to do studies in animals. We didn't have an animal colony at that time, and we didn't have staff with molecular biology experience and stuff like that, so, Jon was interested in carrying on with that. I ran into Jon because I went over to Ted Friedman's lab, and I had spoken with Ted on the phone, because these cationic liposomes that were able to deliver DNA into cells became a real popular transfection reagent, which I arranged while still at Syntex to get BRL, to get GIBCO BRL [Life Technologies] to sell those as reagents for molecular biologists, because I started sending them around gratis to people all over the world, and pretty soon, I was sending out hundreds of shipments a year, you know, and so I inquired and BRL picked up on the reagents, and they did an agreement with Syntex. Now, in remembering that agreement, there was this, they got a percentage of the gross sales, and as their sales increased, Syntex got a higher percentage all the time. So, for like a hundred thousand dollars in sales, they only got 10%, but when it was five hundred thousand, it went up to 15%, and when it was over like three million dollars, it topped out at like 30%. So, 30% of their sales were…because nobody ever figured, at that time, they probably figured, well, it's probably pretty safe, it's not going to go up that high. But it didn't take long, and they were sending, every year, a million dollars over to Syntex, or more, on the sales of those products. So, they were real popular products. And so, I found out about the gene therapy business just by talking to these people who wanted to use these reagents, and had different interests, and Ted Friedman was one of those people, and I spoke with him. So, when I came down here, knowing that he was in the gene therapy area, I thought I'd go over and visit and see what he had going on, and Jon Wolff happened to be in the lab, and Ted was not. So, I talked with Jon about…

JONES: He was at UCSD?

FELGNER: Yeah, in Ted Friedman's lab, working as a postdoc there. And we talked about this project and it was to see whether these same reagents that worked in cultured cells, whether they would work also in animals. And then he said, 'OK, I'm moving to another lab. I got a job as a faculty member at Wisconsin and I'll be able to do this project beginning January 1st, 1989.' So, he got everything worked up and we made up formulations and sent them over there, and he tested them in animals, and right away, we got gene expression. The expression that we got, most of it was in the muscle. When we injected muscle it was the best, and then we did experiments leaving out these liposomes, just using the naked DNA. And that worked as well as anything else we had.

JONES: Do you remember how you came up with the idea of doing that? Because nobody had done it before, and nobody thought it would work.

FELGNER: Yeah, well, the idea of doing gene therapy without viruses came from our experience in working with this lipid reagent which was able to deliver genes very effectively in cultured cells, and where this work was being done in a pharmaceutical company, we were thinking, 'Well, we've got this in a vial.' I mean, here is our lipid and our DNA and they're all in a vial. It looks just like a drug, you know? And what people do, still, today, at a pharmaceutical company, is they have things that they test in cultured cells. And they say, 'Well, OK, it's doing what its supposed to do in the cultured cells, now I'll take that thing into an animal, and see if it works in an animal.' So, we used that same kind of thinking with these reagents. I mean, other people were concentrating on the cells and not the product. Because we were in a pharmaceutical thing, we were concentrating on the product. We said, 'Oh, it looks like we have a product here that might be able to deliver genes, that does deliver genes into cells,' and this is how people do things in a pharmaceutical company, you do things on cells, and if it works on the cells, you go to the animals. So, our next step, when I was just coming to Vical, was to get those things into the animal. So, we went ahead and put those in the animal and right away, we got as much as expression as we were used to seeing in these cultured cell systems, so we were very excited and started drafting the patent. The thing was, it was exciting to be able to see the expression, but it wasn't a home run at that point because we thought that it was something that required cationic lipids, and Syntex owned the first cationic lipid patent. However, I was aware that that patent would allow other groups to come in and develop other cationic lipids that were not claimed in that one, because the Syntex was not claimed broadly to exclude any and all cationic lipids, and that is kind of an interesting twist. In the biotech environment, if you would have made a discovery like was made at Syntex, if that was done at a biotech company, you would patent absolutely as broadly as you possibly could in order to exclude all competitors. In the pharmaceutical business, though, it was a collegial environment where all of the people in the different pharmaceutical companies sort of worked together to keep a good pharmaceutical, and not a combative pharmaceutical environment. So, in patenting, they would patent compounds that the chemistry department at Company A felt that they could do a good job on, and they'd patent, you know, those compounds, and then they accepted the risk that another company would come along and patent their series of compounds. So, these cationic compounds that were

made at Syntex, that were so good at transfecting cells, that patent was a compound patent on a restricted set of compounds and not meant to exclude all competitors coming in. So, this is where we were. When we set up the initial experiment, we said, 'OK, if we're going to make a business out of this at Vical, it's not really going to interest the investors that much because, yeah, we've got our compounds,' I mean, we made some of our own compounds that weren't in the Syntex patent, 'but there's going to be Syntex out there, big old Syntex, and they could just jump all over us.' But then, very quickly we found that we didn't need the lipids in there. So then this patent all of a sudden had much greater significance. We knew that we could make a naked DNA patent, and that was completely as broad as could be, excluding anybody else, and now we had a basis for a new biotech business.

JONES: So, initially, the work that you were doing was sort of a secondary project. Was the main project at the time Doug Richman's stuff with AZT?

FELGNER: Yeah, AZT and liposomes, that was the main thing.

JONES: Did those guys recruit you to Vical because of your expertise in liposomes?

FELGNER: Yeah, they felt that I could do that project, to encapsulate the AZT in liposomes and develop a product, so there was a technical challenge, to develop a pretty complicated delivery system, and a pretty complicated formulation. They felt that I had the know- how to carry that out. And I did. We did exactly what we were intending to do for Burroughs-Wellcome, under contract, that whole thing proceeded for three or four years.

JONES: You were doing the naked DNA experiments and then Burroughs-Wellcome sort of killed the AZT project, right?

FELGNER: We got all the way through, we did our job, the product went into production at Burroughs, so that they knew that they could make the product according to specifications. We tested it in animals and tox studies and everything, so all that was done. Then they had to make a decision whether or not they were going to develop this product. So it was a product, but they decided that it was not a market that they wanted to go into at that time. It was going to be, it was always going to be, an IV, an intravenous product. It was probably going to be a drip, you know, and it became clear that, you know, a lot of their patients were living under bridges and stuff like that, and they didn't see, you know, that they were going to be really able to

offer that type of a product. Plus, there were other things coming along. After three years, four years, went by, other things started falling into place.

JONES: Was it the case that after that, you know, if that wasn't going to be developed, if Vical was essentially done, was it the case that the company was looking around for what to do next and the naked DNA project was ready to go?

FELGNER: I think that at the time it was more difficult than that because they were crashing head on into each other, and it was, 'Are we going to do this, or are we going to do that?' And the original founders certainly didn't want to give up, it was very difficult to give up the original basis for founding the company. And it was an excruciatingly difficult time for everyone on the Board. You know, the Board members understood that they were funding Vical to do this nucleotide anti-viral project, and that's what they had assimilated. And they didn't have, in their minds, they were not prepared for the possibility of a gene therapy business. I think the original founders and I thought that it would come along, but I wasn't thinking until 1995, so I didn't think that we really would have to bring it up yet. So, it was a backburner kind of thing. The Board members then were always asking, well, 'How was this nucleotide anti-viral project going to make money for Vical?'

JONES: Who were the Board members involved?

FELGNER: Oh boy, well, Ted Greene and Tim were both on the Board at that time, and oh geez, I don't know. We had twelve Board members. That was another amusing thing. How can twelve guys, all with egos as big as a house, ever come to any kind of agreement? Anyway, what happened was, eventually Sequoia was one of the key groups there, and they couldn't go back to their partners and keep asking for more money, finally. Meanwhile, though, there were these other venture capital groups like Venrock and Kleiner-Perkins that hadn't invested in Vical, but were extremely interested in the gene therapy opportunity.

JONES: Do you have any knowledge of how they got interested? Who sold the idea to them? Was it Tim and Ted?

FELGNER: Well, actually, do you know Alex Barkus?

JONES: No.

FELGNER: You should probably call Alex Barkus. Alex, I don't know how much he will tell you about it, but, you know, I had many late night phone conversations with Alex who was working with Kleiner-Perkins at the time. Maybe he's still with Kleiner-Perkins, but he really understood everything that was going on at Vical at the time. He understood the nucleotide anti-viral business and he understood the gene therapy business that was coming along, and the opportunity there. So, while there was all this turmoil around trying to figure out how to restructure Vical, one thing that came out was that we were going to have two divisions. So, we had a gene therapy division and we had a nucleotide anti-virals division. But then you had to fund these businesses, so you had to get investors who understood it. So, it was an opportunity for Alex and Venrock to come in. And eventually, Alex, with all the negotiations and everything, Kleiner-Perkins got pushed aside. They decided not to invest and Venrock took the leading position and funded it. Then the terms of their funding were that the nucleotide anti-viral technology would be divested. It would be sold off. So, it was sold, and several million dollars came into the company.

JONES: Who bought it?

FELGNER: Most of that went over to Vestar, which then became Nexstar.

JONES: And Karl Hostetler then became involved with them?

FELGNER: Yes.

JONES: Now originally, the company got started with Karl's work on calcitonin. His idea was to put calcitonin in a lipid envelope, I guess, but that didn't go very far? By the time you came into the company, had that been completely abandoned?

FELGNER: We had work going on in the calcitonin area. Yeah, we identified a number of potential opportunities with calcitonin and liposomes. But where the funding came was from Burroughs-Wellcome. We got about four years' worth of quite a bit of funding.

JONES: So, there wasn't much money around to do that work?

FELGNER: No. It wasn't separately funded. We kept trying to look for partners. I mean, when we would go to potential partners, we would present the whole package, and calcitonin was in there and we kept accumulating data on it. But the nucleotide

anti-viral technology was bought. The calcitonin technology was never bought by anybody.

JONES: Well, let me just back up a little bit. When these guys were first recruiting you to come here, now, did that seem like a risk? I mean, by now, you had a family, right? And you were at Syntex, which was secure.

FELGNER: Well, you know, yeah. I mean, we dealt with that, my wife and I. But a couple of years earlier, my wife had made the jump to Genentech. And that was really fun, you know? We had a good experience there. So, yeah, sure we thought about this risk thing, but we came to grips with it. I don't know. We just felt really confident. When we came here, there was nothing but the lab space, and we built up the labs. I guess I was concerned about practical things, about whether or not the lab would have the resources that we needed, like 'What if we run out of pipette tips?' Things like that. 'What do I do if I need a glassblower,' or, 'What do I do if I need some lucite cut?' You know, things like that. But then, in coming down here, one of the surprises was that we were able to fill out the lab in a matter of a couple of weeks, and we were able to get all of the equipment in, and we were doing experiments. There's infrastructure here. This is such a center of research activity, that the vendors go out of their way to make it as easy as possible for all of our companies to work here. So, this is one of the things about the San Diego area, there's this infrastructure that's in place to allow companies like this to be able to work very smoothly. All of these logistical details, about getting animals, or building up your facility and getting the plumbing right, you know? The architects here know what the government regulations are for the kind of sewage system that you need to dump your washings from the animal cages down into the sewage system. All of these things, there's just this network, that you just sort of fall softly down into when you come into the Bay Area. That was what worried me. You know, I felt confident about the project. I really felt that the AZT project was going to work out, and I was right in the sense that we could do what we wanted to do, and, in fact, it worked in the animal models, but it didn't become a product that went into for other reasons that related to the market and the patient population and other drug entities that came along that meant that it wasn't going to hit, you know, it wasn't really going to be needed. So I was really confident about all of that, about that part.

JONES: And you had a good impression of the people who were involved?

FELGNER: Yeah, oh yeah. I felt really comfortable with Karl, and with Tim, and with Ted, you know. Yeah, I mean, they didn't project any sense of concern, you know, or anything like that, when we came down here. One of the things that they said was, 'It's just like Syntex here, you know, except that everything's spread out and you have different names on the different companies. But it's going to be like one big company.' That was one of the sort of funny things. They would send out this idea like, whenever there was an opportunity for some synergy between two companies like, say, Vical and Cytel, it would be really easy to, you know, get everybody together and work together, and, you know, create a new joint venture and then, things would just move much faster here, even than they would if you had two different departments at Syntex, you know, you wouldn't be able to get together in the same way. Now, I've never seen one of those happen yet since we've come here. But, I don't know, I guess that the other thing we thought about is, we thought about, 'Well, how many of these companies actually go under, and the people end up in the street?' And it doesn't happen that much, you know. It doesn't happen that often. Somehow people manage to do what they need to do in order to keep these companies going. Now, in retrospect, it looks like we were geniuses for coming out here, because Syntex is down the tubes now, and our friends that we have still over there, you know, they say it's miserable. There really wasn't any sign when we left that there was going to be that kind of turmoil over there, but it didn't take more than a year or two after we left, not because we left, but because of all of the other things that were impacting us in this business, you know, it just went down in the dumper. So, it was great that we left before all of that stuff started happening. That wouldn't have been fun at all.

JONES: What was Dennis Carson's role in this? I know that you collaborated with him later. Was he very involved in the early stages?

FELGNER: Well, Karl brought in Dennis and Doug. You know, when you're starting a company like this, you have to have some kind of critical of mass, and what is it going to be? Well, you know, bringing in some people that have reputations. Karl is really an entrepreneur. Doug and Dennis aren't entrepreneurs, but they had reputations, you know, they had strong scientific reputations, and he merged them together to make sense out of what the three of them were doing. And they were friends, they got along well. Dennis understood the potential for the gene therapy opportunity and one of the key things that he did was when we made the naked DNA discovery, he

drafted a letter to the Board to affirm the significance of that finding, so they were hearing it from a different source, a source that they respected.

JONES: Let me ask you about organizing research here. You've been in academic settings, you were at Syntex, which was a pretty big, you know, maybe not one of the biggest, but still a big pharmaceutical company, right, and this was a little rascal start-up where you have to put a research program together. Did you do that with any kind of plan? What was the idea of how you would do it?

FELGNER: Well, yeah, the plan and the staffing was very, very focused, and we brought in staff that were necessary to carry that out. As far as separating academic from industrial research, I don't separate it that well, which is a problem on both ends, whether you're talking to an academic or an industry person, because one guy's idea of what's focused may be different from somebody else's. What we had to do with that project, I knew that we would succeed, but I don't know exactly what was going to succeed. So we had to set up a huge matrix of different formulation variables to look at, and then set up a system for getting through and examining all of those different variables, so that we could get down to one. Now, somebody could have looked at that and said, 'Shit, this is much too broad,' you know, 'Why are you doing all of these zillions of different variables?' And, you know, to me, we were doing it to be sure that we would succeed. And to somebody else, they might figure, well, you should just pick one, something like that. It's easy to get, you know, from a certain perspective, it wouldn't be, somebody would have thought that it was not focused and there were unnecessary things done. But through this process, we covered all these areas, and we learned a lot. We learned a lot that is of academic interest. And sometimes, almost sometimes, it seems that sometimes pragmatic types will even downgrade something because you learn something academic out of it, something of academic interest. Because if you learned something of academic interest, then you must not have been focused. But I think that if you're too narrowly focused, you can sometimes end up in dead ends, and then you get to where you're trying to go as quickly.

JONES: Have you disseminate this stuff? Have you maintained ties with the academic community and published this stuff?

FELGNER: Well, we try. I think that one of my roles in the company is that I'm supposed to do that, I'm supposed to keep ties and connections with the academic community.

JONES: Well, you know what's going on in universities and elsewhere in industry, so you don't have any problems identifying people that you want to bring in?

FELGNER: No.

JONES: Do you have any problems convincing them to come?

FELGNER: No, you know, because this type of technology that we're in is of great interest to many, many people interested in the biological sciences from an academic perspective, and, yeah, I really have a hard time, as I was saying, I have a hard time separating what is of academic interest versus what is pragmatic.

JONES: Well, do you think that companies like this do a good job of integrating these two different approaches?

FELGNER: I don't think that, as a rule, as a general rule, seeing this all over, I think that it's very easy in a biotech company for people to lose sight of technology development, as opposed to product development. So, there's a sense that the technology or the inventions, if you want to call them inventions, are made at universities and then transferred over to the biotech companies, and then it becomes a product development exercise. It's as if you can't have a marriage between technology development and product development in the same environment, and I think that that is a real problem all over. It's because all of these things, when they get into a biotech company, are very virginal, they're very new technologies, and they may not have intrinsic in them everything that's needed. All of the nuances and all of the improvements that need to be developed in order for them to really succeed as, you know, successful products at some stage, and the development cycle is long, so by the time your product comes out, you're using eight year old technology. And again, there is a tendency in the company if you can't say that you're doing product development, then you're doing something academic, and that may be unnecessary. But people in technology development can do product enhancements that may actually turn out to be necessary for the survival of a certain type of product. And it's not that they're necessarily any less focused, you know. So, I think that there's a real tendency for the companies to say, 'We're in this for product development.' In every

company, there should be just as much understanding that there needs to be technology development and product development. Whatever their technology is, they need to develop that technology, you know, and they also need to deal with all the issues that are necessary in order to do product development. And then these things can be made to merge together. But again, if everybody starts thinking about it as a dichotomy, then they end up feeling like it's one or the other. "We can't do both,' you know, 'We have limited resources, we can't do both,' is usually what will be brought out.

JONES: So you consciously try to balance that.

FELGNER: Sure.

JONES: From the time that you really got involved in taking this seriously, getting a PhD, and moving on, how hard have you worked over the years? Harder at one place rather than another, perhaps?

FELGNER: No, for me it wasn't any different. What made the biggest difference for me is my kids, because I used to work at night, but now the kids take the priority. And the kids, as they grow older, they actually become more demanding. So, that has more of an impact than any of the other issues. And I didn't really end up working harder when I came here, I wasn't any more or less motivated. It wasn't that. But, for me, I have prioritized my kinds at a certain stage, because they're going to be, you know, five more years or so, and they're going to be out of the house, and then I can have my evenings free again. So, I'll probably up my amount of stuff I do.

END INTERVIEW

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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.