FREDERICK HAUSHEER ORAL HISTORY

COMPUTERWORLD HONORS PROGRAM INTERNATIONAL ARCHIVES

Edited Transcript of a Video History Interview with Frederick Hausheer Founder, Chairman & CEO, BioNumerik Pharmaceuticals

Recipient of the 1997 Silicon Graphics/Cray Leadership Award for Breakthrough Science

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DKA: Let's start with where you were born and your early interests.

FH: I was born in Iowa, in a very small town, probably 400 population, and I was there until I was bout four years old. We moved to Independence, Missouri. That's where I grew up. It was rally fun. I enjoyed my childhood. I had a lot of interests in a lot of things. I think I had a really good family. My father was a physician, and my mother stayed at home with us. I really enjoyed living in Independence and growing up there.

I had a lot of hobbies and interests in animals and fish, and all kinds of scientifically oriented things for kids. That's probably not too surprising, given what my interests are today. The nice thing is my parents always gave me the opportunity to explore and try things out.

DKA: You were exposed to medicine from an early age since your Dad was a doctor.

FH: Yes, probably before I could read, I was looking at books and pictures of things that he had. So I remember that pretty well, being exposed to it at a very early age. I wasn't forced into it, but it was just an interesting area.

DKA: He was a great role model for you.

FH: Yes he was. I think he was a person who really cared about patients. He always took care of people. He didn't push any of us to go into medicine, nor did my Mom. They were both very supportive of what we wanted to do when we were growing up.

I wasn't sure about going into medicine, because I thought my Dad worked really hard and he was gone a lot, and was too busy. I always knew I wanted to do something that was research and medically related, to try and help people. I had gone to graduate school and I was realizing that there were some really interesting things that were important now, but it's very difficult to take those things from the laboratory and bring those to a patient, and maybe they are not even relevant to a patient. So what I could see was that there was a gap between what a clinician is faced with on a day to day basis, and what a pre-clinical or basic scientist is doing. There's a gap in both of their knowledge. So I guess it was when I was in graduate school that I really started thinking about wanting to do something where I could go from the bench to the bedside with drug development. I wanted to do something particularly in cancer. I had thought about cancer for a long time too because my grandfather died from it, and I was very close to my grandfather. I was about eight years old when he died, and that had a big mark on me, because he was such a funny and pleasant person, and to watch what happened to his life, being taken by that disease.

DKA: You really saw that developing?

FH: Oh yes, I could see it happen. I talked a lot with both my parents about it when it was going on. It was traumatic for all of us because everybody loved him. He was hilarious, great sense of humor and all that, but because of that, I saw that many other people were suffering in the same way. I was more aware maybe than some kids growing up, in part too because of what my father was doing, and a lot of people had cancer. So I knew I was going to focus on something in that area.

DKA: You knew that from an early age?

FH: Yes, I knew it from a pretty early age, and I knew I was going to medical research of some form.

DKA: Did you focus on science in high school?

FH: I was pretty poor in school. When I graduated from high school, my GPA was about a 1.86. It was not very high, but I had very good SAT and ACT scores. I just didn't see any purpose in things. The only thing I naturally did well in was science and music. When I got to college, the light switch went on. My grades went up because I was doing something for a purpose. I did very well in college and in graduate school, and I went through medical school. I finished all the graduation requirements in two and a half years. I tested out of the first year. I don't like to do things unless I really see a purpose. That's part of my personality.

DKA: Were your parents worried about you in high school?

FH: Yes, but I talked to them a lot when I was going through that. I try to put some things back into the system in education. I think the problem for me in the school system is if I would have had gotten exposed to someone, a teacher who could have showed us some interesting things it probably would have been different, but as it turned out I think it was fine, because when I found what I liked I sure made the best of it. But in high school I was basically bored unless I was doing things that I liked, and I could make good grades in those things. The other things I just didn't care about.

DKA: Were computers or electronics part of your interests when you were growing up?

FH: Probably if I had another life or career it would have been in physics or engineering. I liked seeing how things worked together. I would take apart clocks as a very small boy, to look at how things fit together.

I guess from a computational standpoint, when I was growing up it was pretty primitive. I didn't really see much of that until I was in medical school. They had come out with the IBM PC. I had a very good background in some things, and then in graduate school I saw some of these things. I was at the University of Illinois, where they had a good computing group even then.

What I guess what I was interested in computing was the fascination with how the machine worked, how the memory worked together, software and those things. My background was biophysics in which we try to quantitate biological phenomena and statistics. Of course some of the mathematics that are involved in those areas are important, in quantitating observations. To do that more efficiently, you need to be able to calculate faster. In order to ask a bigger question, you need to be able to calculate in a more robust manner. I had all the basic background, without being formally trained as an electrical engineer, but I certainly had an appreciation for it. I guess by the time, some of this was getting more maturity, from a standpoint of knowing what I want to do.

I knew what I wanted to do by the time I had finished medical school and residency. I was trained in internal medicine first and then I went into oncology, which is the specialty of treating people with cancer. This was in 1985. It was 1986 I believe when the NCI purchased the first Cray (computer). I believe that was the first biomedical research institution in the world that had a supercomputer. So I was just down the road at Hopkins in Baltimore. I had gone to Hopkins because I knew I could do this bench to bedside approach. That's what I had really decided on. That was my whole purpose in going into medicine, was I knew I could treat animals or things in a petri dish, but I could probably never be able to get access to what the problems were in the clinic, or not understand them well enough. I wanted to be able to do that whole continuum. So when I went to medical school, I learned some things a little differently because that was the motivation. Hopkins was the kid of place that they want physicians to be trained to go from the bench to the bedside. When I got there I found a lot of people who shared that view and were good mentors for people like me in how to develop a career in that way.

What had happened is the NCI had purchased this Cray so I guess I was in the right place at the right time, and I had the right background. I had gone into physiology, biophysics, anatomy, medicine and computation. The computational side was more from the side of applications and problem solving. When I got to the NCI I didn't know how to use the Cray. I didn't know how to use the Vax, which was the front end of the Cray. What was good is that Hopkins was willing to let me go explore that as an opportunity. It was very risky from a career standpoint. I recall very well the pressure that I felt that we needed to be able to make drugs faster and better for patients with cancer.

I had taken care of a lot of patients. I had seen a lot of people die. That's what really drives me, and I think everybody here at this company, is that it touches all of us. However, when I got there I had never been on those kinds of systems. I think I was pretty comfortable with a PC, that level. It was not very difficult, but when I approached it on the Cray, and I think that's what helped me on this, I took that on almost like I took on learning medicine.

I said, "Okay, if I am going to do this, I have to learn how this works, and I have to learn it at a very, very high level. People at NCI, and actually some of the people that work here, remember that very well. They had a wall that had manuals that were on the hardware side of the architecture, and I took these home at night, and I would read them. I would read them well enough that I would remember most of the things that I looked at. It started to make a lot of sense to me. I would also get on the systems and understand about the operating system on the Vax, versus the job control language, which now they don't even use. It's almost like when you look at a problem with a patient. It was a very similar process for me. It's like being a detective. That's what internal medicine is like, you analyze and take things apart. I was in an environment, and I had mentors that very supportive of me doing that. I realized that I was a clinician, and I had a basic background, but I'm starting down this path to try to become somebody who can learn and use these very, very powerful systems to try to make something that is better for patients. This didn't happen overnight. It wasn't a piece of cake, but what I started realizing is that it was something that I could do pretty well.

DKA: This is a critical time in your life.

FH: A very critical time.

DKA: This was around 1985?

FH: It was 1986, and I would say that when I had gone there it was dawning a little at first because people would talk about the supercomputer. At first, hardly anyone would try to get on this thing. I really didn't care. I was sure that I was going to try as hard as I could try because I just felt like I didn't like the way drugs were being discovered. They were just randomly being screened, and I had seen what had happened to patients. We can cure some people with the disease, but they can't walk 10 or 20 feet because their lungs or livers were damaged. That's not an advance. The quality of life is just as important as the cure. So I believed that quantum mechanics was basically capable of describing the properties and behavior or any arrangement of matter, but the problem is, is having algorhythms and an approach, which would allow us to actually apply this to an area of patient treatment.

It's a complicated machine. It's much more complicated than an airplane. The human body is enormously complex, and when one gets to something like cancer, I think our understanding of that is growing and it's much better now, but you need tools like this. That's really what was at stake was whether or not I could learn some of these things. I think to the credit of both of those institutions, the NCI and Hopkins for basically for letting me go and supporting that, but also training me in medicine and the oncology field and the drug side. That was very helpful.

I couldn't sleep many, many nights, because I was concerned that I had to learn this at a level so that we could write programs, develop software to learn optimally on this very complicated machine. After a while, for whatever reason, I guess some people if they pick up a baseball bat, sometimes people can really hit the baseball, and I found something that I found something that I found very comfortable at swinging the bat at. What's happened since then is it has grown. I have gotten to work with others who are very good at swinging bats too.

DKA: It seems that your college and medical educations were just like a straight arrow at computer applications. Do you remember it like that?

FH: I think from an early age I knew I was going to be a medical researcher. Probably knew that as early as five years of age. I wasn't sure about practicing medicine, but I knew that I wanted to do something like that, because I thought it would be good to just help people. That would be a fun job. That's what I felt my Dad was doing, and he enjoyed what he was doing. It was clinical for him, but I could see that there were lots of other interesting things with that too, because I was exposed to that at home.

When I was in high school, I didn't see the application that much because I guess no one really took it that seriously in school. I liked college. I did very well in the sciences, and I did well in a lot of other areas too, because I worked on it. I found out there was a purpose for learning this stuff, but I really was pretty channeled past that point.

DKA: So through medical school….

FH: There was no doubt in my mind of what I was going to do.

DKA: That you were headed right into research.

FH: That's right.

DKA: Any reason you went to a certain school rather than another?

FH: I had some opportunities. I could have gone to some other schools that were more expensive, and that was a big consideration. We had four kids in my family, and my parents were committed to helping us get our education. I felt like if I had a choice there I shouldn't burn them. I can come out of this just as well with hard work. One of the things about going to the University of Missouri over some other places that was interesting is that I was coming out of a very intensive research background. And here was an opportunity to go to a place where they didn't have so much high-powered research on the basic side, but the clinical side was very, very strong. I felt like it was also good to be back home in Missouri.

So I went through school pretty fast as I mentioned. I guess when I was going there I thought it was a lot easier in some ways than graduate school because it's a different type of learning. Some people said there was a lot of memorization. I guess I had learned what I knew was important. I wasn't going there to just get a degree and go out and do private practice. That's important to do. I'm not putting that down, but it's not what I wanted to do. I wanted to do research. At the end of all this I knew that's what I was going to do.

So I learned medicine a little differently. I learned the physiology a little differently too. I'm a very mechanism oriented person. I am uncomfortable in a setting where I can't put together the pieces. I fell like that's very risky. I do the same thing with a patient. If there's a patient with cancer and they are having difficulty breathing, or chest pain, or some problem like that, or symptom, I try to break it down into pieces and then understand very clearly what's going on, and make a decision based on what you feel is happening. The other thing that was different about my schooling was the way I learned chemistry. I love chemistry. I think about things at the molecular level, not two dimensionally but three dimensionally. I am thinking about the structure and how it might be changed, and how it might fit, or how it might act, and that is something that is very helpful for this type of work. It's not something a lot of people do, but it's an important thing to be able to do.

DKA: So you did your medical work at Missouri and then you went to Hopkins, what was the chain of events that led you to go to Hopkins?

FH: That was another very important decision. When I was at Missouri and I had finished, you go through and you have some work as a student, some in the laboratory and the classroom, and then you go into the clinic. When I was going into the clinic I couldn't wait. I wanted to get all the basics done, medicine, surgery, and pediatrics so I could have a good basis. Then I knew I was going to make a beeline for oncology. I wanted to look at cancer problems.

I met a person there. He's one of the big influences of my life. His name is John Yarborough. Dr. Yarborough is an excellent teacher and he's also an excellent clinician. He is an MD, Ph.D., so he had done some basic research as well as taken things into the clinic before. I think when we met I was very interested in these little details about how the molecules work, and what's different about a tumor cell that we could try to attack it better and develop a better approach? One thing that he did in addition to teaching me many things that are relevant for being a good clinician, is also getting me ready for a career that was going to be pretty much in academic medicine. He also taught me a lot about scientific writing. I felt like I could write reasonably well, but he definitely took me to another level on that. These are things that are life long that some people shared with me. He really had a big influence and taught me a lot of things.

Another person at that time too was Richard Shilsky. He had just come out of the NCI program. So we had John Yarborough, Richard Shilsky and then Mike Perry. These people are very famous oncologists. They are very, very good. Mike Perry is an outstanding clinician. One of the books I've got over there on toxicity, chemotherapy, he's one of the top experts on that. What they did for me was prepare me very well for the future, not only in the clinic, but in the laboratory. When it was time to apply for the fellowships, and to apply for these you have to apply a couple of years in advance, and there are quite a few people that want to go there. They wrote supportive letters of recommendation, and I had done reasonably well in school. So I was hoping just to get in.

I had applied to Hopkins and NCI, and Seattle because they big marrow transplant program, which was an interesting area. Then I applied to Yale, Harvard, and I was just hoping to get into one of these places and thought I would be fine. It was really strange, I will never forget this day. I was in the clinic and within one hour I was called by all the places I had applied to, except one. The director of Hopkins called near the tail end of that hour, and he said, "You're number one for us and we would like you to come." All of them had said that same thing to me. So I had a dilemma there. I talked to Dr. Yarborough and Richard and they said, "These are all good places, but what you should do is think about going to Hopkins because you'll learn a lot about clinical medicine there that's important. And they have tremendous research capabilities. And if you want, you're right next door to the National Cancer Institute, and you can probably combine and get the best of both worlds." That was very good advice.

When I went up to Hopkins I liked it. I liked the people. So when I got there I was pretty much ready. I really was fortunate. I think if you talk to the people at Hopkins they will tell you this too, I was pretty enthusiastic. I still am I guess.

So I went through the first year, and the first year there is very busy with the clinical training. It's an excellent program for that, because what you do is you'll see more complicated patients than you can possibly imagine, just really difficult cancer complications. You get to do a lot of things that in addition to tumors from leukemia and also marrow transplants. So I got exposed to very level training with some very good teachers in all of those areas. I knew I was going to do drug development. We had talked about that when I was coming in. So I started in that area. My interest and some of the aptitude in computing, I was just ready for that to happen. When NCI announced that they had a supercomputer that they were preparing, I was thinking, I've got this background in biophysics, and I know a little about classical mechanics, a little about quantum mechanics, and maybe we can calculate something that would make a better drug for patients. I've actually been able to do that.

DKA: Who did you talk with about your plans?

FH: I talked about it with people everywhere. I talked with people at Hopkins. They were very supportive. A lot of programs they would say well, you work here, but I think they knew that it might be important for a physician to be able to apply things that we have learned in the clinic as well as molecular biology disease. There were clinical people, pre-clinical people, basic research people that were there, that were very supportive, and if that hadn't happened I wouldn't have gone there. I wouldn't have been able to go there. Steve Baylin and Mike Calden, who is a world class pharmacologist, and Steve Baylin is world class molecular biologist in cancer – and actually one of the first simulations I did on the Cray involved DNA manipulation. At that time it was extremely early, controversial as to what the role was in manipulation in the pathogenesis of human cancer. And as it turns out, it's probably more important than P53 tumor suppressor genes, which had been the big thing that a lot of the public now know of. That's because of Steve's work, but in part some of the things that we did on the Cray even then were helpful, because what we could see it what happens to the DNA in the tumor when it gets methylated.

I think what built this was, the people there at Hopkins were mentors and said, this is an unusual situation in terms of having a very powerful computer or technology, and we've got a young clinician, scientist who wants to try to see if he can do something useful there. So we're going to support him and let him try, see what happens.

DKA: Did you get programming support as well?

FH: When we went there I didn't want to bother anybody. I didn't want to cause any trouble. I told them, I'm an MD, I've not been trained in how to run the Cray, or how to run the Vax, but I've learned how to learn. I learned all the stuff on the Vax, the operating system, and got very comfortable with that too after a while.

What also helped is that I didn't have anybody telling me some of these things. I was just learning it. I think what's helped me all the way through is probably from the architectural standpoint, I have a very good understanding a supercomputer hardware, from the mapping. When we write software, I know how things will map to memory. How CPU's work, sectorization, how all this stuff works. NCI was a good environment for that because they had all the books so I could read anything. I could get on the system. Once I got on I was so bad at first I thought I made a big mistake because I didn't know how it worked yet. The thing that drives me, the best description I can give you is I am uncomfortable if I don't understand how things work. It just drives me nuts. I can't stand that. I also don't stop thinking about it. I will carry the problem around for weeks and just think about, why, and how it can be solved.

I got on and I was doing mechanical calculations. I did a very large number. I didn't realize how hard this was for other people, and I didn't have a problem because I had this resource, which at the time was state of the art. So I did thousands and thousands of calculations. I also knew what the drug would do in the clinic and the toxicities and some of the chemical transformations that were known or that were questionable. So I had an experience that was pretty unusual from the standpoint of having the opportunity to ask a very large number of questions, not just from a theoretical vantage but thinking about it from a clinical standpoint. You see that result and what it might mean in the patient. I was also still in the clinic. I was still involved in experimental therapeutics. That's all I have ever done in the clinic is experimental cancer treatment with new drugs. I think it sharpened my sense.

DKA: What particular drugs were you looking into at this time?

FH: There were several things that we were looking at. One was a big one, and still is an important drug today, is cyclophosamine. It's an alkalating agent and it's used for a variety of tumors. There are some questions about the way that the structure of that drug relates to certain of its chemical conversions and metabolites. Then there is a related compound, phosamide, which is structurally somewhat similar, but there are some distinct pharmacological differences along with some of the electronic properties. Today it's still a pretty big molecule to be calculating, but back then I didn't know any better. So I just asked the question. That's one thing that I learned as a kid from my parents is it's okay to ask a question. I'm absolutely fearless about that. I don't care if it doesn't work. I knew these were hard questions but it was important clinically to know some of these things. So I started taking these things apart. I got more comfortable with what could happen. We also looked at the DNA methylation, which as I mentioned we're working on that now because it has turned out that it's such a huge molecular abnormality in cancer.

So back in 1986, early '87, Cray came out with multi-tasking, which is the first version of parallel processing. So when I was thinking about was time to solution. We had a real sense of urgency about all this because so many people were dying of cancer, and we had used all these investigational drugs and we still do and they are very toxic in many cases and bad side effects. So I would have two processes looking at one problem, that's going to be wonderful. That's when I started looking really seriously at this. What I also did with these quantum mechanical and statistical programs, I went back through and read all the FORTRAN. Even today I have got those codes practically memorized. I know them so well because I worked on them for so long. I know how they work, and that's very important for this kind of stuff. What we started to do is make these programs faster. We also made them so they could solve much, much bigger problems. We were dimensioning the programs beyond limits that…no one had been there before.

DKA: What many people may not understand is why you need computers this powerful and fast? How would you explain that to someone?

FH: That's a really important question. We still need very, very powerful computer systems to solve these kinds of problems. These are grand challenge problems. Let me give you an analogy that I think maybe makes this more clear. If you have some people that are astrophysicists. They are experts. They know where to point the telescope and they can interpret what they are looking at. Let's say you give them something that's an 80-inch mirror scope, as opposed to an 8-thousand-in mirror, which is very high quality. They are going to see much farther, much better, and ask even better questions with the more powerful mirror. You need to be able to do that when you're working in an area like this, because it's so complicated. There is not one single experiment, or one clinical trial, or one test of a drug that can tell you everything you need to know. Another way of looking at that is the uncertainty principle that people talk about – I'll use that as an illustration. You can't measure the position of a particle and the linear momentum simultaneously. We were told that in school and I was okay sort of, okay I know that. That's really a pretty interesting problem. Why is that? People don't understand that. I think it's a big mystery. I think it propagates into what we see around us. In our laboratory when we make a drug, I can't use one method to determine that structure from the standpoint of the identity, the stability, etcetera. In a way that's like saying I can get the position but I can't get the momentum. Everything is like that.

The computer removes the limitation of the experimental condition. It lets you look at many, many things with one calculation as an outcome, based on some very good, well-established physical theories that are used every day. Quantum mechanics is used in a lot of other areas. You can add statistical mechanics as well.

You can look at the aerospace industry, the petroleum industry, the automotive industry; they can't do anything today without a supercomputer, or something in that class, to compete and to succeed. The human body is complicated enough. We need this to come up with better things for patients in the shortest possible time.

DKA: So when you were doing your calculations you were doing billions of calculations on the atomic level? How did you find your answers?

FH: You have to go around the problem and ask many questions. So I would break a drug down, or a system down to the smallest pieces. It was like I was telling you that's what we tried to do with every patient. It's the same sort of thing. It's breaking that down and then trying to quantitate the observation. The beauty of it is if you calculate, you can use that to guide and compliment what one is doing in the lab.

One of the most powerful proofs of an observation is not only the power of the experimental result, but it's when it's backed up by a mathematical proof. That's really what this is. You cannot do one experiment and know with certainty some of these performance attributes. When it gets into a drug, I can give you another analogy on this – say a drug is like designing a cruise missile. You can't even see the target physically, but you program it. It's got to fly. It's got to be undetected. It's got to go there not scorch the earth, which would be like toxicity if it was a drug, and you want it to hit just that target. You don't want it to hit the wrong thing. That's pretty hard to do. When you get into the body and you are making a drug, you've got to fly it through whatever route you have, whether it's intravenous or oral, or topical, but it's got to leave everything alone ideally, to get to the molecular aberration, and either interrupt that or modulate that, in a way that is desired. What this does is reduce the amount of questions and the amount of luck and guessing, because it's a model.

If you make a model on the supercomputer and you don't do an experiment, that's not good. You're going to have to always do the experiment. The difference is, is that those experiments can be focused very, very clearly into a yes or no. That's what is very helpful. That's how we've been able to do what we've been able to do from the standpoint of making comprehensive knowledge, hit the target with great precision, and can fly there. Flying there is just as important as hitting the target. A lot of people don't realize that in the pharmaceutical area. The focus in most companies today is, they go around the world, they get tree bark, slime mold, plankton, sea sponges, grind them up. And they put those products into little wells in cancer cells. So if it kills a cancer cell they say, oh, wow, this might be a great drug. I can put jet fuel, and shoe polish, and floor wax in there too, and it will kill cancer cells. But the whole problem, in addition to killing the patient, that's obvious, is the quality of life, and the toxicity, and safety, and the delivery.

That's what we do with this technology that is different. It is really designing a cruise missile from scratch. The other thing is, if you can engineer a cruise missile that was 99% correct, or let's say it's 90% correct, your chances for making something that is beneficial for the patient is pretty significantly improved.

DKA: Sounds to me, with the cruise missile analogy, that medicine is moving from a point of having just a weapon and a target, and what you are dealing with is a whole weapon system, and all the other things that are related in the scientific process. Is that accurate?

FH: That's a very good description. You have to be able to address safety as well as the targeting and being able to deliver it. The other thing that is nice is if you can actually make the drug easily, or more easily. That's probably the least consideration, but it's a very important one as far as the need for the drug.

What companies have done is try to approach that in parallel, and to send away things like the metabolism, or the possible metabolism and the susceptibility. Metabolism is like a chemical change of the drug from A to B, a B can be the active warhead, or it can be inactive depending on the drug. One of the things that we have done is develop software which is capable of addressing all of these considerations in a more or less simultaneous manner.

To go back to that telescope analogy, you need to be able to point that telescope with a team of people, and interpret what's going on. That's really important. You do not want to be pointing it at something that is meaningless. The only way I know how to do that, because it's such a complicated area, is to have a real multi-disciplinarian team in making the decisions about what we should be aiming at.

DKA: Let's go back to 1986, 87. You began at Hopkins, and then for a number of years you also worked with NCI. Can you tell us about that progression?

FH: This really took off. After about two, three years, we had made some pretty interesting observations that were important from a standpoint of a mechanistic understanding and possibilities that stimulated some research and interest in it. What we tried to do, because this all kind of leads up to the company, is we tried to at the time get the NCI interested in supporting the program, to do pharmaceutical discovery research for cancer patients.

We were there probably too early. This was in 1988. We went to the folks there and said, "Hey you folks have got this Cray and you've got some good experimental labs down the road in Baltimore, and we also have some good places to treat patients. So let's make a program for this. At the time they said, "Fred it's a great idea but nobody has ever done it before." I said, "This is a national lab, isn't this what we should be trying for patients?" They just couldn't see it at the time. Now they do. I think they embrace this, but I got frustrated.

I also realized it was going to be pretty hard to do this kind of research with just an academic level of funding. It's very, very expensive to try, because you need to have a multidisciplinary framework. I wrote about stuff in 1986, published, that was basically stating if you take a couple of areas like quantum mechanics and statistical mechanics, we should be able to apply them very productively to medicine. But we also need to have that fully integrated with chemistry, biology, pharmacology, toxicology formulation, all those things. Not as separate entities but as part of a discovery team. I realized that from the outset that it would be a pretty tall order, from an economic standpoint, and also from an operational standpoint. No one was thinking about that, and even today, it's not a widespread operational model. But I really believe in that. I believe in team work as much as the technology.

I had a lot of offers from pharmaceutical companies. They started getting some interest in this. I thought this would be good, that maybe they could finance this. I assumed they cared about getting the drug out quickly and all that. I'm not generalizing to all pharmaceutical companies, but what I learned from all that is that in a pharmaceutical company, they really do have a lot of fragmentation. They have each of these divisions, chemistry, biology, pharmacology, tox, and they don't talk. They don't; interact with each other on a regular basis. You have an x-ray crystallographer for example, and they're thinking about what they are seeing, and they are very, very well trained people. So they can speak the language that is in their discipline. Then you have a biologist, and they try to talk. The biologist is holding up gels, it probably looks like a Rorschach blot to the crystallographer, and the crystallographer is showing the electron density map trying to explain their exciting thing. There's a communication problem. These people that are experts at different things have a mind's-eye view that is different. You need to get a common language.

I think what has revolutionized that is the visualization of molecular medicine, molecular pharmacology that has been brought about by companies like Silicon Graphics. We use that system as well. Simulation is a very important tool because we have chemists, biologists, pharmacologists, all these people and we can teach and talk and all that, but there is nothing like seeing it. They see it and they can also design a better experiment. What buttresses seeing is if there is a quantitative explanation.

If you think about this from the standpoint of screening, and current methods, this is a very risky, difficult area to make a molecule that's really going to do something for a patient. Another area of science that is very well developed and important is probability theory. If you have a false start of failure in the clinic, that's really what you and to try to avoid, for the patient's sake and for operational reasons as well.

Let's say you went up into your grandmother's attic. Let's look at this from a probabilistic standpoint. So you're in the attic and you found a puzzle. It's an ancient Chinese puzzle. It's an 11th Century puzzle. The human body hasn't evolved that much since the 11th Century. So what you find is, you get the puzzle all together and there's one piece missing, and this puzzle has 10-thousand pieces. It's a pretty complicated puzzle, which is kind of like the human body. So what you do is you go to biggest puzzle store in the world in New York City. This store has over 1 million puzzles in it, and each of those puzzles has over 1 million pieces. The probability is you can go through all those puzzles and all those pieces and you will not find a match. And if you do, it's not going to match the color scheme.

That's the kind of problem this is. That's why it takes very powerful technology so that you're not flipping coins. It's more of a directed research effort, where you can use a supercomputer and a visualization system to describe the properties and behavior of a possible new molecule, or a very large of considerations that can be introduced into a new molecule. It's like if you took a cruise missile and let's say you had 10-thousand different types of nose cone, and 10-thousand different types of fuselage, different types of models, and 5-thousand different types of wings. You physically could not go through all those possibilities either. This is what we do at BioNumerik that is different. We can do a combinatorial perturbation on these systems, and we could not do this on a small system.

For one of our drugs, we have looked at over 12-trillion possibilities, and reduced that to a mere 300-thousand chemical possibilities in a matter of months. Then we took it from 300-thousand to 35 for synthesis, in a critical path. Everything we made in the lab was active in killing human cancer cells, a wide variety of them, in parts per billion. It actually created a very difficult problem for us in that, how do you pick the best one when just about everything that has come out is working in parts per billion or less? So we had to address that, but this is the kind of approach that you need to do, I think, and also you need to know that it's a very complicated problem and you don't want to just flip the coin.

Another analogy for you – let's say you have 30 people sitting around a table. You give everybody a coin and you want them all to flip heads. What's the probability that if all 30 people flip the coin that you're going to get heads? It's very low. It's 1 over 30 factorial. It's not impossible, but it's pretty unlikely.

If you approach it with a team and say, "The goal is to get heads and if you turn it until you see heads and then put your coin on the table," that's simplifying it, but that's really what's important. You have to tune people's observations. That's what simulation does, because they all can see this and they can see the result. Some people are quantitative about it too, and that means something to them. They can design a more efficient experiment.

DKA: You said that between 1988 and 1992 you were exploring different ways of putting a team together in an environment where you could design drugs as quickly and effectively as possible. Things weren't happening as quickly as you wished at NCI and with the pharmacology companies?

FH: I got frustrated. I realized it wasn't going to happen in this industry because they were so set in stone about how they had to approach this. They had to have these divisions. They kept everything separate, and after working with the companies I realized we had to do something different. I had made up my mind, before all of this, that is why I was going on this path, I really wanted to try to make some drugs that could cure people. I wanted to be part of a team that did that.

I decided I was going to have to make a company. I talked with my parents about this, and I also talked with some of my mentors, because I was going to do something that was very different. I knew it was different. What I was contemplating was making a company that would be solely devoted to this. My biggest concern was that I really believed that you could have the best science, but it isn't going to happen unless you have that managed with the best business. Business in this case is how you organize your team, and how you operate, how you finance, and many other considerations. It's more than making a lab and having computers, it's how do you make that into a machine to do this and do it effectively.

It took me a couple of years. I am not a risk taker. I try to be very careful, and I really wanted it to succeed. I knew I was making a decision that a lot of people would say put my life and my family at risk because I was going to put everything on the line. When I got ready for this I had read, to prepare, about companies that had been financed, and what the histories were. I had some friends that were in business and I had talked with them. I talked with others I had worked with in the past, and I remember talking with my Mom and Dad, and I was saying, :I'm going to do this, but I really would like to know what you think before I do. Is there any reason you can think of why I shouldn't do it?" They said, "You've got the desire, and you can probably go back if it didn't work out, but you have a very good chance of succeeding. You should try this because it's something that is worthwhile." That's basically what people I had worked with also told me.

I was just so frustrated because I knew the companies just weren't going to do this, and the academic environments just couldn't support this to the right level either.

DKA: How did you pull the resources together to make this happen?

FH: I haven't had any formal business training, but I definitely have the drive. It's the same kind of discomfort I have when I don't understand something. I need to overcome that so I do understand it reasonably well. So what happened was, I got a lease and moved all my file cabinets and records up here. I had no furniture. I was sitting on the floor. It was about four and a half years ago. I was by myself, and I thought, "Wow, this is really different." I took all my savings, everything, into the business and then I went out and tried to raise money. I knew I didn't want to raise money from venture capitalists. They are not all bad, but there are quite a few that are aggressive about how they view financing opportunities. I knew that I was going to being working on something that I would be into for the long haul. This is my commitment, and I knew it would be fairly valuable some day. So I wanted to protect that.

So I went to people that were different, institutions that were different. At first I didn't have anything other than what my background was and some of the results. People were willing to take a chance and my friends, people I worked with in medical school, and others, were willing to invest in me. So I financed this in a very different way. It was pretty unconventional. That's been very good because we have a group of people, shareholders, that understand much better what we're trying to do.

The other part of it is, I recruited an independent board of directors that are very, very successful businessmen, so that I could get good counsel in a lot of different aspects that are important to building a good company. These are people that have been very successful, but their interest in life by and large, is not to just make something and take it public. The motivation for them is, I think, the mission of the company. They've been very helpful in that regard.

Then on the scientific advisory board, it's more of the same. I think we have some of the best people in the world involved in the company, and it's not for show, it's for go. These are people that have been at the very top of their field, and it's relevant to pharmaceutical development, various aspects. Many of them are people who have trained me, have worked with me in the past. It's important to have people who will really tell you what they think, in business and in science, at all times. The objectivity is really important. You can make this arrangement of matter, a scientist makes a molecule or part of a patent, you can dream that this is going to be the one, and this is going to be the molecule that does it, but there has to be real careful testing of that to prove that. That testing needs to be thorough and efficient.

That's a part of what we do with the people. It's not only what's in the company, but it's what's surrounding the company to look at those things with a pretty critical eye. That's what has helped us.

The other part of this is, being able to take a very, very large and powerful telescope and ask huge numbers of questions, and to sum the aggregate of all those calculations to look at what's the best outcome that we can come up with? What the best missile after we've done all of those combinatorial perturbations? That's the best way I can describe it.

DKA: Did you find it easy to recruit talented people to come and work for you?

FH: I never felt afraid. I never felt the risk at all. People would warn me, but once I was ready to start I felt like this was going to go, because I knew the work. To get people here, for one, there are a lot of people that already knew what our interests were. So they said, "Can I come and work with you? I would love to be part of it." And these are people that are really good. Some were people that I knew before. We also put out ads for positions, but a lot of times we don't even have to advertise. Nationally and internationally, people know about this company now. They want to be here because it's fun to be a part of a team that is making something important. As a business, or as a goal in somebody's life, if you get to be a person in the company, or a research team, and you are walking down the street, and you meet somebody. And you hear them say, "I took this drug, and I'm alive because I took that drug," you probably would feel good about something which you had spent some of your time on. I think that's probably what is the most powerful recruiting tool that I have is that mission. People know that's what we're involved with. Talk to anyone here, that's why they are here.

DKA: What are the things that you feel proudest about, your successes in the early history of this company?

FH: What has been gratifying is to when you make a molecule and take it from the computer, into the laboratory where it's made, you test it, and this is a very, very difficult experimental model, including the animal models that we have to do, and seeing that works, and then on into the clinic and seeing that. It's been the first example of that. I think we're getting better as we go along. Every day there is something that we can learn, or we can improve. To me the most exciting thing is actually getting to be a part of that, watching that.

DKA: You set as a goal, cutting the development cycle. Have you been able to do that, and what's the secret in doing that?

FH: Yes, and it's the things that we have been talking about that are really key, and it's going to be hard for the industry to meet the change on some of these things, at least. You really have to have some significant computing power to attack these problems effectively, at least to get them done in a timeframe so that you can ask at least a set of questions a day, where your mind is fresh on it, and then get the answer go to the next.

DKA: Does it take a couple of years to do this?

FH: To do development, the industry norm for a pre-clinical - and this is from the time, not including all of the discovery time, but just from the time they first make the molecule, synthesize it in the laboratory, from the time they get what is called an IND, and investigational new drug application, approved by the FDA to start the first testing in humans – the average is five and a half years. The cost is very difficult to estimate, but it's millions and millions of dollars as the norm.

We've been able to reduce that to 18 months, and we've done that more than once, and I'm including discovery on that time frame. I think that's probably not been done before too many times if it has been done at all. That's because we have this type of technology, where we use supercomputing and the visualization on a daily basis to get these kinds of questions resolved. We can turn it around very quickly in the laboratory, in the same facility, in proximity to that. And all the data in the laboratory is online to the computers so we can analyze it, crunch it, look at it from a lot of different angles in a hurry. Then the other helpful part is we have done a lot of work at the clinic as well, so we're making the transition more efficiently because we have the experiences required for that.

One other point that I think is important- what we do with discovery here is a little different. We don't make something and try to go out and find out what it's good for. We don't make something because it looks cool. We start with the patient, the disease, from the molecular basis of the disease, and go backwards. As I mentioned before, we want to be comfortable that we can se how this might be helpful. So we break it down to the molecular and atomistic level to gain some confidence and understand about, "Okay if we do this, the likelihood is good that we're going to find or engineer a piece for that missing puzzle." It won't work with just blind screening and seeing if we can get lucky.

The other thing that has been important is if you make a novel chemical and you go to talk with a chemist who has made a blockbuster drug, and you ask him, "How many times did you have to try to do that?" A lot of people will tell you that they spent years on it, or many, many tries. The whole point about that is the experimental conditions required to make a new chemical entity or drug, are just as novel as the drug itself. And because of that, one thing that supercomputing and this approach removes is the conditions. You can make anything on the computer. You can ask the questions; is it targeting, can it get converted, all those things. My assumption is, if it's a very good drug, if it's going to work for patients, ultimately you can figure out a better way to make it. That's a real important piece to this.

To me the most exciting thing is just patients getting treated. What I'm really looking forward to is getting down to the observation of somebody that is alive because of what we are doing. I think that is going to happen pretty soon.

DKA: You've got things in trial now?

FH: Yes, they are not commercially approved. It's going to take still some time because we have to show to the FDA and other regulatory agencies that these things are safe and effective.

DKA: Do you think that part of the process can be improved?

FH: That's an important question. It's going to be important for regulatory agencies to find new ways to be more efficient about the process, because I think medicine is changing. It's important to recognize, if somebody has a serious problem like cancer, there are a lot of other serious diseases too but, it's pretty hard to beat the price of a pill in keeping a patient out of the hospital and healthy. That's a very important consideration from a quality of life standpoint. If you are a patient with cancer, wouldn't you rather get treated easily, without toxicity, and be home, not be in the hospital? The way it is set up now, it still is inefficient. Some of the hurdles may be that there are not enough people in the FDA, but the other problem is there needs to be some outside, independent review, that basically will look at this more quickly. They have made some progress, but my own experience with it is that some of these things could be looked at in a more efficient way that what they are currently doing.

There will be change because I think there are a lot of people that have these diseases, and they will push the government to do this, but it needs to happen all over the world. The other thing that needs to happen is - and there is an effort for this - is the harmonization. We're doing something that very few companies have done before, if at all. This is related to using a clinical protocol that is basically identical in the U.S., in Europe, and in Japan.

It's hard to get physicians to agree on what's the best thing to do, but we have endeavored to do that, and I'm excited about that. Part of what has helped us to do that is the quality of the data. The quality of the data is directly related to how we have used our technology. We've been able to dial this is pretty quickly on the performance attributes of the drug and the safety issues. We have saved a lot of time.

DKA: If this approach works, seems like developing drugs is going to be a whole lot easier. How do you think it's going to look like 5, 10 years from now?

FH: In five or ten years we're defiantly going to have people that are alive because of our work. We were all jumping up and down on several occasions here because we tested drugs and we've seen a curative outcome in some very difficult tumors. These are human tumors in the pre-clinical models. If somebody had something that would do that with a molecule that is a pill, I think anybody should be happy about that.

We're going to get better at it. We're going to get to appoint where we can do things probably more than just cancer. Hopefully this is an approach that I believe can be applied to any area of medicine that is amenable to pharmaceutical intervention, which is just about everything. We're dealing with the most complicated machines, but this is why and how we can do it, by using this type of technology. We're always going to need the most powerful systems to do this, and I think it's justified for a number of reasons, not the least of which is people's lives are at stake, or their quality of life, among other considerations. That is why it's something that deserves this type of attention from researchers all over the world, and it's getting it. I think there are a large number of people that are very committed to this. Fortunately we've had computer companies that have been committed too, to building these kinds of systems to let us do this type of work.

DKA: Do you think everybody is going to jump on the bandwagon and take this type of predictive teamwork approach based on numerical calculations to get these drugs developed?

FH: Ultimately, I believe it's the model that will succeed. It will be the most successful because of that. I think there is a lot of history of companies in general that have been very successful, that are focused on a team, and a technology, and a business model, that takes the problem, like what we do with the patient, they aim backwards, but then they apply that teamwork to try to generate something that is aimed at the right target. Yes, we will see that.

In this particular industry, what's going on right now is there is an innovation deficit. That is very clear. The deficit is because of some of the problems that I have mentioned. It's fragmented industry where there is some poor communication. The other problem that has led to this in the industry is that some of the people that are in these companies believe that technology alone will solve the problems. Our view on that is that the technology is only as good as the people that use it. It's important to have this team, and equip them with what they need.

A lot of people can go out and buy and use the F-18 – there are a few people who can fly an F-18 – the problem is, can you fly it at peak performance? The other part is, can you build custom parts for the F-18, and still fly it at peak performance? That's really what the attitude has to be. You have to have people. People always make the drugs, and if you equip them with the best available technology, they will be more productive. You have to have the environment, and you have to have the business operations to support that.

So what is going to happen in the pharmaceutical industry is that there will be a contraction. It's going to shrink in terms of the number of companies, because the lifeblood of the industry is the ability to innovate. If you cannot create a new molecular entity and the time to market is slow, there is no way you can survive in this industry. It's very analogous to the computer industry, look at the time cycles there for chips and other things. It's slower here because of the regulatory time that is involved. That's what has to change. To my knowledge there aren't a lot of companies that are doing this sort of approach. We have our own software. We have a propriety code that is over a quarter of a million lines, and it has been honed over a period of time to solve these problems. It still isn't perfect. I don't know if it ever will be, but it's one thing that helps us a lot. That's a custom part for our F-18. You can't design those unless you have access to these types of systems. That's the other piece. That's why it's important. That's why people like Seymour Cray, or Gordon Bell, people that made these wonderful systems, grew the industry, are important. There's no question that that will continue to be important, because you need to be able to always ask these kinds of questions. What we think is important now is only limited by our vision.

DKA: What would you say to a young person in high school or college thinking about going into designing drugs? What kind of advice would you have for them?

FH: I think it's a really fun area. What I do now is I have high school students and grade school students and college students brought through here and encourage them. I feel strongly about is, I am a product of the system, and I want to put some things back. So I have tired to encourage students by showing them what we have, what we do. I am hoping that if it's one person out of a hundred that does some of this, that it's going to be worth it.

What we need to do more of on the educational side would be embrace the notion that somebody should be a multi-disciplinarian in terms of their background. That happens at some places with the right people. They foster that idea. I sort of did it by accident, but I also had some people that were willing to let me try some things.

It's definitely going to be an industry that will grow. It will shrink. Companies will have to merge because they can't sustain growth because of the innovation deficit. A lot of the blockbuster drugs are going to be off the market by the year 2000. What they are doing now is using robots to try to synthesize 10-thousand compounds a year, just chemical substitutions that are not purposeful by and large. They can't even tell from that if they made what they thought they made, because the analytical methods in the laboratory aren't fast enough or precise enough. So what will happen is management in these companies will realize they need to have a team of people that know what they are doing, and make sure that there are no divisions between them, none. It shouldn't be a titled division. You are all discovery. You are all part of the team. They need to have rapid communication. They need to have computational models that are sophisticated, quantitative, and visual so that they can get rapid information.

The other thing that is going to happen, and we're going to do this too, is that there is definite application for this in the clinic. As we move through the clinic we are going to develop methods there too to try to make it more efficient, and how we escalate doses of the drug, or look at the best way to give it by simulating this based on the blood levels of the patient.

Even today it's one of the most successful industries out there, but the turmoil at the moment is the innovation deficit. That will drive them, and the survivors are going to be the ones – the best will be the ones that will innovate. The only way this happens effectively is through teamwork. There's not one person that is going to sit there and make the difference. There are so many components. It's very a very complicated process.

DKA: Those are all the questions I have. Thank you so much for your time and a wonderful interview.

FH: My pleasure.