William Rastetter

Interview conducted by

Matthew Shindell, Historian

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Dr. William H. Rastetter, Bill, Ph.D., co-founded Receptos, Inc. in 2007 and has been its Executive Chairman since May 2009. Dr. Rastetter served as a Partner at Venrock which he joined in 2006 until 2013. Dr. Rastetter focused on biotechnology investments. He served as an Interim Chief Executive Officer of Receptos, Inc. from May 2009 to December 2, 2010. Dr. Rastetter served as the President and Chief Executive Officer at Biogen Idec Inc. from December 1986 to January 2002, the Chief Executive Officer from January 2002 to November 2003, the Chairman since 1986, a Director from 1986 to December 30, 2005, and served as an Executive Chairman. He served as the President at IDEC Pharmaceuticals Corp. from 1986 to 2002. Dr. Rastetter served as the Chief Financial Officer at IDEC Pharmaceuticals Corp. from December 1986 to November 2003, the Chairman from May 1996 to November 2003, and a Director of IDEC Pharmaceuticals Corp. since 1986. From 1984 to 1986, Dr. Rastetter was a Director of Corporate Ventures at Genentech Inc. and served in a scientific capacity at Genentech. He has been Non-Executive Chairman of Illumina Inc. since January 2005. Dr. Rastetter has been the Chairman of Fate Therapeutics, Inc. since November 2011. He was an Interim Chief Executive Officer at Fate Therapeutics, Inc. until October 15, 2012. Dr. Rastetter joined Fate Therapeutics on December 14, 2011. He has been Chairman of Neurocrine Biosciences Inc. since May 25, 2011. He served as Executive Chairman of Biogen Idec Ma Inc. since December 31, 2005. He has been a Director of Illumina Inc. since November 1998. He has been a Director of Regulus Therapeutics Inc. since April 1, 2013. Dr. Rastetter serves as a Director of Argonaut Technologies Inc. and Neurocrine Biosciences Inc. since February 8, 2010. He has been Life Director at BIOCOM, Inc. since April 2007. He is a Board Member of the California Healthcare Institute. He served as a Director of Spiros Development Corp., since 1998. Dr. Rastetter served as a Director of the Biocatalysis group, and a Director of Chemical Sciences. As a Director of Corporate Ventures at Genentech Inc., he served as a Director of Spiros Development Corporation II Inc. and Spiros Development Corp. since 1998. Dr. Rastetter served on the Boards of Directors of Genentech's joint venture companies, Genencor (with Corning and A.E. Staley), HP Genenchem (with Hewlett Packard), GLC Associates

(with Lubrizol Corp.), and Travenol-Genentech Diagnostics (with Travenol Laboratories). From 1975 to 1982, Dr. Rastetter held various faculty positions at the Massachusetts Institute of Technology. He held various faculty positions at MIT, won the award for “Excellence in the Teaching of Chemistry” at Harvard, and is an Alfred P. Sloan Fellow. Dr. Rastetter is an R. B. Woodward Visiting Scholar of the Department of Chemistry and Chemical Biology at Harvard University. He is the author of numerous scientific papers and patent applications in the fields of organic and bio-organic chemistry, protein and enzyme engineering, and biotechnology. Dr. Rastetter holds a Ph.D. and an M.A. in Chemistry from Harvard University and an S.B. in Chemistry, Phi Beta Kappa and Phi Lambda Upsilon, from Massachusetts Institute of Technology.

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SHINDELL: It is June 27, 2008. This is an interview with William H. Rastetter. I am Mathew Shindell. So, Dr. Rastetter, why don't you tell us, well, as far as you want to go back. At what point did you become interested in biotech or things related to biotech? Was it during your education or even prior to that?

RASTETTER: Well, I was an associate professor of chemistry at MIT and I think found work within a very narrow defined discipline to be somewhat frustrating and confining, if you will. And, saw the biotech industry starting with certainly some promise, and I think the thing that struck me at the time was that it was an endeavor that was intensely interdisciplinary and that, by its very nature, of interdisciplinary interaction, teaching, learning, and collaboration was of interest to me. So I, I left the Department of Chemistry at MIT and went to Genentech in the early days, and assembled a group of actually very talented scientists who had gotten their PhDs, gone on and done postdocs, and very good labs around the world. And, I think the thing that was unique about our group is that we pulled together mathematicians, and x-ray crystallographers, protein chemists, biochemists, microbiologists, molecular biologists, organic chemists, and had then collaborate and create in an environment that I think at least at the time would have been impossible to assemble within the academic sector.

SHINDELL: Uhm-hmm. And so at this point this is sort of the Boston biotech scene? And how, how developed was that scene at that time?

RASTETTER: Well, that was Genentech. It was San Francisco.

SHINDELL: Oh, you, you had moved to San Francisco to do that?

RASTETTER: That's correct.

SHINDELL: Oh, okay. But, there is quite a large biotech sector in Boston?

RASTETTER: Certainly.

SHINDELL: So, were you exposed to that at all while you were at MIT?

RASTETTER: Well, most of the, most of the action was confined to about five companies at the time, Cedes, Genentech, Amgen, Biogen. Biogen was in Cambridge and in Geneva, Switzerland, but I had really no contact with Biogen at the time.

SHINDELL: And, how about before you were a professor at MIT? You got your degrees from Harvard, is that right? You have an MS and a PhD in chemistry from Harvard?

RASTETTER: I have an MA and a PhD in chemistry from Harvard.

SHINDELL: Oh, an MA?

RASTETTER: Yeah.

SHINDELL: Okay. Was it not in chemistry?

RASTETTER: It was in chemistry.

SHINDELL: Oh, okay, but they don't, they didn't do an MS.

RASTETTER: Chemistry, chemistry is both an art and a science. [Laugh]

SHINDELL: Well, I think that's probably true, historically.

RASTETTER: Right.

SHINDELL: And in your education had you thought at all about technology or biotech, or were you a more sort of academic-focused student at that time?

RASTETTER: Well, I was doing chemistry at the interface with biology. Even as a graduate student I was doing what became known as bioorganic chemistry, use of synthetic chemistry directed at elucidating or mimicking biological mechanism or biological molecules. And, it became pretty obvious to me that the tools of organic chemistry were somewhat limited and one should use things like ribosomes, RNA, and so forth to make, to make molecules. That is the tools that were evolving, coming

out of academia into these interdisciplinary groups at places like Genentech. So, I assembled one of the first groups to do what has become known as protein engineering, where you make mutants of naturally-occurring proteins as a very defined, very precise way of studying structure and function, to understand how mutagenesis and changes of often single amino acids change protein structure and function.

SHINDELL: Uhm-hmm. Okay. So you, you were doing work on the interface of chemistry and biology pretty much throughout your entire career. So, how did your move into biotech change your approach towards science, or towards innovation even? How would you characterize the, the change in your own personal work?

RASTETTER: Well, I think the tools that are available to people who bring together many, many disciplines' tools are, by definition, much broader. So, I can think of engineering entire microbes, entire microbial pathways to make, to make new chemicals. For example, we were able, in the early years, to take an enzyme from corynebacterium and put into our [winia] and eliminate the first seven steps of the Reichstein Synthesis to make ascorbic acid by engineering a microbe to do those steps. So it, it was the type of thing that would have been if not impossible at the very least very difficult to do within a chemistry department.

SHINDELL: Oh.

RASTETTER: Right.

SHINDELL: And, is there anyone in particular who played a role in either convincing you to make the transition to biotechnology or in facilitating that transition, or even a group of people?

RASTETTER: Well, there was a fellow by the name of Ray Gomez who was on the faculty with me at MIT who actually made the leap about a year before I did. And, I stayed in touch with him and, you know, at the time it seemed like a brave new world, but he convinced me that, you know, perhaps there was life after academia. [Laugh] He was certainly correct. Uhm-hmm.

SHINDELL: Okay. And, so tell me how you wound up making the move from San Francisco down to San Diego, if we're not missing anything in between there, if you want to talk a little bit more about your time in San Francisco.

RASTETTER: Sure. I was at Genentech for about five years and was recruited out of there by someone at Kleiner Perkins Caufield & Byers, Byers in particular whom I had gotten to know. KPCB was the founding . . .

SHINDELL: Was that Brook Byers?

RASTETTER: Yeah.

SHINDELL: Brook Byers?

RASTETTER: Yeah. KPCP was the founding venture capital firm behind Genentech. I'd gotten to know Brook and he was starting a company in the antibody area and I agreed that, that I would become the CEO. So. Easy as that. [Laugh]

SHINDELL: And, did you find it a different experience being the CEO of a company versus a working scientist, or did you find you were able to maintain your role as a working scientist even as CEO?

RASTETTER: Well, I'd say that the, the running of a group of twenty-five very talented scientists at Genentech versus running a group starting even smaller than that at IDEC was actually very similar. The problems were different, but the tools were very similar. The pressures to perform, to stick to time lines, to raise capital and use capital very efficiently were all the same. So no, I don't think it was very different at all. Ultimately, at IDEC I was one of the inventors of Rituxan. It went on to become the world's, is today the world's largest selling cancer drug. We'll have worldwide sales somewhere between four and five billion, with a B, dollars this year. And so, I think often the CEOs who are best prepared to make decisions that are good for small companies are CEOs who have technical background, understand the risks inherent in certain decisions, rather than relying entirely on the intuition of others who, who have the training.

SHINDELL: Uhm-hmm. And could you elaborate on that a little bit, maybe with a story from your own experience about how it is that your technical training helped you in that?

RASTETTER: Well, I will, again, give you the Rituxan example. IDEC was founded in 1986 around a similar technology involving use of antibodies to treat non Hodgkins B-Cell Lymphoma. I say "similar" but at the same time it was extraordinarily different because the technology that we started with was a customized approach to antibody

therapy of lymphoma. That is, if Mr. Smith would come in and be diagnosed with lymphoma we would be able in three, four, maybe six months to make a monoclonal antibody for Mr. Smith. It would work for Mr. Smith but it would not work, presumably, for anybody else because it was customized only to his tumor. Recognize the, the very specific antigen on the surface of his B-Cell tumor, an antigen known as an idiotype. We found by about 1990 in our fourth year of existence that we had some absolutely remarkable remissions of disease in lymphoma patients who had perhaps six, nine, twelve months to live, and they would go into remissions of five, six, and seven years. The unfortunate thing is that that would happen in only about twenty percent of the patients that we treated. The other eighty percent treated with what would become, if we commercialized it, a very expensive therapy, because it was customized to the patient. The other eighty percent had responses that were really no better than what those patients could achieve with fairly inexpensive chemotherapy, relatively inexpensive chemotherapy. So, the pharmacoeconomics of the approach became problematic to us. I mean, imagine a commercialized therapy that only works remarkably well in twenty percent of the patients that has to be priced at like $50,000 per patient. The third-party payer wouldn't see that as a $50,000 therapy. They'd see it as a $50,000 therapy that had worked in one patient in five so they would see it as a $250,000 therapy. So, I had to make the, at the time, remarkably hard decision to abandon the technology around which IDEC had been founded, and in 1993, two years after we had gone public and raised $51 million to take this customized therapy to the market I had to make the remarkably difficult decision to kill that program and substitute a generic or off-the-shelf antibody, what's known today as Rituxan in experimental clinical trials. And, you know, hindsight is pretty good, you know. Today, I told you that drug will sell four to five billion dollars worldwide, and so gosh that was a no-brainer. [Laugh] Right? Well no, we didn't, we didn't know that at the time. And, the, the antibody was designed, in fact, to, to eliminate not only the B-cell tumor but all the normal B-cells in the patient's body. And so, there were two potential risks. One, would the patient survive the massive tissue destruction of the tumor by this antibody? Would the kidneys, for example, be able to withstand the, the influx of all these waste materials as the, the tumor would burst open, as normal B-cells would be liced by the antibody. And number two, would the patient survive without normal B-cells for long enough for the bone marrow to replenish the normal B-cells? And, we didn't know the answer to either of those, and I think there was some substantial risk in doing that. But, it seemed to me that the alternative of taking both programs forward until we knew the answer to that was, was a nonstarter

because neither program would succeed because we, we wouldn't have the capital to, wouldn't have the capital to get to answers with either one. I think, in the end, we made the, the correct decision. I can remember sitting in a conference room in Mountain View, California, where we had about half of our people at the time, and my colleagues were arguing over a manufacturing issue with the customized therapy, trying to figure out, "How can we make this more cost effectively?" and it, it just, I kind of was daydreaming. I kind of went somewhere else, had kind of an out-of-body experience, I suppose, and it dawned upon me [snaps fingers] that we, we needed to begin a program with an antibody that could be made kilograms at a time, hundreds of kilograms at a time, in large manufacturing vessels where you could make the stuff really very inexpensively. And so, with the combination of, of business training and scientific training was able to understand the inherent risks and unilaterally made the decision to go with a new program and eliminate the, the old one. I guess that's the, the luxury of being and the risk of being a CEO. Fortunately, I was right. So.

SHINDELL: And, did you get much resistance to that decision?

RASTETTER: Oh, absolutely. Most of the founders left, left the company.

SHINDELL: Well. Let's step back a second to the more general picture for a second, because I realize we didn't really touch on this. What about sort of the academic science versus the culture of, of biotechnology, and sort of corporate science and innovation? Did you notice a big difference between those two cultures and how did you deal with that? And then, sort of related to that, how did your academic colleagues treat you once you've made this move into corporate science?

RASTETTER: Uhm-hmm.

SHINDELL: Okay. Sure. Well, maybe I just need to – there we go. Now we're started again. Okay. So, back to that question, the cultures of academic science versus corporate science and the ways in which maybe the new culture, the ways in which you took to the new culture or adapted to the new culture, and then also how your academic colleagues treated you once you'd made that move?

RASTETTER: Uhm-hmm. Well, I think the cultures are, are remarkably different and perhaps not apparently so to someone who's been immersed in the academic sector for a long time. I think generally in the academic sector we think of the superstars as being individuals. In the corporate sector, at least among companies that I think are

good companies, productive companies, superstars are teams. And, often there is no place within the corporate culture for the, let me call it the "prima donna" superstar that might thrive in the academic sector. And, I like to think of the distinction in the corporate sector. I mean don't, don't get me wrong. You want very, very good people in, in the, in the industrial sector, but I think the distinction, the very important distinction is that between the prima donna and the leader. Okay? The prima donna is very "me, me, me, me, me" focused and "Look at the papers I've published. Look at the ideas I've generated. Look how many seminars I'm invited to give. Look how many awards I've gotten," etcetera, etcetera. And that's, that's fine within that culture. In fact, those who succeed do all of those things, and do them in spades. The, the "me, me, me" person doesn't do nearly as well in the industrial sector, because the "me, me, me" person isn't a very effective leader. Okay? A leader has to be able to motivate, to coalesce, to communicate, to cause a group of people to become much more than the sum of its parts. And so, the intense focus has to be on the individuals that, the focus of the leader must be on the individuals who form the team, has to be on the job at hand, has to be on the deliverables, the timelines, and so forth, but also has to be focused on providing for the team members context, big picture. That is, the teams who maybe well-coordinated and communicate well, but where every individual only knows their little piece and knows when to hand off aren't nearly as effective as teams that really understand the context of what they're doing, why it's important, how it's differentiated, why it's going to make a difference in peoples' lives. So, the "me, me, me" guy from the academic sector isn't often very effective industrially, because he or she doesn't understand the nuances of leadership and team coalescence. Does that, that make any sense?

SHINDELL: Yeah. Yeah.

RASTETTER: Okay.

SHINDELL: Where do you think you learned those skills? Did you know them prior to entering the industrial sector or is this something you had to learn on the job once you made that move?

RASTETTER: You know, I probably didn't expect that there would be any cultural difference between academia and, and industry, and so I think that came as a bit of, you know, cold bucket of water in the face. Because, I was kind of used to being the focus of attention, whether I was, you know, teaching six hundred premeds, or

leading a research group kind of one-on-one with individuals. And, all of a sudden you had to learn about teamwork and making these twenty-five people produce what fifty individuals working alone couldn't possibly do. Right? So. But, you know, I think, I think I, with some help and coaching from the right people was able to pick that up.

SHINDELL: Is there anyone in particular that you think, in terms of coaching, anyone in particular who had an influence on your management style?

RASTETTER: No. I don't think any single individual stands out. I think it is a mix of good examples and bad examples. [Laugh] I think it's important to learn from both, from both sides. Yeah.

SHINDELL: And, I'm sure learning from mistakes as well is instructive? Do you remember any sort of anecdotes from your early days in this that would sort of demonstrate the confrontation of maybe the old you with the new environment? Or . . .

RASTETTER: Oh, none that come to mind immediately. But . . .

SHINDELL: No? [Laugh] Well, that's okay. We can move forward. And, if any occur to you while, while you're talking please, you know, go ahead and, and tell them. Now, what about your academic colleagues? Did they view you with suspicion once you moved out of academia or did you find your relationships with them stayed pretty much the same?

RASTETTER: Well, I think the move to Genentech from MIT was seen as, as a fairly daring move. Genentech certainly had a reputation for attracting some of the best academic minds in the world. And so, it wasn't, it wasn't as if I was leaving a center of academic excellence to go to ABC Commodity Chemical Corp or, you know, just to make up a disparaging word, disparaging name. So, certainly the types of problems that Genentech was, was tackling at the time had never been solved before, were directed at good purposes, development of human therapeutics and so forth. Human therapeutics that were quite different from what had, you know, come out of small molecule work. So, I think there was perhaps some, "Wow, he's, he's nuts to, to do this," among some, and perhaps others were, "Wow, you know, if anybody's going to succeed Genentech will succeed. This is a good, good move. This should be a good adventure." I think, though, most people reserved judgment. I think, in the end, there was, there, there is today, if I may say so, some admiration for what I did with the

discovery, development, and commercialization of the first monoclonal antibody approved by the FDA for cancer therapy that has become the largest selling cancer drug in the world. So, I think at least with, with hindsight my colleagues today tend to greet me quite warmly and without, without disdain. [Laugh]

SHINDELL: Uhm-hmm. These days it seems like there are a lot of people who manage to maintain their academic posts while also working in, in biotech. Maybe not on the level that you were working. Was that possible at the time or was it, is that a more recent phenomenon, that people are able to stay at UCSD, for example, while also being on the board of one or two biotech companies?

RASTETTER: Well, I think it's quite different being on the Board and being engaged in real day-to-day decision making. I serve on the Board of a local company, a very successful local company, Illumina, where the founder, David Walt from Tufts University, is still on the Board and contributes a tremendous amount, but is employed full-time by Tufts as a professor in the Chemistry Department. The, you know, the involvement of Board members is more for governance, strategy, and oversight. It's quite different from the day-to-day activities of the company. So, I think scientists who believe they will split their time for day-to-day work between academia and the industrial sector will probably do neither job as well as if they committed to one or the other.

SHINDELL: Oh really? Okay. Well, let me ask you then, while we're on this subject, about sort of more generally, what do you think the role is of the university and of university scientists in a successful biotech sector? And, in answering this, I mean, you could, you could talk about the specific San Diego example and how UCSD, and Scripps, and the other institutions maybe play a role in the success of the sector here? Although that one success shouldn't, you know, color your answer if you feel like it's not a healthy relationship or it's not as good as it could be.

RASTETTER: Well, I'm, I'm going to step way back in answering the question and I'm going to go to the national level first.

SHINDELL: Okay.

RASTETTER: And, I think it's quite clear that United States is pre, preeminent in biotech. There are other regions who are doing it, but certainly we led and maintain, by far, the critical mass of people, of discovery, of successes in terms of product

launches, in terms of innovation. And, I think the uniqueness of biotech in the U.S. comes from a three-legged stool, if you will. One is the National Institutes of Health and the often-enlightened funding that Congress has provided. Though, certainly I think that's jeopardized today. There is a common misperception among the U.S. public that the National Institutes of Health has developed all these wonderful drugs that we enjoy and pharmaceutical industries are just kind of marketing arms. That's certainly not the case. The NIH has, perhaps, taken one or two drugs, in their entire existence, all the way through to approval and commercialization, or out-licensing. But the, the extraordinarily important thing that the NIH has done is to provide the capital and the ability to educate and inform individuals with interest in biological and life sciences on, in the tools, the theories, the methods of science that are applied to biotech problems. And, without that funding the science that we call biomedicine, if you will, would be confined to the pharmaceutical companies. And, the richness of discovery, even within the pharmaceutical companies, would be curtailed. I think it is the, the funding of academic research through the NIH, the extramural grants and whatnot, that has ceded the ideas, the intellectual property, has given incentive to the people who have become the founding scientists in, in biotechnology. So, that's one leg of the three-legged stool. The second leg is venture capital. And clearly, in primarily the Bay Area and the Boston area venture capital firms are very plentiful. There's a lot of capital that can be deployed for really, really good ideas, or really, really good people have good IP protection and want to start companies. And, I think that while there is some of that in Europe, it doesn't parallel what we have in, in the U.S. The third leg of the stool is the NASDAQ, and the ability to take companies that have parlayed forty, fifty, maybe sixty, or seventy million dollars from venture and partnering sources into public companies that have access to public capital. And, the three of those together have been, have been remarkable for, for creation of biotech industry. Now, how does that apply to San Diego? Well, with Scripps, Clinic and Research Foundation, with the Burnham, with the Salk, with UCSD, with what, I'm guess, twenty-five, thirty thousand people employed in this area in, in the biosciences, and a lot of that funded by NIH funding, we have a very rich, very rich environment for the starting of companies. Okay? And, venture capital is available. There aren't as many venture capital firms down here as they are in the Bay Area but, you know, it's, what, an hour and a half flight away. So, and certainly the NASDAQ is available to us. I think some of the difficult decisions that local organizations have had to make relate to access to capital. For example, Scripps has had a number of relationships with large pharmaceutical companies where they have sort of an

exclusive relationship with, with one pharmaceutical company at a time that lasts for a number of years, and I think that has constrained the flow of intellectual property out of the Scripps, because the large pharma partner has had really first right to negotiate these things. And only when they pass can these things become companies. So, while that access to capital, I think, and large amounts of capital has been very good for the organization per se, I don't think it has spawned as many companies as might have been spawned had there been equal funding with less restrictions applied to them. Yeah.

SHINDELL: And, do you feel that the closeness of the companies and the universities here in San Diego plays a role? And, by that I mean is there a geographical closeness, the fact that the cluster sort of literally is geographically a cluster and people see each other quite a bit due to that fact? Do you think that plays a role in the process of innovation here or the success of companies here?

RASTETTER: Well, I think it makes access to human capital much easier. I think it makes interaction to borrow equipment or to share space for an animal facility, or something like that you know, much easier. I guess the other side of that is that companies tend to conduct their research for reasons of intellectual property protection under kind of a shroud of secrecy. So there, it isn't as if twenty local biotech companies are like twenty small universities that are sharing ideas with each other. It just doesn't work that way. But, I think one of the, one of the things that we really benefit from down here is that most of our biotech companies reside within the same city, City of San Diego. And so, there's a single set of regulations and fairly easy to get the attention of the right people in the city and get your permits, and so forth. In the Bay Area, the companies up there are spread among, I mean jeepers, you know, there's Redwood City, and there's Palo Alto, and there's Menlo Park, and there's Atherton, and there's South San Francisco, and Burlingame, and San Mateo, and – I mean, whoa. Who are you dealing with? Well, you're dealing with a number of municipalities, but none of them really has the critical mass that we have here in terms of having one central place in the city. So, I think that has made it easier here. The commute, at least to-date, is a bit easier down here because we don't have bridges, and bays, and whatnot. Interacting with people in the East Bay, in the Bay Area, if you are on the Peninsula, is a hassle. You can pick up the phone. You can email them. But, actually getting over to a seminar in the East Bay is something you probably would do with some trepidation. Much easier here if you're in a biotech company to go over to Scripps to watch a seminar or something. So yeah, I think the

cluster is important. The cluster has changed in its character. I've been in San Diego now for twenty, twenty-one going on twenty-two years and I think that twenty-two years ago the cluster here, with some exceptions, were, the cluster was populated by a bunch of refugees from academia. That is, mainly people who were still trying to figure out how to do this thing called "biotechnology." Now it's a much more mature cluster where you don't really have to go outside of the San Diego area to recruit, and you can get just about anybody you want, from manufacturing, to quality, to regulatory affairs, to clinical science. In other words, the things that you don't normally practice in a biology department or chemistry department, but are absolutely necessary within biotech, are now here. That is, the professional staff that are required to build a fully-integrated company are now available, and they were no twenty years ago.

SHINDELL: I remember, I read one paper that characterized that early stage of development of, of the biotech sector here as, you know, the high-risk time period of getting involved in biotech, and that maybe those sort of initial companies laid down a sort of a backbone that has made it far less risky, although still risky, to start companies today. Would you agree with that assessment and if so, what are the major steps do you think that happened to, to lay down that backbone?

RASTETTER: Well, one of the most important pieces was the acquisition of Hybritech by Lilly. And, what we saw at the time were the, the doors at Hybritech flew open and everybody just escaped, went out and started companies. Right? So, that was, that was good for seeding of little pockets of talent, and ideas, and intellectual property that became a number of companies. Right? Gensia, and Genta, and Gen-Probe and, you know, the list goes on. It was, it was a risky time. It is certainly not risk-free today. I think the risks have changed. I . . . the uniqueness of the biotech sector in 1986, to pick a year, was that large pharma didn't have many of those skills. Okay? Biotech, today, is riskier because large pharma does have those skills, either through acquisition or through, in some cases, organic growth of, of groups that have, you know, protein biologics-based people in science. The, the risks back then were also, to some extent, lower because some of the targets were obvious. Let's make real human insulin rather than bovine or porcine insulin. I mean, you knew it was going to be effective. There was very little clinical risk. It was, "How do we make this? How do we formulate it?" Well, even the formulation, you know, is pretty, pretty much a cinch from the formulation of the very similar porcine or bovine material. Or, "Let's make growth hormone. Rather than from cadavers let's

make it in e coli." And so, a lot of those risks, a lot of those targets with reduced risk, don't exist today. Okay?

SHINDELL: So, the obvious ground has been covered, basically?

RASTETTER: A lot of it has. Yeah. Yeah. The biology that we're dealing with today, I think, is much more complex. I think we're talking about SNP genotyping, we're talking about whole genome sequencing and trying to pick patients for certain therapies, or avoiding certain therapies in certain patients. And, you know, just the bioinformatics has gotten tremendously complex. We're talking about systems biology where entire metabolic systems are the target rather than single receptors or enzyme active sites. We're talking about tissue regeneration in stem cells, good or bad. Stem cells for tissue regeneration or stem cells that cause cancer. So these are, the problems get more and more complex and more and more difficult. So, still, it's still risky.

SHINDELL: Yeah. Let me ask you about organizations that have also played a role. What about organizations such as, for example, UCSD CONNECT, and also maybe in a different sort of capacity, Biocom, and the roles that they have played here in solidifying the biotech sector or, you know, helping to make it stronger or more successful?

RASTETTER: Uhm-hmm. Well, I think organizations like Biocom and CONNECT have been particularly important for the entrepreneur who doesn't have all the connections, all the relationships within the community. The ability, for example, for a small company to use and leverage the purchasing power of forty or fifty companies for the Biocom Purchasing Group. You know, obviously, if you're negotiating for fifty companies you have a lot more leverage with the vendors than if you're a small company just getting started. So, yeah, no. I think these things have been very important. They, they're kind of the glue that holds the cluster together.

SHINDELL: Uhm-hmm. A couple of people who I've interviewed, for example Howard Birndorf and Bill Comer, they both pointed to Bill Otterson as being instrumental in sort of creating the atmosphere of San Diego biotech, of sort of collaboration among companies, and making people come together on a, on a frequent basis. Was that your experience as well?

RASTETTER: Yeah. Absolutely. Bill was an intensely social, collegial, collaborative, cohesive force in the community. Absolutely.

SHINDELL: Okay. Let me ask you something a little bit more maybe nuts and bolts about your experience with biotech. Prior to going into biotech I'm guessing you didn't have any experience with the patenting process and how that might affect the research process. Could you say a little bit about how patents – or first, you know, whether patents were an obstacle to you at first, or whether you feel like these things are important for the research process in biotech? You know, basically, what's your view on, on the patenting process?

RASTETTER: Well, patents are absolutely critical for biotech as it relates, let's say, to therapeutic product development. It took us, from company founding to the FDA approval of Rituxan took us eleven years. Now, if somebody could come along and rip off, if you will, that invention, those eleven years from us, the next day, there would have been no incentive to invest that capital. So, we would not have had capital to develop the product. I guess what I'm trying to say is that the longer the development cycle – eleven years is pretty fast, actually, from concept to, from founding actually. From concept it was seven years, which is perhaps a record for something of that magnitude. But, the longer the development cycle the more important patents become. If you can show what compositions matter, how to use them, what clinical setting, what doses, how to formulate, how often to treat, easy for somebody to come, come along and copy it. Okay? On the other hand, at the other end of the spectrum, devices that can be produced and marketed without regulatory approval, say, not necessarily for human healthcare, maybe, you know, a new mouse or a new flat screen or whatever, it can be developed in twelve or eighteen months, I think patent protection is less important because there's more than one way to skin a cat for those and the development cycle's much shorter. So, it isn't always obvious that someone needs to infringe your patent on your mouse in order to make a better mouse. But, you know, because of patent protection, Rituxan's been on the market for over ten years and nobody has come along and ripped it off. So, the incentive still exists for people to invest for a decade to a decade and a half to get these medicines on the market. Patents are absolutely critical.

SHINDELL: Uhm-hmm. Do you think that they've at all changed the way that academic scientific research is done now that there's sort of this model of university scientists patenting their discoveries, founding companies? Do you think that

university scientists think of their work in a different way now that there is the potential that they could, say, at, they're working at UCSD, they're so close to this cluster, if they have a discovery they can patent it and make money as well? Do you think this changes the way that they do their work or how they think about their work?

RASTETTER: Well, probably that question would be best answered by a group of academic scientists, and I think what you would find is that the answer is fairly personal and fairly individualized, and is probably, varies also by scientific field. Right? People developing nanoparticles within a Department of Materials Science are probably acutely aware of the importance of patents as it relates to being able to deploy their science, their technology, into the commercial sector. At the other extreme, a mathematician, who's developing a new proof of a theorem or something probably, you know, has no, no reason to even think about patents. Right? And so, I think it's, I think it's field-specific, but I think it's also depends on, on the individual. Some individuals may dream about starting a new company and participating, at least from their academic perch, and the thrill and the victory of taking a company public and getting products launched, and whatnot. I think those people will be more aware of the importance of patents than folks who may not be so keenly interested in the, you know, if they're more theoretically inclined. The theoretical physical chemist, for example, at least in certain fields, may not be as interested in doing that as compared to a biologist studying the immune system and how it can go wrong in autoimmune disease. Right?

SHINDELL: Yeah. Well, let me rephrase the question a little bit so you can speak maybe more from your, your own personal experience. Do you have university scientists come to you on any sort of regular basis, maybe, saying, "Bill, do you think this is patentable or do you think that I should follow this line of research?" I mean, do they look to people like you, with expertise in patenting or expertise in the biotech sector, with questions about their research and whether or not it's marketable?

RASTETTER: Well, I'm currently a partner in Venrock, which is one of the large venture capital firms, and so on a weekly basis I interact with academic scientists, or scientists who have licensed or proposed to license things out of academia. I would say that it isn't often the question, "Should I patent this?" It is often, "Look, patents have been filed, or patents have been issued, this is my intellectual property fortress and this is why you should give us some capital." So.

SHINDELL: So, they mark their territory first before coming to you, most of the time?

RASTETTER: Well, sure. If they're coming looking for venture capital they'd better have their IP ducks in a row or we probably wouldn't talk to them. [Laughter] Right. No, I think, I think people seeking to, to found companies and to get capital are reasonably sophisticated in these things, and we will always do a, an intellectual property due diligence through an outside patent lawyer or patent law firm before we invest. It's a critical step.

SHINDELL: Oh, okay. Now, back to the question of San Diego and Biotech Beach. How would you compare San Diego's biotech sector to say, you know, Boston's, and San Francisco's? Aside from the fact that things are closer together, do you feel like – well, how do you feel like this sector compares to those other two?

RASTETTER: Well, the other, the other two have a little more history under their belts, so the successful companies have, are older, and have gotten somewhat larger. I think that we see, however, the growth of successful cash-flow-positive companies. I mean, after all that is the objective, isn't it, to become profitable and self-sustaining so you don't have to always rely on NASDAQ and venture capital. But we, we see an increasing number of companies, who have made that jump, IDEC, now Biogen Idec, Illumina, Invitrogen, Amylin. So, I think we are maturing as a sector in San Diego, and the two most important hallmarks of that are more large companies, cash-flow positive profitable companies, and a greater diversity of the professions from soup to nuts that are required to run a fully-integrated company within the cluster. Okay?

SHINDELL: It seems like for a long time San Diego was very strong in sort of maybe the discovery side of biotech, but development was maybe stronger in these other sectors. And, do you think that development is maturing here? Is that, is that what is one of the hallmarks of a mature biotech sector and do you see that happening here?

RASTETTER: Yeah. Well, the conventional wisdom is that what biotech companies do is discovery, development, manufacturing, clinical trials, and commercialization. And, I think that often is a recipe for failure. I think that successful companies have to start with development, manufacturing, clinical trials, commercialization, and then go back to discovery. That is, they need to find something that is mature enough where a lot of the science and biology risk has been removed from it so that they don't spend all of their capital doing discovery only to find that they don't have

enough to show for it in terms of progress into the clinic to raise enough capital to actually get there. And so, I think one of the mistakes that a lot of biotech companies have made, not only in San Diego but elsewhere, is to think that if they focus on discovery and just do that well enough that people will come running to their door with more capital to take these things forward. Well, they ignore the fact that as you move down this pipeline from discovery, to development, to manufacturing, to clinical, to commercialization you're using more, and more, and more, and more money per unit of time. And, simply defining a molecular entity through discovery that you want to take forward doesn't reduce the risk sufficiently to get the investor to be so enticed that they're going to put this huge amount of capital into taking it forward. So, I think the staging, that is the point at which you decide you're going to raise capital and bring people together, is very, very important and I think it has to be around something that's fairly well understood so you don't have to spend, you know, twenty, thirty, forty million dollars to do discovery. So, yeah, I think that is being learned but I think it's being learned the hard way. Right. When we founded, when we founded IDEC the customized antibody therapy was already in the clinic. We already knew how to manufacture it, not cost-effectively but knew how to manufacture it. And, the things that we learned about formulating, about quality control, about the stability of antibodies, how to keep them in acceptable form for human delivery, the things that we learned about how antibodies are distributed within the body, how fast it takes them to get into lymphatic systems, all that stuff, all that know-how was directly transferable to Rituxan when we had Rituxan. So, and all of it was very development oriented but all, all that know-how, all that knowledge, all those skills were directly transferable to the new product. So, very important.

SHINDELL: And, was much of that sort of developed at Hybritech prior to IDEC? Because, they were sort of the first to work with monoclonals?

RASTETTER: Yes, but you have to realize that Hybritech was focused on in vitro diagnostics, where they're using tiny amounts of monoclonal antibodies. We needed to make grams at a time. When we started IDEC we knew we would have to deliver maybe three or four grams of antibodies patients for a full-course of therapy. And, in 1997, I'm sorry, 1987 I called my friend Charlie Benton, who ran Antibody Manufacturing Company in St. Louis, and I said, "Charlie, we've got to decide whether we're going to become experts at manufacturing or whether we're going to outsource manufacturing, and so I'd like for you to think about this question. I'm not going to negotiate with you. I'm going to ask you, as a preferred customer how much

would it cost if we didn't manufacture, if we did it all with you, how much would it cost per gram of antibody manufactured?" And, gave him some parameters about the hybridomas that we were using, and whatnot, and I said, "Just get back to me with a single figure. With that figure I can go to my colleagues and we'll make this very important decision for the company." And, he got back to me and, this is 1987 so 1987 dollars, and he said, "Bill, we would love to have your business and we think we can deliver to you, as bulk product, monoclonal antibodies for $5,000 a gram." Okay? I said, "Charlie, thank you. Goodbye. We're going to make them ourselves." [Laugh] Well, today Rituxan is made for – I don't want to give away any proprietary information – [Laugh] but let's say somewhere in the $100-$200 gram range, and you give, you give about four grams to a patient a year. Well gosh, you know, at Charlie's price the selling price is, I mean, what you'd get for bulk product. So, it would have been impossible with the technology back then. So the, the elements of process development, of how you do these things, on a scale that enables therapeutics is not something that Hybritech had developed, because they weren't using – I mean, grams of antibodies would be enough for ten thousand patients, right for in vitro diagnostics.

SHINDELL: Well, that's interesting. According to Birndorf, they were sort of convinced by their investors, when they started Hybritech, Brook Byers and others, that they should actually focus on therapeutics as well, but I guess they never got to that stage at Hybritech?

RASTETTER: You know, they, they tried for a while. I think it is extraordinarily difficult for a small company to have a business and cash flow and profitability that depends on one use of a technology to actually create and nurture a separate group that uses the same technology for a completely different purpose, where the cost of goods, where the delivery, the purity, everything else has to be extraordinarily different. And, now, did the acquisition of Hybritech by Lilly help Lilly understand the development of biologics? Don't know. You have to remember that Lilly took the Genentech process for human insulin and adapted it to full-scale fermentation and commercialized the human insulin way long before they, they bought, they bought Hybritech. So, I don't know. But, and certainly there was some knowledge about quality and formulation and so forth for human use that Lilly got from that. But, I think Hybritech will be remembered for their contributions to in vitro diagnostics. Certainly not for antibody therapeutics.

SHINDELL: Uhm-hmm. Let's see. I think you've addressed much of these sections. So, since we're coming up on an hour maybe we should go to the last part of the interview then. So these, these are questions that relate most specifically to your, your own career and your own experience. So, what do you think, based on your own experience, was the most important change in Biotech Beach during your time here? Do you think there was any one thing that stands out, or it may be even more than one thing that stands out as, you know, a pivotal moment in your time here?

RASTETTER: Well, the pivotal moment for me personally, professionally, and for the company was the approval of Rituxan the day before Thanksgiving 1997. [Laugh]

SHINDELL: Must have been a good Thanksgiving?

RASTETTER: Yeah. It was a darn good Thanksgiving. You know, cash flow, self-sufficiency, the ability to fuel your company through product, product sales is the objective of every company. I, [Laugh] I went to, I went to Havana, Cuba to teach a week of business school. I was part of a group from the Rockefeller Foundation and had been invited to go down and teach the tools of capitalism to the 1,500 people in Cuba who do biotechnology. And, I was asked to spearhead a group that looked at all their efforts in biotech, in Cuba, and what I saw was about 1,500 people doing human therapeutics, human diagnostics, or doing vaccines. They were doing transgenic animals. They were doing industrial chemicals by microbial pathway engineering. They were doing industrial enzymes. I guess thinking about commodity chemical production, and so forth. And, they asked the group to critique it, and I was the spokesperson. At the time they had commercialized, in countries where there was no patent protection, streptokinase for blood clots. They had alpha interferon for a variety of uses, and had hepatitis-B vaccine. So, they know how to develop stuff, okay? And, they were doing all this discovery research all over the place and when asked to critique it I said, "Well, look, it seems to me, based on the cash flow, that you generate from streptokinase, alpha interferon, and hepatitis-B vaccine that you can probably take four hundred of these 1,500 people that are doing biotechnology and call them "company" and take 1,100 and call them "university," and have the university do the discovery stuff and have the four hundred do the stuff that's very development oriented, that is closest to human application and/or commercialization, as the case might be. And, in order to do that you've got to pick one field because four hundred people can't possibly be good at doing all these things that you're doing. And so, pick something. And, it seems to me it's probably human

therapeutics, if you look at alpha interferon, and streptokinase, and hepatitis-B vaccine. Vaccine is not quite therapeutics, but I think that's what you should do." And, I drew this picture up on the blackboard where I had a dollar sign and then over the arrow the word "stock" implying the sale of equity in the company to fuel R&D. And then from R&D I had an arrow that came down. I'm going to form a full circle here. R&D to products to sales, generating dollars, closing the loop to R&D, and then I put a big X through the stock sales. And my point was that "If you succeed after you've seeded the company with selling some initial stock to venture capitalists, through the NASDAQ, whatever, the objective of any company has to be to become self-sustaining. In order to do that you have to know what you do, what you can become the best in the world at. And so, you guys need to focus and you need to separate this academia from corporate, and the corporate has to be incredibly focused on doing one thing and doing it better than anybody else in the world if you really want to succeed and have that circle get bigger, and bigger, and bigger, and bigger, because you have more and more products and more and more sales, hence more and more R&D and generate this, this perpetual loop, this cash flow machine." Well, I finished my speech, my analysis, my recommendation, and there was this room, it was probably 150 of the managers of the 1,500 people who do biotech in Havana, Cuba, and there was this complete silence. This complete silence. It was embarrassing. And, about two minutes later a guy who's in the very back row kind of leaned back in his chair against the wall, put up his hand, and he said, "Bill, here in Cuba we don't have to do that." [Laugh] I said, "Okay. Why don't you have to do that?" He says, "Bill, because at the end of the year Fidel writes us a check." [Laugh] Okay? Moral of this story, for me at least, is that unless you create a system where people have to make very hard decisions because capital is scarce, unless you create a system where people have to define what they're going to do and become the best in the world at doing it, then you spawn and perpetuate only mediocrity. And so, I think that the Cuban system will be fairly good at copying stuff that's been done elsewhere. They weren't the first to do streptokinase. They were the first to do alpha interferon or hepatitis-B vaccine. But, they won't ever create this critical mass of people that are so focused and so determined and so able to transcend this kind of pseudo academic, pseudo commercial atmosphere that they live in. So, I think the transformation that we're seeing in San Diego, to close the loop for us here, is that you are seeing companies that are not only profitable and very successful, they're very focused, they're cash flow self-sufficient, they're able to pile more and more back into R&D. You know, these are the Biogen Idecs of the world, the Invitrogens, the Amylins, the

Illuminas of the world. So, that's the real, the real difference and hopefully some of the smaller companies will learn from the business model that these people have applied. I think all of them have really stuck to their knitting and have applied their capital in a very focused, intense way towards single objectives that have gotten them to the point of cash flow self-sufficiency, profitability, and growth. I think the mistake that an awful lot of entrepreneurs make is they try to create their new companies in the image of Big Pharma that they left last year, and they say, "Well, I need to deploy capital and I need to diversify risk." Wrong. If you diversify risk across too many things, the way the Cubans do it, okay, then you won't have enough capital to deploy in a focused area to ever succeed. So, it is the investor who must diversify risk by investing in ten companies. The company, small company, who invests in ten projects is doomed to failure. And so, I think we are seeing the emergence of successful large profitable companies here that will provide, you know, some of that model for how it was done to the smaller companies who will take discovery out of academia, become very, very development oriented, extraordinarily focused, and hopefully become best in the world at their own little narrow niche in order to, to succeed as cash flow self-sufficient companies.

SHINDELL: And this has been your, your business model and you've been pretty successful with it. Do you think that, that your example has had an influence on the way that biotech is, is done here in San Diego?

RASTETTER: Hard to say. [Laugh]

SHINDELL: Hard to say? Okay. [Laugh] Let's see. Maybe I should just ask you now, you know, what, what should I have asked you? What didn't I ask you that you would like to tell us? Or . . .

RASTETTER: Oh, I think you did a pretty comprehensive job.

SHINDELL: You think so? Okay. Well . . .

RASTETTER: Thank you very much. [Laughter]

SHINDELL: Then let me ask you one last question. Is there anyone that you would recommend we interview for this project?

RASTETTER: I'd interview Jay Flatley, who is the CEO of Illumina.

SHINDELL: Okay. I don't think we have him on our list right now.

RASTETTER: Okay. Jay has built Illumina into a very successful company in the genome instrumentation space. And, I'm the chairman of Illumina, so I'm biased, but I think it's a, [Laugh] I think it's a great company.

SHINDELL: Okay.

RASTETTER: So.

SHINDELL: Well, we'll put him on the list then. Is it F-L-A-T-L-Y? Or, is that . . .

RASTETTER: Yes.

SHINDELL: Yes? Okay.

RASTETTER: F-L-A-T-L-E-Y.

SHINDELL: E-Y? Okay.

RASTETTER: Yeah. Yeah.

SHINDELL: All right.

RASTETTER: Yeah.

SHINDELL: Okay. Then if there's not anything else you want to add, I think that would be the end of the interview.

RASTETTER: Good.

SHINDELL: All right.

RASTETTER: Good speaking with you, thanks.

SHINDELL: Yeah, it was a pleasure.

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.