Gunars Valkirs

Interview conducted by

Mark Jones, PhD

June 4, 1997

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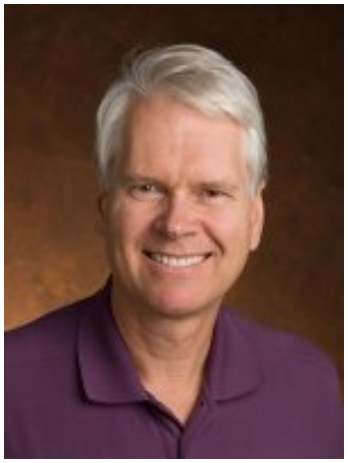
Gunars Valkirs



Dr. Gunars E. Valkirs, Ph.D. has been Senior Vice President of Biosite Discovery of Biosite Inc. since October 22, 2004. Dr. Valkirs served as Chief Technical Officer of Biosite Inc. since 1988 and also served as its Vice President of Biosite Discovery from April 2001 to October 22, 2004. Dr. Valkirs is a founder of Biosite and a Co-Inventor of certain of Biosite Diagnostics Inc.'s proprietary technology. He led the development of Biosite's unique antibody technology, which supports Biosite Inc.'s research of novel biomarkers for critical diseases. He also led the initiative to form Biosite Discovery, a collaborative research program intended to fuel Biosite Inc.'s research and development effort. He served as Vice President of Biosite Discovery from April 2001 to October 22, 2004 and Director, Vice President of Biosite Discovery since 1988. Prior to April 2001, he served as Biosite Diagnostics Inc.'s Vice President of Research and Development. Before forming Biosite, he was a Scientific Investigator with the Diagnostics Research & Development Group at Hybritech, where he was the primary inventor of Hybritech's patented ICON technology. Dr. Valkirs serves as a Director of Nautilus Biotech. He served as a Director of Biosite Incorporated from 1998 to April 2003. Dr. Valkirs holds a Ph.D. in Physics from the University of California at San Diego.

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INTERVIEWEE: **Gunars Valkirs**

INTERVIEWER: **Mark Jones, PhD**

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JONES: Let me ask you about the early stages of your career. I know you have a PhD in physic from UCSD. Did you specialize in biophysics from the beginning?

VALKIRS: Right, at UCSD, I was in a biophysics specialization program within the physics department, and as a result of my proximity to Hybritech, I was aware that there was this emerging community of biotechnology companies in the area, and that's sort of where I focused. Toward the end of my graduate student career, I focused my attention on those sorts of opportunities rather than going into academia, which I really had no interest in pursuing.

JONES: Why were not interested in pursuing that, and what made industry look attractive?

VALKIRS: I was just more interested in applied science, and I think that the opportunity for tenured positions at that time was scarce, and it's getting scarcer. So, I think I made the right choice. It's not easy to find a tenured professorial position anymore.

JONES: And how did you get interested in science in the first place?

VALKIRS: I think I was naturally good at it. I think the first thing that got me moving toward science was that I had a natural ability in mathematics, which I was quite proficient at, and from that, but I didn't see a career as a theoretical mathematician as a possibility, so I moved toward the sciences, and in particular physics, because it's very mathematical in its

application. But then, as I got into it, I found the biological sciences even more interesting and complex, so I moved in that direction.

JONES: How did you get to UCSD? Were there particular faculty that you wanted to work with?

VALKIRS: Initially, no. I'm a San Diego born and bred, San Diegan, and UCSD was, is a very good university, so as an undergraduate, I went there simply, really, for economic reasons. It was cheap, and it afforded an excellent education. So, after my undergraduate degree, actually, I had applied to other universities and was accepted into Harvard, and my undergraduate research advisor, who became my graduate research advisor, convinced me not to take the position, and said that he would offer me a research assistantship, which was sort of a plumb, because research assistantships mean that you get to do research and you get paid for it, versus teaching assistantships, where you have to teach undergraduate classes and you get paid for that. And I preferred the research to the teaching, so that was a good incentive, and he convinced me, basically, to stay in San Diego, and I'd never lived in a harsh climate -- it didn't take a lot of coaxing to convince me that it was a good opportunity.

JONES: And what was your research for the PhD?

VALKIRS: Membrane proteins in the photosynthetic bacterium, *Rhodopseudomonas spheroides*, specifically, photosynthetic reaction center membrane proteins and characterizing them by immunological means, so I was doing a very biological, immunochemical type project, yet I was within the physics department, and I had to qualify as a physics graduate student, which sort of was difficult. It's difficult to study physics and go the laboratory and do something that's not physics.

JONES: Did you have a mixed committee?

VALKIRS: Yeah, I did have a mixed committee, but it's still difficult to focus on studying on classical physics, then doing something totally different, which was not what most physics graduate students were doing. They were focusing on classical physics.

JONES: What were the years here? The time frame?

VALKIRS: I started in graduate school in 1974, and I graduated in '82.

JONES: And while you were at UCSD, you were aware of Hybritech?

VALKIRS: In the later years, Hybritech was started in '78. I don't think I was aware of it in '78, but probably in 1980 or '81, as I saw that the end of my graduate student career, at least I saw that it was going to end at some point, I started looking for opportunities because I had made the decision that I wasn't going to do a post-doc, I wasn't going to look for an academic type career, so I was just reading the paper or anything I could find that gave me an idea of what the opportunities were, and I heard of, you know, Genentech, Cetus, and all of the biotechnology companies that sprang up in the San Francisco area, and those were possibilities, but here was something right next door that looked interesting.

JONES: And what they were doing was very closely aligned....

VALKIRS: It was aligned to what I was doing as a graduate student. I mean, I was working on immunoassays and characterization of proteins using specific antibody reagents, and that's not all that different from what Hybritech was doing.

JONES: So how did you get to Hybritech? Were you recruited?

VALKIRS: No, I just showed up at the door, and I applied.

JONES: Who did you talk to?

VALKIRS: Initially, I just talked to the personnel people when I filled out an application. I'm not even sure that I knew they were hiring at the time I did that. They were in a hiring mode because they had actually just finished their IPO in October of '81, and I think I applied in December or something like that, and started interviewing there in January or February. Actually, it was January when I was interviewing, of '82. And after the personnel people had filtered through my resume and saw I had some potential as a candidate, and I interviewed with Dennis Muriyama, who was destined to be my immediate supervisor, and Tom Adams, who was the Vice-President and Chief Technical Officer at the time, and who else? I'm not sure who else I interviewed with, that might have been it. No, Russ Saunders who was the Director of Product Development, I interviewed with him as well.

JONES: Did you seriously consider other opportunities at the time?

VALKIRS: Actually, no, I didn't.

JONES: This looked good?

VALKIRS: Yeah, I could have stayed for UCSD for a period of time following my degree as a research associate or something like that, so I didn't feel pressured to look at a lot of different opportunities. This one looked good to me, and if I got in, and I had the ability to go there immediately because I was finishing my graduate work, and I would have the freedom to do so, but I also didn't feel like I was being kicked out of the lab and I had to go. So, I felt a lot of flexibility, and if it worked out, fine. If it didn't, I would look elsewhere, and potentially leave the area.

JONES: So you didn't perceive a lot of risk in going to this start-up company?

VALKIRS: No, I didn't perceive risk, not knowing what a start-up company was at the time, I guess I was just naive, but then, with the initial public offering, you know, they were a real

company. You know, they had money in the bank, they weren't profitable yet, I learned terms like burn rate, and what that meant after I got to Hybritech, because that was all disclosed to the employees, everybody knew that our objective was to become profitable, and our burn rate this quarter was two million dollars a quarter, and you know, if we meet our plan, that will bring us to zero, and then we'll start making profits, and that was all very well communicated about on a quarterly basis to employees, so everybody knew where we were, what the risks were, and given the amount of money they had in the bank, and the direction the company was taking. I didn't think the risk was that great.

JONES: And you were impressed with the people there?

VALKIRS: Yeah, very much. I really enjoyed the informal atmosphere, and it seemed like a graduate school, but with a different focus, plus you were making more money than you would in graduate school, so that was also attractive.

JONES: And you received stock?

VALKIRS: Right.

JONES: Did that mean anything to you?

VALKIRS: It did. It did. I did perceive value in that at the time, and I'm not sure that it had a huge effect on my decision to go to Hybritech. I think I would have gone without the stock, but I did perceive value in it, and I understood that it was going to be a chunk of money if the company was successful. You know, when I got there, I didn't have anything like founder's stock. I had what was called restricted, I think it was Series B to begin with, and Series C. It had performance goals associated with it. The stock was worthless until the company reached these goals. And as a result of that, the option price, these were stock options, the option price was reduced relative to the fair market value of Hybritech's stock. So, it was, for instance, a

dollar a share, but it only became viable stock when the company met fifty million dollars in sales. I forget the exact milestones, but milestones associated with sales of products, and unless the company met those objectives, the option was worthless. I don't think they can give out options like those anymore, I think that was a law that has been eliminated, but in those days, you could give out, you could give a discount price for a stock option, with the contingency that you had to meet a certain objective before it became a real stock option.

JONES: Do this serve any real motivating purpose individually?

VALKIRS: Sure. Sure it did. Of course it did. I mean, you wanted the company to reach fifty million dollars in sales, and whatever you could do to make that happen, you would attempt to do so.

JONES: What were the facilties like when you arrived?

VALKIRS: Good. The company was in a very high profile building up on the top of the hill. The building's still there. I'm not sure that Hybritech still occupies any of it. If you walk out our door, you can look up and see it, so the laboratories had an expansive view of the East County from the top of Torrey Pines Mesa, and it was all very elegent, and the equipment was new, and everything was unlike UCSD, where a lot of laboratories had been there for twenty years, and some of the equipment was twenty years old, and, you know, dusty and musty in some areas. It was more polished than I was used to, but that was fine. It was all basically new, I mean, nothing was more than three or four years old there.

JONES: Who did you work with when you got there, and exactly what kind of work were you doing?

The reason I was hired was to work on the TANDEM assay, which was the two site immunometric assay, sandwich assay is sort of the common terminology, where you sandwich

the target that you're trying to measure between two antibodies, one that's labeled, and one that's attached to a solid phase, and they had products on the market for pregnancy testing, for HCG detection, which is the hormone that's released as result of pregnancy, they had other products for prostatic acid phosphatate, but I was mostly focused on the pregnancy test, and making it faster, making it more sensitive, and the project was called, generically, TANDEM improvement. So, it was sort of, what's the next generation of this, the next generation form of this product, how do we make it better. That was the objective, and I worked at that for perhaps a year and a half before I discovered something that led to different avenues.

JONES: When you arrived, you started doing the work that led to ICON?

VALKIRS: Yeah, it wasn't directly related to ICON. I was working on the pregnancy test, the HCG test that was done in a tube by the standard method that was in the product they were marketing at the time. And the generic objective of TANDEM improvement was to make these products better, which means faster, more sensitive, less non-specific binding, so I started developing methods for the existing product, to improve it, and some of those were implemented, and at the same time, we came out with this visual, well it actually led to this visual format that was a blue color developed on a white bead in a tube. So, I developed the white bead part of that in the tube, and others worked on, like the conjugate, which is the signal development element of the assay, and Bob Yoshida was working on that, and together we sort of came out with this visual system of a bead in a tube, that became, not a replacement for the basic pregnancy test that they were selling, which was both enzyme labeled and radio-labeled, but became like a third product, like a visual product, for rapid detection of HCG to determine pregnancy. But it was still a bead in a tube and it was still an hour long as a test, and that's sort of what got me in the thought process of how to make things run faster.

JONES: Was the visual format a novel introduction at that time?

VALKIRS: No, other people had been doing things like dipstick tests, visual dipstick tests, but they were all at least an hour long, and I think our bead in a tub test was probably a little more sensitive than the basic dipstick tests, even though it still suffered from being an hour long. So, it was a reasonable product, actually. I think it had decent sales until ICON came out, which made it obsolete. But working on those products and working on HCG, in particular, led me just to consider the physical parameters that cause immunoassays to work as they do, and in thinking about that, I came across the idea that perhaps the solid phase shouldn't be a bead, perhaps it should be a membrane, perhaps the sample should flow through it, because the reaction kinetics are most favorable if you configure it in that way.

JONES: Do you think that they hired to this kind of work?

VALKIRS: They didn't hire to me to do that. They hired me to like support existing products, and develop improvements for existing products. They didn't really expect me to invent anything, I don't believe.

JONES: Well, how can you expect that?

VALKIRS: Well, we do that now, I mean, we set aside people here....

JONES: To invent something?

VALKIRS: No, no. We set aside people and say, 'This is the kind of product we want. The technology doesn't exist today, so go ahead and work at it. Develop something that makes it work like this.' So, they could have easily set me aside and said, 'We want a pregnancy test that has state of the art sensitivity and works in five minutes. Go ahead. Do whatever it takes to do that.' They didn't say that, but we take that approach now, and I think our, at the least

the cardiac marker panel that's coming out on our new technology platform is a result of exactly that kind of objective, where we set an objective saying, 'It has to work like this. We have nothing today that can meet that objective. Go ahead and develop it, invent it.'

JONES: Do you think you've modeled the way you organize R&D here on the way it was at Hybritech.

VALKIRS: Yeah, I think so. I think it's very much modeled on our experiences, we know what didn't work there, we try to avoid the mistakes that were made at Hybritech, that without creating a risk-free environment. You have to take risks if you want to be better than somebody like Abbott that has an enormous budget to do research, and you know, two thousand people doing research. And you have to be able to be willing to take risks, which we do here.

JONES: What types of mistakes are referring to at Hybritech. Were risks taken too cavalierly?

VALKIRS: No, they weren't taken cavalierly. I think that, you know, in hindsight, you can always say that you could have developed something better. I think that Hybritech was driven to put products on the market that made money, and sometimes products were introduced probably a little bit before their time, or before they should have been, and you fix problems after the fact. The products worked very well for all intents and purposes. Every immunodiagnostic product on the market has problems. You know, the problems that you see as the developer of the product are a minute fraction of the total number of tests that are done, and they are usually results of very unique circumstances, but you see them because, as the developer of the product, you get all the complaints. So, if you have .001 complaint rate, and you're selling a million tests, you're still seeing a lot of complaints. And so, you're inundated, as the developer of a product, you're inundated with the problems. You never hear anything about the successes. All you hear is, 'We need to fix this.' And I think because the

technology was so new, none of these problems really had been seen by anybody in the past, because the products were different. So, to some extent, you could say, yeah, maybe we pushed these things out, but we would never have uncovered some of these problems if it hadn't been out in the field and been exposed to a hundred thousand different specimens. You can't do a clinical trial on a hundred thousand specimens, it's just not possible, it's not economically feasible to try a diagnostic product on a hundred thousand specimens before you introduce it. But once you introduce it, you do eventually reach those numbers, and then you see the very infrequent problems that these formats do have.

JONES: Would you say, just in very general terms, that here at Biosite, you wouldn't push a product out quite as fast?

VALKIRS: No, I think the same thing about the infrequent problems, we will see those in the field only after we introduce products, and we will deal with those, and we have done that for the drugs of abuse product, which has made, has been improved substantially since its introduction. I mean, part of the reason for its success is that it has been improved substantially and the frequency of these occurrences is now minute, whereas before it was maybe 10x what it is now, or twenty 20x what it is now. Now, it's so minute that it's just not an issue at all. But without pushing something into the field, at some point in time, you're never going to see that, and you're never going to fix that problem unless you see it, and you won't see the problem unless it's out there being used a hundred thousand times a month, which is basically the kind of running rate we're at now. So, no, I don't think it's wrong to do that, because I don't see any other way of doing it.

JONES: Well, what other kinds of things did you learn from Hybritech?

VALKIRS: I think that manufacturing issues are something that we are very attuned to, and developing a process that's very manufacturable. I think a lot of what Hybritech, a lot of

problems that Hybritech faced were scale-up problems, developing things in R&D on a certain scale, and it works just fine in R&D and you can make this product in, you know, a thousand test lot sizes, but when you go to operations, you want to make it in two hundred and fifty thousand test lot sizes. Now the process is different. Developing a process that is manufacturable from the beginning is something we focused on here. The other thing is automation and developing automation processes. I don't know if anybody showed you our manufacturing operation, but it's highly automated. Things like the ICON were assembled by hand, by armies of people. We saw that and said, 'This doesn't make any sense if you're going to make ten million of these a year.' So, at the very beginning we decided that we were going to develop processes that could be automated. When we first intriduce a product, because the volume is not as high as it is, you know, when the product is mature, you don't necessarily invest in automation from the beginning, but each step in the process is capable of being automated. So, over the last five years, we have pretty much automated the assembly of our drugs of abuse device, and we couldn't reach the kinds of gross margins and efficiency of manufacturing that we have today if we didn't do that.

JONES: Was that an option for Hybritech, though?

VALKIRS: It was always an option, it's just that things, I mean, I was naive. When ICON was invented and developed, I was naive enough to believe that the people who were manufacturing it were proceeding with the best possible look toward the future. And maybe nobody realized how successful it was going to be, and they said, 'Why invest?' I mean, I wasn't part of this conversation, I never heard anybody saying, 'Don't invest in automation. Don't invest in high volume manufacturing techniques,' because we were in such a hurry to get that product to the market, it was deemed to be such a revolutionary product that David Hale basically said, I think it was in June, actually May, yeah, May of 1984, and the product was then in its infancy, it hadn't gone through clinical trials yet, he said, 'We want this product on

the market in five months.' That was just unheard of to try to accomplish that. As a result of that, you know, I guess the time factor just said, 'There's no way we're going to do any planning and high volume manufacturing for this product, we'll just have to do it manually, because it's the only way to accomplish that objective. Whether it was the right decision or not, I don't know. I mean, I really don't know what sorts of manufacturing problems they faced with the ICON and the high volumes that were made, but I know that they can make it cheaper, and it probably would have looked a whole lot different if we had decided up front to develop a process that automatable and, you know, where the scale-up to high volumes was rather straightforward from what R&D was doing.

JONES: Now, Ron Taylor was there at that time?

VALKIRS: Yeah, Ron Taylor was the Vice-President of Operations and he wasn't really that closely involved with the ICON project. It was more Bob Wang who really became sort of the director, I think he was a Director of Operations at the time, but he was really responsible for the process overall and the engineers, of course, were responsible for the plastic parts, but I think the manufacturing process was really in Bob's hands, but based upon what I had done, you know, we took what I had done and said, 'Let's make this in large lots. How do we do that?' And so, the process for doing that was developed based on what I had don ein the lab.

JONES: Can you recall your though process when you were running experiments trying to get this to work?

VALKIRS: Well, I didn't have an objective to do this. I remember distinctly that David Kabakoff had asked me to, we had sort of these R&D research scientist meetings where we gave presentations on progress in different areas of R&D, and he had given me the task of talking about reaction kinetics in immunoassays, and so I just started reading about reaction kinetics. I had known quite a bit about it anyway, but in reading about it and thinking about

our formats, the thought crystallized in my mind that you really don't want a solid surface and a solution surrounding it where the molecules in the solution have to travel long distances to reach the solid surface, which is what our bead in a tube technology was all about.

JONES: Is that why it took a long time?

VALKIRS: That's why it took an hour. And, you know, there were really no other formats on the market that were any different, you know, it was all a bulk solution around, on a sort of a flat or round solid surface, and they were all the same time frame -- slow -- or relatively slow, now. And it occurred to me, and the other thing that I think played into that was that some people were using latex particles as solid phases, or small beads as solid phases, that you could actually mix with the sample, and had demonstrated that you could do immunoassays in a much faster time frame if you had the surface area distributed throughout the sample. And so that led me to say, 'Well, what if we took a porous matrix as the surface area and we drove the sample through it? Are the reaction kinetics fast enough while the sample is in the porous matrix to bind everything, all the target, that's in the sample? And, you know, I did a few calculations and it seemed to make sense to me that we could put enough antibody in that porous matrix so that while the sample is flowing through, which is just a fraction of a second, you could bind everything that's in the sample, and on paper, it looked decent, the numbers looked decent based upon what was known about reaction kinetics. So, I tried it and it worked the first time, and you know, it's fairly astounding to see, after having worked on the blue bead assay in a tube, so-called TANDEM visual assay that took forty-five minutes to an hour, it was sort of astounding to see, in five minutes, a color develop, to have the sensitivity of the assay greater than what the tube assay was, and to see it develop in five minutes, rather than hours. Everybody was working with making twenty or thirty percent improvements in products, and all of a sudden, here was a factor of ten, you know, improvement just by

changing the solid phase and the way the sample was applied. It was pretty astounding. I was surprised. I was surprised it was working so well the first time out.

JONES: And then, who did you tel?

VALKIRS: I don't know exactly who I told first. I'm sure I told David Kabakoff and then, you know, it started getting around to people, like Cole Owen was involved early on, because he was Director of Marketing, so I think he was told very soon, and he got involved with, I mean, this was at the time when it was nothing like what an ICON looked like. It had a cigarette filter in a plastic tube, and I had membranes that were just sitting on top of the cigaretter filter, and the membranes had antibody immobilized on them, but it really looked nothing like an ICON. It worked by the same principles....

JONES: Chemically?

VALKIRS: Yeah, chemically, it worked by the same principles, but people like Cole Owen were brought in, and Phil Levenson, he was the Director of Engineering at the time, to sort of shape it into what a product should look like. Now, what I had demonstrated in the laboratory was an apparatus that worked according to the principles, but didn't look like an ICON, and it really wasn't a manufacturable product, either. You know, we had to develop something that was marketable and was manufacturable. So, Cole and Phil got involved in the project to sort of move it toward a direction that resulted in a marketable product that could be manufactured. And that led to the development of immobilized zones on a nylon membrane, rather than putting the antibody over the whole surface, which I had done in the first experiements. I'd localized it, just by spotting it on a memberane, a so that the area around the spot was white and clear, and you developed a blue spot, well that was perceived as a distinct advantage, because previously, immunoassays, if you got a non-specific background response, you got a color, you didn't know if it was a real positive or not. It could be a false

positive. So, this blue spot an a white background, if the background was white, your non-specific binding was zero, or clean, so you'd know that this blue spot was a true positive response. In fact, it isn't quite that simple, but that's the way most people perceive it. And so that was also viewed as a distinct advantage over existing formats, not only is it far faster and more sensitive than existing formats, well, actually not more sensitive, equivalent to the state of the art formats in sensitivity, but far faster, but you also had this built in negative control background, and all of those attributes really added up to a very marketable and interesting product opportunity.

JONES: This was early in '84 that you were doing this?

VALKIRS: Yeah, I'd say the nylon work, the first spot type of work was done probably in April, March to April of 1984, maybe even May, and when that was shown to people like David Hale, that was when he gave us, you know, a five month decree, 'It will be marketed in five months.' That's what really started turning the wheels.

JONES: And it was introduced in October?

VALKIRS: Yeah, it was introduced in October, 1984, after a very hectic summer.

JONES: So, through the summer, you were working on improving this, turning it into a product.

VALKIRS: Turning it into a manufacturable process. We did the clinical trials internally at Hybritech for the FDA submission. We had, you know, urine samples, obviously, from our other product that was on the market. We had lots of urine samples in house. We got them from Planned Parenthood Clinics in the community, so we had six hundred or so urine samples that we ran with product that was assembled in R&D by hand in reusable ICON canisters that were machined, so you could take the, they were basically clear plastic and had

a bottom which was detachable, so you could turn it upside down and assemble it, but the bottom on, tape it on, turn it right side up and run the assay, we had twenty of these things, and then when you did the twenty assays, you would dump out all the disposable contents, wash the plastic, and reassemble them. So, we did that by hand for all the clinical trials. I mean it looked like the ICON, but they were just machined plastic pieces that could be reused. They weren't disposables.

JONES: How hard were you working during this time period?

VALKIRS: Pretty hard.

JONES: How many hours?

VALKIRS: Ten or twelve hours a day.

JONES: Weekends?

VALKIRS: Yeah, off and on. On Saturdays, at least. Not usually seven days a week.

JONES: Was this a departure?

VALKIRS: It was definitely a departure. That was not my normal, and is not now, my normal working mode. I don't find that I'm efficient in that mode for very long. I'm not a workaholic. I can't do that for extended periods of time.

JONES: You were given a lot of freedom to do this?

VALKIRS: Well, when I did all of this ICON stuff in the beginning, nobody told me, 'You can do this.' I just did it, on the side, because I thought, as a result of what I told you before, the thinking about reaction kinetics and their existing formats, I just thought it was going to work, and it didn't take that long to demonstrate it. But as soon as it was demonstrated, then it

generated all this interest, then everybody said, 'Yeah, forget this TANDEM improvement stuff, you know, this is what you're working on.'

JONES: And you had plenty of money to do whatever you needed to do?

VALKIRS: Yeah, money was real, I mean, we never talked about budgets, it was just, 'Let's get this done.'

JONES: In October, you have a product, did you then stay with this project to take care of problems that appeared in the field?

VALKIRS: Yeah, and to develop a serum application. I mean, the original product was a urine application, and we developed a serum version, which had its own individual problems because serum has interfering substances in it that urine does not. We solved those problems, and that was hective, too. And then, we started working on the next generation of the ICON, which was the internally referenced ICON, where you have two spots. One is a reference spot that always develops color, and it's actually used as a calibrator to determine whether the color of the test spot, how the color of the test spot is related to a specific concentration of HCG, and in general, that reference spot was set so that it developed color equivalent to 25 milli iu per mil, which is generally used as a cutoff concentration. Anything below that could mean, it might mean pregnancy, but it could also mean that there was spontaneous abortion, somebody who had been pregnant and had started to develop the embryo, but it didn't get implanted properly, or whatever happened, the HCG level went up slightly, but there was a spontaneous abortion, it might never have been noticed by the woman, but she might have a slightly elevated HCG level because of it, but she's not pregnant. So, pregnancy tests are not perfect if they're highly sensitive, because there are these conditions that can result in a low level of HCG, just a temporary low level of HCG, so we had this reference spot at a recognized cut-off spot for HCG that was equivalent to what people had been using in the field, and it was

a color, visual reference that internally developed on the same device for each different sample.

JONES: And it turned out that that standard was a good one?

VALKIRS: Yeah, that's the way the product exists today, so I guess it's a good one. I think they still sell a lot of it. The only difference in the product was the way it was manufactured in '84, '85,' and even '86, was changed in '87, to a method where the antibody is deposited by a different mechanism. It's deposited by taking latex particles and immobilizing the antibody on them and then spotting a latex circle of particles on an inert membrane. The ICON device, as assembled now, is basically inert, with no antibodies on it until this latex material is applied on the finished device. So, the method for the immobilization of antibody has changed since it was first developed. I was involved in that, too. It was just that, in 1986, I sort of got fed up with the whole atmosphere at Hybritech and voluntarily removed myself from product development -- at the suggestion of my supervisor, but I was more than happy to do so.

JONES: When did you learn about the sale to Lilly?

VALKIRS: The day it was announced to all the employees.

JONES: And what was your reaction?

VALKIRS: My initial reaction was, 'Things are going to change. I'm not sure how, but things are going to change.' I was somewhat happy because it really crystallized the value of the stock, you know, you knew what your stock was worth, you also knew that you had Lilly stock warrants that could be valuable in the future. It sort of set a concrete level of what the value of the stock was, with potential upside. So, that was good, that was fine. But, I also knew that there would be changes, and Ken Buechler, who is one of the people here, one of the co-

founders, I had hired him in 1985 at Hybritech, to work on a new technology development there.

JONES: Apart from the ICON?

VALKIRS: Well, it was related to the ICON, but it was for unique visual labels, basically, is what he was working on, trying to come up with labels that didn't require an enzyme, were highly sensitive, and visual. And so, at the time, he knew Lilly very well, because he grew up in Indianapolis, and he had visited the labs and he had worked there summers, or something like that, and he knew what the corporate culture was like, and he knew it was nothing like what Hybritech was like. So, we had discussions about it and he knew, he said, 'Things are going to change, and you'll find a different philosophy working in no time,' and that, in fact, is hwat I found.

JONES: What happened?

VALKIRS: What I found was they had a total de-emphasis on research and development. They would call it research and development, but what, in fact, they did was take probably half of the R&D resources and move them into a technical product support function, which was, they perceived the products in the field to be flawed and the processes for manufacturing them to be flawed. They wanted to fix that. And they weren't under the kind of control that a pharmaceutical product is. And they perceived that as a problem.

JONES: Now Lilly wasn't in the diagnostics business before?

VALKIRS: No, not at all.

JONES: Why did they buy the company, what's your perception?

VALKIRS: My perception is they bought it for therapeutics and the diagnostics came along for the ride. You know, in the end, the diagnostics was the only thing that was worth anything at the company. I don't think they probably recognized that until too late. And their intial approach at managing the diagnostics business was incorrect. So, they basically failed on all fronts, what can I say? They failed at every aspect of what Hybritech was. It was poorly managed.

JONES: How did this affect you personally, I mean, you said that you got upset about things?

VALKIRS: Well, it affected me personally because what I was most interested in was the research and development, new product development, new concepts of new products. That's how the ICON came out of the organization, and there was, literally, Ken and I were it. We were the only people working on that, and there was no importance, there was no management at the time, devoted to our efforts. It was like, 'Let's put these guys off in the corner and forget about them.' That's what it seemed like to me.

JONES: Did you have problems with money, too?

VALKIRS: No, money was not a problem. You had equipment to support your work, but the number of people you had was a problem. You can imagine, half of research and development was off solving manufacturing problems, and you know, developing better processes, and it really wasn't resulting in anything new. Nothing new came out of that. They may have shored up some of the manufacturing processes, but they were really not, it's not like this was in total disrepair and Lilly came in and saved the day. That's not at all the case. You know, they changed things, whether they changed it for the better or not, that's debatable. But this spend a hell of a lot of effort doing that, a lot of research and development resources doing that, and in the process, they instilled the philosophy of 'We will take no risks. We will not fail. We cannot afford to fail,' was the message that I got. And that was most apparent when I was

trying to get the new ICON format, which involved this latex deposition for the pregnancy test, and the internal reference. I was trying to push that through in the summer of '86, and I ran up against a stone wall. The stone wall was operations, and they were afraid to fail.

JONES: So, it was important, then, for you to be in this atmosphere where you could take risks?

VALKIRS: Absolutely. Absolutely, and I expected that from the rest of the organization. When I saw that the rest of the organization didn't have that philosophy anymore, then that was it. I mean, I didn't want to butt my head up against this stone wall for a year. I mean, I was very frustrated in the summer of 1986, and this is only three or four months after Lilly took over, but the philosophy had clearly changed. Whatever they told the people in operations, I'd sort of like to know, and I don't know whether they, the management just sat them down and told them this is how it's going to be, or what they were told, but it was very clear to me that there was a lack of cooperation, and that people there just did not want to fail at what they were doing. They would rather not introduce a new product than to have even a slight risk of failure.

JONES: So, after Lilly took over, were there any new product introductions?

VALKIRS: No. Not for any....Rick Anderson, who's also a founder here, finally did get the process for the new ICON through. I mean, I was totally frustrated, I got out of product development, I went into a sort of researc mode where I was independent of anybody. Basically, I did whatever I wanted for about a year, and I was working on the Photon Elite, and you know, unique assays for that.

JONES: I'm not familiar with that.

VALKIRS: Photon Elite is the instrument development project that was done with Toyo Soda, now called Toso, that was axed, I don't know exactly the date it was axed, but the project was ended. That instrument is now on the market, and actually could have been very successful. In fact, it would have saved Hybritech from being decimated by Abbott in the PSA market if they had pursued the agreement.

JONES: Who developed the product?

VALKIRS: Toso developed the instrument. We developed the immunochemistry. Hybritech developed the immunochemistries that went on it. So, when the agreement was ended, Toso got rights to the assays that had been developed, and in fact, are marketing them, but you know, their marketing presence in the United States is poor because they're a Japanese company, relative to what Hybritech could have done with it. But, you know, the details of the financial arrangement, I don't know. I just think that without that so- called random access analyzer, Hybritech has been, Hybritech's PSA product, for instance, has been decimated by Abbott.

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.