Project: Genetic Engineering and Society Oral History Project
Interviewee: Mary-Dell Chilton
Interviewer: Matthew Booker, Alison Wynn
Also present: Chris Tutino (Syngenta) and Maurizo Lewis-Streit (camera)
Interview Date: February 17, 2016
Location: Hunt Library, North Carolina State University
Length: 01:12:59

START OF INTERVIEW

0:00

[Matthew Booker]: It's February 17, 2016 here in Hunt Library. My name is Matthew Booker. I'm here with Alison Wynn and Maurizo Lewis Streit and Chris Tutino with Dr. Mary-Dell Chilton. We're conducting an interview for the archive of Genetic Engineering and Society. Could you please tell us your name, your institution, and your role?

[Mary Dell Chilton] My name is Mary-Dell Chilton, with a hyphen. I go by Mary-Dell, not Mary. And my institution is Syngenta Biotechnology Inc. and my role—I guess I had a significant role in the discovery of the methods for genetic engineering of plants.

[MB] So on a daily level, what is it that you do when you're in your lab or at Syngenta?

[MDC] What do I do all day? I manipulate DNA [Deoxyribonucleic acid]. I work with large DNA molecules. The bigger they are [and] the more difficult they are, the better I like them. They're more of a challenge.

[MB] And how is that work done? Do you do that work alone or do you do that work with a team of people?

[MDC] It's a little complicated to explain how that is. I am a part of a team but I work by myself. That is, I have a particular part of a puzzle that I work on, but it will make a big picture with the work of other people.

[00:01:53]

[MB] So if you were to name yourself as a particular kind of scientist, what branch of science would you identify with?

[MDC] That's a difficult question to answer. My training was chemistry. Molecular biology didn't really exist yet when I was a student and plant genetic engineering didn't exist yet. I had no idea I would end up right here but it's been fun.

[MB] Did you start out as a child with an interest in science? Was that something you imagined yourself doing from an early age?

[MDC] No. I liked horses and I liked painting pictures and I liked all kinds of other things but I didn't know anything about science until I got to high school.

[MB] And what happened? Why did you become interested in high school?

[MDC] I took a course in general science. It was kind of a remedial course because the junior high that I went to didn't have any science classes. So as a freshman in high school I had to take a makeup course in general science. And the teacher called me in after school one day and he asked me whether I remembered some aptitude test that we had taken and we talked about that a bit. And he told me that I had done so well on the science aptitude part that the guys who handled the testing thought I must have cheated. They never saw a score as high as that. They didn't believe it. So he suggested if I liked science then it might be good for me to think about for a career. So that got my attention I would say.

[00:03:51]

[MB] And did you pursue science as a university student?

[MDC] I did, yeah. I started out as a—well we have to back up a little bit because where I started out from was kind of unusual. As a high school student I did a science fair project with one of my girlfriends. We made a telescope mirror and then all by myself I went on to make yet another telescope mirror. And I entered it as a project into the Westinghouse Talent Search and was lucky to be one of the top forty people that got a trip to Washington D.C. and that was great. And that [project] got me interested in optics and somewhat in astronomy but more in optics in how the telescope worked—how you design it [and] how you make the mirror. So I went to the University of Illinois because of the instate tuition. My father was, I would say, not prosperous. He was okay. He was not poor enough that I could get a scholarship but he was not wealthy enough to send me to a private school. So we were kind of in between levels. So I went to the University of Illinois and the closest [degree] to my field of interest was physics. So I started life as a physics major. And I found that I fell asleep in my physics lectures, so I changed my major to chemistry. And that kept me awake. I liked chemistry. So I stayed with the chemistry curriculum, as it was called, for the rest of my college career.

[00:05:44]

[Alison Wynn] What was it about chemistry that you liked?

[MDC] What I liked about chemistry— [As a chemistry student], I could ask a question that hadn't been answered yet. In physics, they seemed to know all the answers. Everything I asked they could tell me. But in chemistry I could see things needing to be done. You know, there were still a lot of mysteries in chemistry. And when I got interested in biology a little later on, that was even more the case. So that attracted me even more strongly. I like the unknown. I like mystery.

[00:06:30]

[MB] So what years, to put a year on things, what year did you enter the University of Illinois?

[MDC] 1956 and I graduated four years later. And it was not until seven years later that I got my PhD degree. I started out as a graduate student at [the University of] Illinois and my professor moved to Seattle to the University of Washington in the midst of my—after my course work but in the midst of my thesis research. So I went with him and I did my thesis in absentia. It took a lot longer because of that.

[00:07:11]

[MB] Had you traveled much before? Was this your first time in Seattle or outside of Illinois?

[MDC] I don't remember that I did a lot of traveling. We moved around a bit. The family moved around a bit. I traveled as a little kid. I came to North Carolina to live with my grandparents and that turned out to be a long visit. I was here from maybe age three or four until I was a teenager. And then I went back to live with my family. I never completely understood how that came about, how that happened, but I think it was—I had a brother who was a year and a half older than I was and he was a handful. He was mean to me and I think they were afraid for my safety, literally. He would tell me, "I'm going to beat you to a bloody pulp," and he meant it. So anyway, by the time I was a teenager I was big enough to stand up for myself I guess.

[00:08:23]

[MB] So it's a bold move to go to Seattle from Illinois. Were you, at that time, really committed to the doctoral work? Was that what drove you?

[MDC] To the graduate work? You know, the move to Seattle—the distance was nothing compared to the intellectual distance. I had been in the chemistry department and what we did was move to the genetics department. There was DNA in both. Okay, genetics is DNA but chemistry—DNA is a macromolecule and physical chemists study that. So that was where I started out, with physical chemists. So let's see, you asked [if it was] a bold move. There was nothing else to do. I wanted to go. I was ready.

[09:23:07]

[MB] So you finished up at the University of Washington.

[MDC] Yeah.

[MB] And then what? Did you imagine yourself being an academic? Did you imagine yourself returning to Illinois? What did you think would happen next?

[MDC] I wanted to be a professor of the genetics department at the University of Washington. I loved Seattle. It's a beautiful country. I loved skiing and hiking and all the Seattle things you can do. So no, I wanted to stay there. The colleagues there were wonderful. I expect every graduate student that you ask will tell you the same thing. They don't want to leave. Being a graduate student is a very nice time of your career.

[00:10:15]

[MB] So I take it you did not stay at the University of Washington or you weren't able to be a professor at the genetics department.

[MC] I couldn't get a job.

[MB] So where did you go?

[MC] I subsisted without a job—without a real job—that is to say. I never did get an academic job in Seattle. I had the problem that married scientists encounter, that my spouse had a tenure track position in chemistry in Seattle and I therefore—and we loved living in Seattle. Therefore, I had no way to go on a national job search. Seattle was it. There were two to three colleges/universities around there, but I wanted to do research. I didn't want to teach undergraduates and so what I did was I applied for any research position that came open, but the job that I ultimately took was one that I kind of created myself and that's the beginning of the Agrobacterium story actually. I've written this in the form of a memoire. It's published in *Plant Physiology*—about fifteen years ago I guess. What happened was I was at home after having my

second baby and after having been a postdoctoral fellow for three years and I got a telephone call. It was Helen Whiteley from the department of microbiology and immunology. I sometimes think that Helen Whiteley knew exactly what she was doing when she called me. She was calling me back from being a housewife—but anyway she's the only female faculty member I knew. Helen Whiteley told me that the department had assigned her a teaching post that she wondered if I might like to do it rather than she. She didn't especially want to do it and she thought it would be right up my alley. And I said, sure what's that? And she said, it's laboratory methods in DNA manipulation. And I said, great. When do we start? So I came in and I had a halftime—I guess it was an instructor's position, temporary, visiting, whatever—all those terms that we use for people that we pay less to do our work. Anyway I loved it. It was a great experience and, in teaching that class, I had a student named Tom Currier who presented a paper. I had my students each give a paper that illustrated some of the DNA methods that I had taught them about. And Tom Currier presented a paper on Agrobacterium and the paper that he presented showed that the—it presented evidence that a plant tumor was receiving genetic contribution from a bacterium that caused the tumor—which seemed like a rather wild claim at the time. There were two to three fragmentary evidences for that, but he presented the DNA evidence and the evidence was like this—If you took DNA from the tumor and bound it to a cellulose nitrate filter and then if you showed that it [the filter] radio-labeled DNA from the bacterium—the labeled DNA from the bacterium would bind to this filter. And that's supposed to show DNA homology. And they also did a control where they put bacterial DNA on the filter just to show they knew what they were doing. And they showed that their labeled bacterial DNA would stick to the bacterial DNA filter also. But the amazing thing was that it stuck to the tumor DNA filter much better—ten [two is more precise] times more as I remember it—which I knew, in my heart, was impossible. That just couldn't happen. It defied thermodynamics or something. So we talked [about that] in the class. It was a good paper to present because they hadn't done some essential controls and we talked in the class about what further controls could be done. And I could see how to write a very nice research proposal on this. And it turned out that Tom Currier was aware that Dr. Gene Nester, in the microbiology department, was interested in studying these tumors. So I went to Nester and I convinced him that he needed my DNA experience—that I could write a proposal and get us some money and create a job for myself. So he accepted my proposal and I went home [and started writing a research proposal]. At first he [Gene Nester] wasn't going to pay me [for my time], and I said, "You've got to pay me because I have to pay the babysitter!" So he did. It was against his better judgment, but he did. And we sent in the proposal under his name, not mine—I couldn't [sign it] because I [wasn't] a faculty member. And we were funded by two different agencies and we took the one that gave [us] the more money. And that created a position for me and a stipend for Tom Currier. And we were on our way. So Tom took the tobacco plants and inoculated them with Agrobacterium from the American Type Culture Collection, and sure enough we saw these little galls sprout on the stems of our plants and we could grow them in culture just the way it said in the literature. So the fun started there. It seemed as though the first two or three years of that project were spent

debunking published findings of other people—people who had done DNA experiments that seemed to indicate that there was DNA transfer from this bacterium to the plant cells—but we made model mixtures of bacterial DNA and plant DNA, and what we could show was that the techniques people were using were not even near sensitive enough to see it [bacterial DNA in the plant DNA] even if it was there. So we published a series of papers showing what was not in those tumor cells, and finally a discovery was made in Belgium that these bacteria had a communicable agent called a plasmid. And that plasmid was present in bacteria that were virulent and made galls on the plants, and it was not there in avirulent strains. And they proposed that the plasmid would be the tumor inducing principle. And so we immediately got busy with my fancy DNA technology and studied whether the plasmid DNA was in the plant cells. Finally, we had the right probe to look for it. If you're looking for the wrong thing, of course you can't find it. And we did not find the whole plasmid. I proposed that we wrap up this study by doing one final experiment, and that was to cut the plasmid into gene sized pieces and look for those—because if only part of the plasmid had been given to the plant cells, we wouldn't have been able to see it. So when we did that experiment, now for the first time we had clear evidence that something was in there and that was the beginning. We did a brute force experiment—the entire lab was involved in the thing because we labeled DNA that was so hot that after three days the refrigerator—it would suicide itself—it would blow itself apart. So we had to use it within three days. So we scheduled the thing to run over the weekend so nothing else would interfere. And on Thursday we would get the labeled precursor from New England Nuclear and label our DNA fragments, our plasmid DNA. And Martin Drummond was the specialist who took care of the labeling part of the project. It's easy nowadays—we have kits to do all of these things, but [at that time (early 1980s)] there we had to do everything basically from scratch. So Martin would label the plasmid and give it to me and I would give it to Daniela Sciaky, who would cut it into pieces with a restriction enzyme, and I would run it on a gel and do an autoradiogram to see that every band got hot. And then I would cut the slices [bands] out of the gel so we could separate each fragment of the plasmid and Don Merlo, on our project team, took [got DNA from] the gel slices. He made an invention—he put each gel slice in a little dialysis bag and he attached it to an electrophoresis machine—and he called this thing "the cow." You can kind of imagine what that looked like from the name that he gave it. Anyway, after electrophoresing for an hour or two, the DNA came out of the gel and was in the baggy so we could go in there with a pipette and suck that out. And then we set up DNA hybridization experiments. The idea of the experiment is that DNA renatures—when you separate Watson from Crick you can [incubate] anneal them at 60 degrees centigrade and they [Watson and Crick] go back together again—and this [the rate of the process] is concentration dependent, so if you make it twice as concentrated it goes four times as fast. So the idea was that if we put a little concentration of labeled DNA in a test tube and then put it in a lot of tumor DNA, if the tumor DNA had any copies in effect it would raise the concentration and it would make [the probe DNA] — the hot stuff — renature faster. So we did that and— What we found was that two of the fragments out of the whole plasmid indeed renatured faster in the presence of tumor DNA.

So we concluded that, that part of the plasmid apparently [had been] contributed to the plant cells by the bacteria. The idea had been around for a long time. We had debunked all the earlier evidence and now we had a new kind of evidence that it was hard to argue with. [After repeating this experiment several times], we wrote it up and submitted it to a journal called *Cell*, which was kind of the premiere journal for things of this sort, although there was nothing of this sort around really. It was sort of hard to decide where to submit this. But anyway the reviewers of the paper liked it but they wouldn't accept it because it was such an amazing claim. They wanted to see more evidence is what it was. So they said, well [one of the positive fragments is] you have a doublet band. If you could just separate band 3a from band 3b and show that one of them does it and the other one doesn't, then we'll believe you. Well we had no idea how to separate band 3a from band 3b. We tried a number of different things. Today it's easy but back then, there wasn't any decent technology for that. And I finally got the bright idea that what we could do is run this doublet band on the gel, and when it got to the end, cut it out, and cast some new gel around it, and run it down the new gel again. And [then] we did a third time, and each time the space between 3a and 3b got a little bit bigger. [After three trips down the gel, that space] finally it was big enough that I could get a scalpel in between [3a and 3b] there and separate them physically. So I did and we showed that 3b did it and 3a did not, and they accepted the paper. So it was a brute force experiment with a brute force follow-up separation of band 3a from band 3b. Many details of this process came out little by little by little. It took, I don't know, eight or ten years to unlock many of the secrets of Agrobacterium, how it does this and why it does it. In the end, it turns out that Agrobacterium is a genetic engineer. It is putting genes into the plants for the same reason that I might. It wants to improve the plant cell from its own point of view, not mine of course. It doesn't know me. But Agrobacterium wants food and those plant cells [with new DNA in them] make a new metabolite called octopine that Agrobacterium can eat. It can live off octopine as the sole source of carbon and nitrogen and most other bacteria cannot metabolize octopine. So it's a perfect storage form for a food, for agrobacterium, for the lone hunter—is how I look at it. It's quite literally being a genetic engineer. We went on to ask Agrobacterium—to ask the plasmid—how do you decide what part of this plasmid goes into the plant? Does the whole thing go in and then only the plant cells that get this part grow out as the gall? Or is Agrobacterium clever and it puts in only one of the parts of the plasmid. It turns out that sort of both of the above are true. The process is a little bit ragged but basically Agrobacterium aims to cut out a part of the plasmid. It has some repeats in the DNA sequence at the beginning and end of the part that it transfers to the plant cell. Very clever. It's a slightly imperfect process because once in awhile it skips the border and puts in the entire plasmid or more of the plasmid. But basically the intent is to put in this particular part and in this part of the plasmid—what it does is it causes the plant cells to synthesize octopine and it causes the plant cells to make two plant hormones that make it grow. So it makes cytokinin and it makes auxin. It takes three genes to do that. So we called this T-DNA (Transferred DNA) because it moves from Agrobacterium to the plant cell and, you know, in one of the tumor inducing plasmids there's a series of about fifteen genes in T-DNA and to this day we don't

know what they all do. We know about the ones that are there [common to] all the different kinds of Ti plasmids. We know about the octopine gene — or [another type with nopaline genes (we call these "opine genes")] the nopaline gene, the opine genes, and we know about the plant hormone genes. But there are some other mysterious genes that—I think there's more to be learned from Agrobacterium yet. And nobody's working on that that I know of. Interesting. Next question?

[00:29:10]

[MB] Yes well I want to ask you a follow-up because you described a fascinating intellectual problem and question that you pursued with a group of people and you described the realities of that took, running a proposal, convincing this professor to pay you to do the work so that you could pay others to give you childcare. But what did you imagine this basic research question might result in? Did you have a sense of how revolutionary the discovery would end up? You said it took about eight to ten years for the full ramifications to play out. But at the time you were doing the work, did you think that this would have applications beyond answering a fundamental question? Were you interested in those?

[MDC] You know at the beginning, before we knew about the DNA transfer, I was in it to debunk the whole story. I didn't believe it. One of the reasons I didn't believe it is I was more of a bacteriologist than anything else. I had done my post-doctoral work on bacterial genetics and what I knew from all the bacterial genetics that I had studied was that in order for DNA to go into a different bacterium and get integrated into it—in order for that to happen it had to match. It had to be from the same kind of bacterium. So the whole concept of a bacterial gene getting into a plant and functioning was wildly impossible and it would never work. I didn't believe it. So this last experiment that I described to you—this was going to kill the whole idea once and for all. This DNA is not in there. And what we found when we did the experiment was that it was [in] there. It did work. We know now that DNA in animal cells and in all God's creatures—it seems like—if DNA is put into a cell it does get picked up by the chromosomal DNA. And the reason for that in hindsight, I think—this is not the proof, this is my view of how it is. I think this is right. I think the way that it happens is that chromosomal breaks occur now and then in the cell and it has means of repairing those breaks. It puts ends of DNA together and when it sees a T DNA floating around in there, it thinks that's a chromosomal end and it puts that into the first break it sees. So I think it's a normal plant process and it's a normal animal process and Agrobacterium somehow cleverly got onto that and used it—exploited it. Okay you were asking did I know where this was all going? No I wasn't—once we knew that T DNA was going into the plant cells—I was so busy being amazed by what I saw going on in front of me, I wanted to know how it worked—what made it tick. How did Agrobacterium do that? Because it was a marvel. It was absolutely surprising. It was an interesting thing. I went to a Gordon Conference every summer on plant molecular biology and the plant molecular biologists couldn't get enough

of this. They loved it. They loved this story. They sat on the edge of their chairs when I got up to talk about it. Every year I had one more piece of the story—one more element about how it worked. My competition was in there working on it too. The earlier guys who had proven with some of these spurious experiments that the DNA was in there—they had come along behind us and convinced themselves that indeed this was right. And there was plenty of competition. There was competition from the laboratory in Belgium [where] the author had written that paper that Tom Currier discussed in my class and that people—a different laboratory had discovered the plasmid in Agrobacterium—so those guys were in Belgium and then moved to Germany—that was Jeff Schell and Marc van Montagu. I didn't really think about the applications for this. Maybe in the back of my mind, but I had no idea. My big concern was would I ever get a job—I'll never get a job. Here I was, sitting in Seattle, and finally it happened that it was time to leave Seattle. I think the collaboration with Gene Nester—I think he got tired of people giving me more credit than I deserved probably. It was a true collaboration. He did his part of this work and I'm the first to admit it. He believed in some "foolish" things that I didn't believe in and he reproduced some findings that I would never have done, but the fact that he had done it put us way ahead in the competition. So it was a good collaboration, but nevertheless it was time to go. So I did go out and look for a job on the national market and Washington University in St. Louis seemed delighted to get me to come there. It cost my husband an important part of his career. He was, by then, an associate professor with tenure in chemistry, but he was a good sport about it. And we moved—[Washington] the University made a laboratory for him to work in and he collaborated with me and he collaborated with all kinds of other people. And it was a biology department so he found plenty to do there and he had a good time [doing research with] no teaching responsibilities. So that was good. We stayed in St. Louis for four years and we would be there yet but for industry coming and looking for a new director. I had a visitation from Ciba-Geigy executives—there were three of them that came to my lab one morning and talked to me for a couple of hours. And they wanted to know whether I'd be interested in being considered a candidate. And so I talked with Scott about it and we recognized that this new lab was going to be in North Carolina. We recognized that our parents were getting older and they lived here. So he was agreeable to move. He had nothing further to lose at that point.

[00:38:02]

[AW] So what was the culture—how did the culture diverge in industry than it was when you were in academia? What sort of switch was that for you other than—so you're going to a lab that the way they were run—how you felt being in, you know, sort of one institution to a different type of institution?

[MDC] It was very different. I suppose if I had known at the beginning [what] I know now; I probably wouldn't have taken the leap. I had no idea how hard it would be. I mean it wasn't like I was moving to an established thing. There was nothing. My job was to recruit scientists.

We had zero. I had to recruit them all. And we had put up a building. We had to settle the issue of where the building was going to be, and put up a building and develop a portfolio of projects, and talk to academic people who needed a hand, and make friends around here. I was probably best at the recruiting part. I built us a nice lab. It's a beautiful lab. And I think that [during] one of our earliest projects we discovered that it was kind of an unhappy marriage because the only plant I knew how to do anything with was a tobacco plant. And we were not in the tobacco seed business. That was no business. Ciba-Geigy wanted me to make transgenic hybrid corn seeds. So the first task was to hire a tissue culturist who knew something about corn plants. And we did. We got Christian Harms to come and head up our plant tissue culture group and he was pretty good but corn turned out to be very challenging. Not only did corn not like to regenerate but Agrobacterium hated it. Agrobacterium was a pathogen of dicot crops—these are broadleaf crops. And none of the food crops is a dicot except soybean and cotton—cotton is kind of a crop, I guess. So the first thing we did was we bought a cotton [seed] business and thought about what we could do for cotton plants in the more near term because we could see it was going to be a while before we could make genetically engineered corn plants. So the BT cotton project was one of our earliest efforts. Even that turned out to be very challenging but putting BT into plants—I think it's one of the greatest achievements that the whole field has made for farmers and for people—for the environment. You know, most of the insecticide used in agriculture is used on cotton plants and we replaced a lot of that insecticide, not quite all, but we replaced a lot of that by putting BT into the cotton plant, making it insect resistant. So that's a very big achievement that I feel very proud that we did. I got lost in the middle of that question—let's see. Did I answer what you asked me?

[00:42:47]

[AW] I think so. I was really wanting to know sort of the difference in what the culture was from one to the other and I think you did it a decent amount.

[MDC] Yeah I didn't really answer that. I'm not sure how to answer that. The thing is, in industry, the attitude is get it done—achieve. And in the university, it's publish or perish. And those are different things. The difference is, you know, in academic life something has to work well enough to publish a paper. You have to have a significant difference—a significant improvement. But if Ciba-Geigy wants to sell a corn plant to a farmer or a cotton plant or whatever, by God it had better work. It had better work every time and no messing around about it. No marginal effects, no working every other year, none of that—it has to work. So industry has a very can-do/must-do attitude. And I like that. I think I have the mindset of an engineer rather than a fundamental scientist. So what it meant was that the resources were there. If we needed something we could get it, whatever it was. If we needed a person we could go get him.

[00:44:36]

[MB] I'd like to ask you another follow-up about something you've said before. You mentioned that the only women you knew in an academic position was Helen Whiteley—I think that's the way you put it. And she was very important to you in a particular moment in your career. We've noticed in our interviews that there seem to be more women in biotechnology than some other fields of science. Was it your experience that there were women around? Or were you alone in many of these kind of critical moments as a graduate student, as a faculty member, in industry? Were there other women around or were you pioneering?

[MDC] There were other students but there weren't any women on the faculty that I could remember except Helen.

[MB] And did that matter? Did you think that that mattered? Did it have implications for your work or for the career?

[MDC] Well it probably added a little fuel to the fire of my concern for whether I would ever get a job. But Washington University hired women. They had a lot of them. They had four or five in the plant biology program.

[MB] And was that fifty percent of the faculty?

[MDC] Maybe not quite but they had a lot compared to other places. Did it bother me? No I don't think so. I guess I always felt like I didn't want to be hired or advanced or anything because I was a woman. I wanted to be advanced because I was the best. So I made myself the best. I was the best in school. I made straight As. My graduate professor—my thesis advisor told me that I was his best student recently. I was only the second student he ever had. That was Benjamin Hall.

[00:47:28]

[MB] You've mentioned a few people—a few names along the way—some of which are quite well known in the history of genetic engineering. And I'm wondering if there were particularly important figures for you in terms of collaborations like master, for example, or others once you entered industry. Were there people you collaborated with in industry or people you competed with in those early years in industry who you thought were particularly significant in pushing your own discoveries?

[MDC] Well I haven't mentioned the name of Ernie Jaworski. Ernie was very important to me at the time I moved to Washington University. That's a little earlier than you're asking about. But he contributed two post-doctoral stipends to my project and without that I don't know where I

would be. He set me ahead by a year or two when he did that because I would have had to apply for grant support and I wouldn't have had any people in my lab for a while. So Ernie was an early believer and supporter of my work.

[MB] Who is he and why did he do that?

[MDC] He's retired now. I don't know exactly what his title was—but he was a high executive at Monsanto and he was the one who set Monsanto's feet on the path of genetically modified plants. That was his brainchild and it changed the whole company. He hired all the young people and set them to work. He sent Rob Fraley to my university lab to collaborate with me and suck all the information out of my lab that he could find.

[MB] Was he one of the two post-docs or were those separate?

[MDC] No he wasn't my post-doc. He was an employee of Monsanto. No my post-docs were—it turned over—but Michael Bevan was one. Ken Barton was one. And Annick de Framond who works at Syngenta now was a graduate student in the lab at that time. And Tony Matzke. These people have gone on and done very well for themselves. I'm sure I'm forgetting a few names.

[00:51:03]

[MB] Your comments about Monsanto and the funding of post-docs and Fraley's presence and so on are a reminder of something that I've noticed in—they're a surprise in some ways because some people believe that there's a hard line between universities and industry. This is a common perception out there in the world and that's not your experience. Could you discuss this idea or how this worked in your own experience?

[MDC] I don't know how that is as a general thing but certainly at that time it was a real fuzzy business. They needed to get up to speed and I was at speed and I think that's why he really gave me those post-doctoral fellowships. It was his entrée into my lab. I was so grateful I would have washed his feet. I would have done anything for him. I taught a course in Recombinant DNA technology at Washington University and some of Ernie's people came and took my course. [They] weren't always the best ones in the class.

[00:52:36]

[MB] So when you moved over to work for Ciba-Geigy it wasn't the first time you had interactions with industry, of course, as your describing. But was there a fundamental shift? You've already described some changes but was it less of a shift working with industry?

[MDC] I worked with Monsanto but the relationship between Monsanto and my research team was I think kind of unique. Monsanto had a relationship with the whole biology department that was also kind of unique. They contributed a couple of post-doc fellowships to the plant biology program—that's in addition to what they gave me. And exactly what Monsanto got for that I'm not sure. But I know what they got from my program. They got information. When they went to find out some detail about something, Ernie would ask me questions about this and he would say, "Why don't you write me a proposal about that?" And I would start a project like that. So I'm not critical of anything that happened. We got it done. Okay I was happy. I assume they were happy.

[MB] But in some ways this comes back to your point about publishing versus producing—that is when a researcher publishes her work, it's out there for the world to see and she's staked a claim on that work. When something is produced, it's not as obvious, perhaps, who did the work to make it happen because there may not be a publication involved. Is that what you're suggesting or am I misunderstanding? I'm trying to understand the difference between the two ways of creating knowledge and how they're acknowledged by the wider society.

[MDC] Well you file a patent application is one way. We did—only one. But that one was a honey. And that is a quite interesting story but I'm afraid it's not my story to tell—I don't know. I've never asked. Chris, do you know any more than I do about whether that's regarded as secret stuff?

[Chris Tutino] I think you should feel free to speak about it because we can cut it out of anything that would be publicly available. That's the agreement that we have here.

[Track 1 ends; track 2 begins.]

[00:56:17]

[MB] Matthew Booker here on February 17, 2016 with Alison Wynn and Maurizo Lewis-Streit and Chris Tutino with Dr. Mary-Dell Chilton. And we're back interviewing you again. One of the last things you said was that you had filed one patent but that it was a "honey." Why was it a "honey"? Tell us what you mean by that.

[MDC] Well one of the issues with which the patent office was dealing back in this era—their very first [question] was could you patent a plant? And eventually it came down that indeed they did allow a plant to be patented—a different thing from a plant patent. This was a utility patent on a plant. They did allow that. A second issue that the patent office was dealing with in the whole of biotechnology was how broadly to [allow] an issue of claims. Applicants would write

very broad claims and sometimes did, but often did not, deserve such broad claims. And the patent office would ask the inventor, "Did you enable that? Did you describe how one would actually do that?" That's how they decided how broadly they would allow you to claim things. So the one patent application that we filed that I said was a "honey"—the history behind that story [went that] there was a race to produce a genetically modified plant and the different—when Agrobacterium causes tumors on plants, you get a material that's a gall and it has unusual properties. I mentioned that the cells make auxin and cytokinin and apparently because of the abnormal levels of auxin and cytokinin in the cells, these plant cells are not able to regenerate into a complete plant. You could sometimes get a shoot, but you couldn't get roots or there were different fertility problems. But you never could get a complete plant that would pass the trait to the progeny. Except once in a while you'd get a complete plant out of it, but when you looked, in fact, it had deleted all the T DNA that you put in there. That's why it was able to regenerate. So the race was on to figure out what was the matter, why that was happening, and what one could do about it. And I think we all had the idea that you could disarm the T DNA that Agrobacterium put in the plant. You could somehow knock out whatever gene was preventing the thing from regenerating. So we were working on that sort of project and we modified the plasmid. And when we tried to get the gall to grow, it kept dying on us. And finally I asked my friend Andrew Binns at University of Pennsylvania if he would help us, because Binns was good with tissue culture, especially with tobacco tissue culture. And so we sent him the material and he called me up a while later and said he had figured out why we were having trouble. He said, "What you needed to do was feed these plant cells a little cytokinin. You apparently knocked out the cytokinin gene, so it doesn't make its own cytokinin anymore." So he said, "They are very happily growing. I put a little cytokinin in the medium." And he called me back a couple of weeks later and said, "They're making these beautiful shoots." And I said, "Oh that's nice." And he called me back a couple of weeks later again and said, "They're making roots." And I said, "They're doing what?" This had never happened before. And he said, "The roots are making nopaline. This is transgenic stuff." He had regenerated dozens of genetically modified plants with our stuff. And he got these plants to flower and set seed and the seeds still made nopaline. They still had lots of T DNA in them. So we knocked out a [gene at random] and the first thing we hit was apparently the crucial gene that had been blocking regeneration with this plasmid. And I knew that this was important. I thought that we ought to file a patent application but the university patent office—this was at Washington University—was not interested. They had spent all of their money on someone else's patent and they didn't have any budget left for this. And well it got to be November and I went to my mother and dad's house for Thanksgiving and I told my dad this story about how we had invented the wheel and the university didn't file for a patent on it and my dad, who's this corporate boss—he was a president of the Continental Insurance Companies—and he said, "Who's the big boss?" And I said, "That would be the Chancellor, I suppose." And he said, "You go talk to the Chancellor." And I thought, oh that's an interesting idea. So I went to the head of the plant biology division, Joe Varner. And I said, "Joe we need to talk to the Chancellor." I told him about this invention problem and so he called

up the Chancellor and the next day we went to talk to the Chancellor. And I didn't really need to say very much. Joe did all the talking. He knew exactly what we had done and he told the Chancellor, "Mary-Dell has invented the wheel. You could use it for anything. You could make whatever." That was a high moment, listening to Joe Varner extoll my plants. Anyway, the Chancellor shook my hand and he said, "I'll have a patent attorney in your office tomorrow morning at eight o'clock. Be there." And he did. So we started writing and because we had made the first genetically modified plant that kept its T DNA, didn't delete it the way all the previous ones had, we thought we should be able to claim the moon, you know. We can claim all genetically modified plants because we have proved in principle that a plant can tolerate having all this T DNA in there. So we did write very broad claims into that. It was an interesting exercise because this patent attorney was a chemist and he had no idea what we were talking about. But he wrote it all down and we got it done and got it filed. The filing date on that patent application was just a few days before the one-year deadline passed. If you have spoken publicly about it, you have one year to file in the United States. You shut [lost] your international rights, but you have one year to file in the U.S. This is the rule. You have one year to file in the United States before you've lost your possibility of having the patent. So we got it in just in time. And I went to Miami to a symposium in January 6th or 7th of 1983 and talked about these plants. I talked about the fact that we had progeny and that the progeny still had all the DNA in there. And time passed. Ciba-Geigy came and hired me away. And the sole patent application was lurking there in the patent office and about once a year I'd get a letter from them saying, "Well we've had an office action. What do I answer to these questions?" I would fill out the form and send it back to them. And then after three, four, or five years, Washington University called me up. They had a new patent lady there. Universities were hiring patent agents by then. And she told me, "I'm sorry to tell you that we're going to abandon your patent application." And I said, "You're what?" And she said, "Yeah, it's too expensive and it's taking too long. It's dragging on and on. And we just don't have a big enough patent budget to do that." And I said, "Hang on. Let me make some inquiries here." Because I knew that Ciba-Geigy would likely be interested in this patent application. And because I was involved in it, I had to get my hands out of the thing and I turned the whole story over to the patent attorney that we had then at Ciba-Geigy. And he went to management and other people made decisions about what to do because I was certainly not a disinterested party. But anyway the patent made it alive and I don't know how much money got spent on it but I feel sure it was in the millions of dollars—probably not very many millions, but probably millions of dollars of prosecution to hire a fancy New York law firm prosecuting this thing. And the prosecution went into a pause because the patent office had recognized that there was interference between three different patent applications that they had—three different parties had applied for basically the same invention. It wasn't exactly the same. It was different language, but basically only one of them could be issued and they had to decide who would get it. And that is kind of the end of my knowledge of the story. I don't know. We merged with one of the companies and so we acquired one-third of this three-way interference. I think three-way is the right number. It might

have been four. So that left us and I think Monsanto and maybe that was all in the interference. And somehow or another a bunch of lawyers got together and they decided to stop spending money and start settling. And I don't know what the terms of the settlement were but suddenly peace reigned. My Swiss bosses way back at the beginning had told me that there was what they called "bad blood" between these companies. I can imagine but I've never fully understood what that meant. I gathered that some unfortunate thing must have happened in the past that was remembered on both sides, but I don't know, to this day, what it was. Anyway our patent did finally issue and I don't know what happened to the patents of others. That's as much of the story as I remember. But it was enough. It was good.

[01:10:40]

[MB] Were there direct consequences for you when the patent process completed? Was it something that affected you in any particular way?

[MDC] Well yeah. Some royalties went to the inventors from Washington University. Okay this is still Washington University's patent. Ciba-Geigy—when they acquired the rights to it, they didn't acquire the patent. I think you don't transfer the ownership of the patent. So it's still a Washington [University] patent. And the arrangement between Ciba-Geigy and Washington University or between—it's not even Ciba-Geigy, it's one of the legacy company names. We've had three names up until now. And the terms of the agreement between Washington University and this company—whatever name they had—have changed actually, because I think the attorneys were worried that the first arrangement that Ciba-Geigy made with Washington University would look exploitive. So they went back and were more generous with the university then they had been. That's kind of hard to believe, isn't it? But it happened. I was told it happened. The university told me that it happened. So I guess it did. It's interesting.

[01:12:29]
[End Interview]