PROJECT: GENETIC ENGINEERING AND SOCIETY HISTORY PROJECT
INTERVIEWEE: JOHN RYALS
INTERVIEWERS: MATTHEW BOOKER, KATHERINE RINDY, AND ALISON WYNN
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[Matthew Booker.]: All right. We're good. This is [ph 00:00:05 Matthew Booker with Alison Wynn and Katherine Rindy]. We're here with John Ryals. It is September 9th, 2015 and this is the Genetic Engineering and Society Archive.

Could you please tell us your name, your institutions, and your roles?

[John Ryals]: Oh sure. You mean like as a history?

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[M.B.]: Or even just your current position or your jobs as you imagine them.

[J.R.]: So my name's John Ryals. I'm a Ph.D. in molecular biology. Right now I'm the CEO of a company in Research Triangle Park called Metabolon. Also founder of another company which is an ag company in the park called AgBiome.

[M.B.]: And what would you—how would you describe what you do every day?

[J.R.]: What I do?

[M.B.]: Yeah.

[J.R.]: I oversee the running of the company. It's about 150 employees. We do as much—I do as much science as I can but not a whole lot. I kind of guide where things are going. And we have a novel pioneering technology that's being applied in healthcare and been applied in various applications in agriculture. So we just keep trying to see where it's going to go.

[M/B.]: So is that mixture of entrepreneurship and science something you imagined being when you were growing up?

[J.R.]: No. Not at all. And I think growing up, I don't know, I had various ideas of what I wanted to be. And when I got into science at first there was no real industry that you could go into. The biotech industry was not in existence. I started graduate school in '77 right when genetic engineering tools were coming around, and there was no—they started Genentech in '77 or '78 so it's—but as you got going through and seeing what could happen and so the way I got into this… Do you want me to talk about that?

So I got my Ph.D. in molecular biology working with a scientist—a pretty well-known scientist in Texas in Dallas. And it was at an institute of molecular biology, and that was a very rare thing back then. There were only five or six departments in the country in

molecular biology because it was such a new field. And I studied E. coli so it was bacteria and that's about the only thing you could work on back then. I got a Ph.D., and then things were happening.

So Genentech had started up, Biogen and started up, and I was able to land a position at the University of Zurich as a post-doc for one of the most famous guys in molecular biology. His name was Charles Wiseman. And Wiseman had cloned interferon which was—that was the big splash of biotechnology at the time. He was quite a pioneer. And I got a job there and went there and was working on interferon and working on how genes—the interferon genes were being expressed. And he had a group in his lab of about 40 people but then he had a Biogen group that was about another 40 people. And we were all doing the same thing except they were getting paid twice as much.

And I thought well, I could do that. It ended up I could have probably gone into interferon, but right at the time I was coming out they had the first clinical trial results on interferon. Now it's a multi-billion drug, but back then it crashed. It didn't work. It wasn't the cure for the common cold which everybody thought it could possibly be.

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And so I was thinking oh, I have to change fields. And I was giving a talk one time at Oxford University in England in a seminar, and I was part of a symposium where a guy named [ph 00:04:08 Jeff Schell] was giving a talk. And he was talking about agrobacterium and how this bacteria actually injects its DNA into a plant and can naturally genetically engineer it. And being from Texas and being from—my parents were from rural Texas—that sounded very logical that you could actually use this to help farms and help farming and help farmers. But it was a very new field, and I started looking into it, and through a series of circumstances that I still don't understand exactly how it worked, but I met [ph 00:04:53 Mary-Dell Chilton] who was a real pioneer in the field, and she had just been hired by Ceiba to open up an institute here. It's now called Syngenta, but at the time it was called the Agricultural Biotech Research Unit of Ceiba. And so I talked to her at the airport in Zurich and somehow convinced her after a while that she should hire me. And I thought well, okay I'll try this. It's a new area. It's a grand idea because nobody had ever really genetically engineered plants. You could see the applications.

And so I went to—I came here the first time I came to this area was to interview. And I flew in in 1984, and if you think of Research Triangle Park in 1984, it was vastly smaller than it is now. And I got off at the airport—I landed in an airplane at Raleigh-Durham airport which was much much smaller than it is now and actually had to walk off the plane because they didn't have gates back then. So you had to take the stairs.

Went there and interviewed, got an offer and I started here on January 1st, 1985. So I moved from Switzerland to Raleigh. And that—and it was new. I mean we had—she was commissioned to hire about 50 people initially. And so I was one of the first crop of senior scientists that they hired. So they hired 16, to begin with. And the first—should I keep going with that?

[M.B.]: Yeah.

[J.R.]: So the first day it was the first week that I started the job here because I really didn't—I wasn't trained in plant biology so I didn't know much about it. And they got me on a project they called induced resistance. And after a while of working on that—so I was to take it over and I was to try to figure out how it worked so that we might be able to genetically engineer plants in order to be more resistant against pathogens. And that started about a 13-year quest of trying to figure out how this thing worked. And eventually, we figured it all out.

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We renamed the response systemic acquired resistance which is what everybody calls it now. And I'd seen, because interferon—interferon it's a piece of the innate immune system in humans, so it comprises a piece of innate immunity. And this systemic acquired resistance looked an awful lot like innate immunity. And so we started chasing it down, and it was innate immunity, and in the end, we were able to show it very clearly by cloning the genes that actually induced it. They were the same types of genes that induce it in humans and so that was the type of work I did.

It gradually—as things were working better and better I got more and more responsibility, so I became a manager and then I became a director of the research—a large research group that was about 25 people and then eventually I actually succeeded Mary Dell when she retired—she wanted to step down from management. She wanted to go back to the bench, and I was so—they had to replace her, and I think that was in 1993 that I became head of research for Ceiba and during that period is when we launched genetically engineered corn. Just keep going or what?

[M.B.]: Yeah, would you tell us about that because that's a momentous—it's a big moment in the history of genetic engineering and agriculture.

[J.R.]: Yeah, it was—so when I started in '85 about the only thing we could transform was tobacco and petunias I think.

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[M.B.]: What do you mean by transform? Would you tell us what that means?

[J.R.]: Right, that means getting the gene to go into the plant and being able to then be a part of its DNA and then be able to regenerate the plant back. And then get it to set seeds. And then get the seeds to grow out and make more plants. So that—you couldn't really do it in corn. Nobody ever had, and people actually thought it was impossible.

So we had groups there working on that, and the first gene that we were looking at seriously was the gene for BT, and the reason was is that it's an insecticidal protein and so the protein itself can kill an insect. And corn has a lot of insects—insect pests. And in particular corn borer. And so [ph 00:09:34 Mike Kazill's] group took over the quest of trying to get that gene into corn plants. And there were several really notable people involved.

So Mike and his team [ph 00:09:46 Christian Harms] who had started the transformation group, so he was in charge of transforming the plants and developing technologies. And he took a—Christian took a pretty brave move of choosing to engineer elite corn lines and so these were lead inbreds, and that's really what won the day for us. Because Monsanto got the genes into corn about the same time, we did at Ceiba. But they then had to do a lot of regression breeding to get a clean elite line. And so it took them several years. And it only took us about a year or two of backcrossing in order to re-establish the elite line and then we could make corn seeds because corn is a hybrid and so you'd have to cross that to another parent and grow that out.

So I think for Christian's work and being able to get corn transformation and then Mike's work with insecticidal genes it was pretty great. And we were the first ones to ever launch corn that was genetically engineered. People think it was Monsanto, but we had beat Monsanto by one or two years.

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And so it's just—after Ceiba, after that had happened at Ceiba then Ceiba merged with Santo, and that really stopped a lot of the progress because of all the political infighting in the companies and that always happens in a merger. So they lost their lead and Monsanto really beat them then commercially.

[M.B.]: So you've described a couple of interesting mergers in your own life that are perhaps unusual, or at least we think of as unusual. The first is that you moved from thinking about molecular biology in humans and in medicine in particular and then moved into agricultural biotechnology and at least I had thought of those often as separate worlds. Was that an easy transition for you?

[J.R.]: No, it was pretty difficult. The easy part was what was happening at the molecular level because that's all the same. And so whether you're in a bacteria or you're in eukaryotic organism whether it's a human or a plant the genes all kind of operate more or less the same. So that part was the easy part to grasp. So it was easier to turn a molecular biologist into a plant scientist than it was to turn a plant scientist into a molecular biologist because that's a much bigger leap at the time it was.

Interviewer 2: Is it still a big leap? Or is that different now because—

[J.R.]: Well I think now it's so ingrained in biology that everybody is trained in it now. So, in fact, that's probably an overshoot of science right now. We've got too many molecular biologists, and too many people are thinking that genes are a one to one correspondence with what happens to a phenotype or two the way a plant works or the way a person works. And it's not. And so we don't have biochemists anymore. We don't have metabolic scientists being trained, so Metabolon is the company I'm at now that's what we do. We work on the small molecules.

But at the time I think it was a stretch for people. I mean you had hardcore molecular biologists, and we had several of them at Ceiba. And then you have the plant scientists that were more microbiologists or plant scientists, and it was just the blend of everybody that had got it to work. And like I said—I mean after Ceiba and after Novartis I started a company called Paradigm Genetics, and that was—do you want me to talk about how?

[M.B.]: Yes, because that's another interesting combination that you represent in your story so far. That is you moved from being a lab scientist to being someone who managed a group of scientists to being an entrepreneur and that's another combination that I think is unusual.

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[J.R.]: Yeah so the idea—I mean Novartis formed because of various reasons. I had been at the company for 13 years and after a while things get a little old. They get a little stale. I was ready to move on. My role going forward in Novartis was head of agriculture biotechnology research, but after a while, it just lost its—I lost the enthusiasm for it.

What was happening at that time was Genomix was starting and the ability to sequence genes, industrialize things. I had been recruited by [ph 00:14:36 Craig Venter] at the time back in probably '91 to actually run a group out of what was called Tiger. And that was the Institute for Genome Research, and Craig had started that as a public institution. But it was funded by venture capitalists and they kept spinning companies out of it. And they wanted me to run one of those companies. And I turned it down but I liked the idea of Genomix and it was starting—everybody thought that once we understood the genome structure and how the DNA worked we'd be able to figure everything out. And we're still—40-30 years down the line, and that's not happening.

But at Paradigm people were taking off and doing sequencing and we knew a little company—if we were going to start a company it couldn't compete with Monsanto on sequencing. You know they had way far more resources. We couldn't compete with the other ag companies and so a group of us and it was four—two of my—two guys that worked in my lab and then another guy that I'd known for a long time so [ph 00:15:43 Sandy Stewart and Scott Yugness] who was a post-doc for a time with me and then he became a senior scientist as I was running research there—or I mean a director because I was running research there at Ceiba and [ph 00:15:58 Urwin Gerlach] who was also in a shared lab of mine.

And we were sitting in a room, and this is how it always kind of starts, right? And trying to think well, what do you do? And we came up with the idea that we could—no one at that point in time was looking at gene function. Which was going to have to be the next thing you did because you could sequence the genes and you could get the gene information but most of the genes we don't even know what they do. It's still that way.

I mean we only know really about what a thousand genes actually do. And how they play roles in biology in a human, and there's 23,000 genes you know. So most of it we don't understand what they're doing. And we thought well what we'll do is set up a huge phenotyping facility. It wasn't actually going to be huge at first because we hardly had any

money. But we were going to race ahead and just get the function without worrying about the genome. And so we could industrialize how you clone genes out of plants and then we could stick them back into other plants and see if they would do anything.

And we had developed a phenotyping lab which actually still exists in the park. It's now Monsanto. And so Monsanto ended up buying that after a while. But we could score 150 different phenotypes at once. And we could grow 100,000-200,000 plants at any given time. And so we were doing that. We were putting genes in at a very high rate. We would see phenotypes, and then we would try to figure out what the gene was doing. And so all the phenotypes we were measuring could be an interesting trait to put into a crop plant.

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And so but then in talking about what you're asking so I mean yeah, you had to go from being a scientist to learn how to raise money and learn how to get people to invest in you. And that yeah, I was kind of a born sales guy anyway. I used to sell encyclopedias door to door when I was in college. So I learned how to raise money, and in the end, we raised $125 million and did $200 million worth of deals with Monsanto and Bayer. And we had quite a big group. I mean I think it peaked at around 200 people. And we developed an incredible facility where we were phenotyping things like crazy.

But we could never figure out what the gene function was. And so you'd get a gene into the plant, and you'd see useful trade like maybe they'd have more seeds or maybe it had more oil, but you had no idea why. And so we tried transcriptional profiling. And that was available. We're all molecular biologists, so we thought okay, that will tell us what's happening. We did 10,000 experiments and people—that baffles a lot of people, but we had a lot of money. And so we did 10,000 experiments and in trying to figure out—we could not figure out what a single gene was doing. And it was because we didn't know how the genes interacted with each other and they now call that ontology. And we didn't have ontology in genetics in genomics. And we got onto the idea of why don't try to look at all the small molecules.

And anyway Paradigm went public. I took it public in 2000, and I did not like running a publicly traded company. And you know some people love it, and some people hate it. And at the time I was not liking it and so in about 2002 I left Paradigm and started Metabolon and Metabolon was started in order to develop the technology where we could use small molecules that comprise metabolism and do something like transcriptional profiling but measure all these small molecules.

And that's—we thought maybe if you could figure out how to do that then maybe it would help in understanding how genes work. And so it took a while, so I've been at Metabolon now 13 and a half years working on that. And we're the leading group in the world doing it. And it does work. We can measure all the small molecules all at the same time, and it does tell you a huge amount of information. And the reason is because we know the ontology of small molecules, so we know how a small molecule—how metabolism works. You know there's all kinds of pathways that have been worked out, so we know where they all fit.

And so now we've launched a major initiative with a couple of—especially with the UK where we can actually now start assigning functions of genes and so we are going to look at the idea is to do 500,000 people, and we're got our first 50,000 right now. And really try to associate gene function to the small molecules and how the small molecules work.

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So it's been a long haul but throughout all of that you had to look—you had to know how to talk to investors. If you didn't you didn't stay around long, and so it's you're either going to swim, or you're going to sink. And so now Metabolon has been similar. We've raised about $65 million, and we've done projects with companies that are valued at about $200 million and so learning how to do that was critical to being able to do it.

And now I think the thing that's kept me in this and kept me doing that sort of thing is that I never could have done something on this scale that I could do with a private company or a public company. So in universities, I would have never been able to get $200 million dollars. And so being in the company and learning how to really apply the technologies to the market you're getting access to huge amounts of capital, and that's what it takes to solve the really difficult problems. And so we're applying this technology now with Syngenta and others for agricultural purposes, and it's working very very well there. But then also in human biology.

[M.B.]: So your last comments really help answer a question which is you've described a series of terrific basic science questions that you pursued in the same way that a graduate student might want to. And you explained why teaming up with private capital could really make that possible. You could do things on a scale, perform the 10,000 experiments.

Did you ever see or feel a tension though between the need to wear your sales hat and your science hat? Did the basic science projects ever—did investors ask for example when is this going to pay off?

[J.R.]: They always ask. So yeah, constantly. And yeah, they tend to be impatient because they're venture capitalists most of the time, so they've got to get a return for their investors. I've been pretty lucky with investors that were able to stay into technology for a long time. But yeah, I mean there's always a tension between the commercial side versus the science side, and you just have to learn how to navigate your way through it.

[M.B.]: So some of your colleagues I imagine are in academia. And how does that work—that relationship how does it work for you over time? Do you, for example, you're producing an enormous amount of scientific information which is valuable for them. Is there any give and take there? Do you publish your work in science journals as well as producing it in products?

[J.R.]: Yeah, I mean that's one area where I was kind of unique versus a lot of the people and companies. I mean I published over a hundred papers—a hundred scientific papers out of Ceiba on this phenomenon of systemic required resistance. And Paradigm has now

published over—well over 500 publications out of the 4,000 projects that we've worked on now over the years.

And so yeah, the academic groups—the problem in academia and a lot of these technologies I mean—academia can—like Mary-Dell Shelton came out of academia, so she was able to figure out through grants and things how to do basic science and really solve the problem of the agrobacterium transformation that plants. But she couldn't have done it at the scale that Ceiba came in to do. And so it took companies to take it to the next step.

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And the technology I work in now we invented that technology, so there wasn't a university working on it and the problem with that right now is that it's so multidisciplinary, so we have to have computer scientists. We have to have mathematicians. We have to have statisticians, biochemists, and these big teams and you can't do that in the academic environment because the academia really rewards more individual effort than it does team effort and that's the whole system of getting tenured and things like that. That's well and good, but you can't put together a very complex team, and you can't attract a mathematician to work with biologists that much so I think those are the benefits of really being able to get people to finance it.

[M.B.]: You mentioned that you felt that your own work and your own publications were somewhat different from other companies. Is that right?

[J.R.]: Well, a lot of companies have the attitude that they don't want to publish anything ever. Because that tells people what they're doing and things like that. I never thought that was that important because we could file patents on what we're doing and protect from the patent perspective and you didn't want to get the publications ahead of the patents but as long as you would patent your findings then, you were protecting them. And I thought that creating the competition with the publications was going to push us harder and harder and harder to get things better.

But a lot of groups don't think that way. And when I left Novartis they quit publishing entirely and so I think I was at the time what they—when it was still Ceiba I was called a Ceiba fellow and I was the most highly patented scientist in Ceiba but also the most highly published and so I thought it was all very important to do. And you're not going to solve every problem yourself. And if you require that to happen then it's going to take you a long time to get somewhere. So you sharing scientific results was pretty important in my opinion.

[M.B.]: Do you think that connection to—or that back and forth with the universities has paid off for universities as well? Has some of that basic science flowed back into those programs?

[J.R.]: Yeah, I mean especially in the first work I was talking about acquired resistance. I mean that's now one of the models of plant disease resistance. And many people across the world study it. If you look at what we're doing with metabolomics now universities are

catching on. I was eluding to this a while ago, but when I started in science, molecular biology was very new. People weren't really doing much of it. It was more molecular genetics and things like that, but the pharmaceutical companies didn't even move into molecular biology until the '80s the late '80s before any of the pharma companies would say well, yeah, there's going to be a business here in healthcare.

Now what we've done we've swung way too far. So every scientist that we're putting out in biology is more or less a molecular biologist or at least the vast majority and they're not being trained in some of these other fields. And so we're now trying to swing them back to where you need a much broader training because this idea that we're going to figure it all out from the genes isn't going to happen.

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Craig Venter who is a friend of mine and I've known him for a long time he's got a great quote that he talks about when he gives a talk, and he was the first human to have their genes sequenced because he used his company to sequence his own genetic material. And he's written a book about it and everything and so back in 2002 or '03 somewhere in there they had the gene sequenced, and they had analyzed his genome. They knew what mutations he was carrying and things, and he wrote a book about it and it's called A Life Decoded. And he says now I don't know anything more about my genome than I did in 2002 because people just are not advancing the understanding of what the genes do. And that's going to be multidisciplinary.

So just as a point, everybody is trying to go from the genome down to a phenotype. And it just doesn't work. We don't know enough about the ontology of the genes to figure these things out. And 12-13 years after the human genome has been sequenced we really don't know much more about the genes than we did before it was sequenced. But with our technology and different approaches you can figure these things out.

[M.B.]: Do you think that blockage—that lack of progress in the ontology area has hampered agricultural biotech? Has it—are there other paths that might have been taken had that been known?

[J.R.]: Yeah, I'm sure. Still today people are putting genes into plants and getting results and getting phenotypes, and they still don't know what they are. We've worked on several projects at Syngenta where we can actually go in and say okay this is what this gene did in metabolism and biochemistry. And this is why it's causing that phenotype.

But yeah, I mean that's one of the major limitations in biology today is we just don't know what all these genes do. If we did, we'd have a pretty good idea of how to engineer something. But it's progressing. I mean you know Venter and his group have some synthetic what is it called? Synthetic genomics I think is what the companies call it, to have completely synthesized a bacterial chromosome, so we're making progress on understanding these things. But a bacteria is far from a human. So it's got a long ways to go.

[M.B.]: So one of the striking phenomena of discussions or debates over genetic engineering, it seems to me, is that people seem fairly—the public seems fairly okay with genetic engineering in human health products and pharmaceuticals, for example. And they seem much more concerned about, or at least there's a lot more discussion about, genetic engineering in agriculture. Why do you think that is? What explains that gap?

[J.R.]: Well I think there's several things and one—the original products that were released didn't really have any anti-GMO activity. There wasn't that. There were some activists involved people like Ben [ph 00:31:53 Hareland] from Green Peace who—you know, I asked him one day, I said, you know, why are you doing this? What drives you to be an activist against GMO's? Did you work on a farm and did you come from rural parents who had farms? I said well, did you ever—were you ever on a farm? Did you ever grow a crop? And it's like no. And he told me the story.

He said you know he was arrested in the 80s as one of the original Green Peace or Greens in Germany and while he was sitting in jail he decided that he needed something that he could champion as a cause. And so he wanted to do this. And he was a politician is what he is. And so anyway that was a sentiment that started developing. Now it didn't develop in the US much at first. And so when we launched the corn it was not—there wasn't an anti-GMO movement in the United States.

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But if you go back in time and you look at these things one of the things that happened in the mid-80s leading up to the 90s was the mad cow disease scare. And the scientists all banded together and said it's not going to be bad. It's not going to spread; it's not going to kill. And in the end, they almost had to slaughter every cow in Europe. And so Europe was very concerned and they were very untrusting of scientists at the time. And so when Monsanto decided to move BT corn into England initially it was a huge backlash. And I don't think they appreciated it and I think they would say that they didn't really appreciate the environment that they were trying to launch that crop into.

And then several steps that happened after that just inflamed the whole situation and till you've got now where Europe is almost banned all growing of genetically modified crops. And so I think that was a big mistake of industry. That they didn't really appreciate the political environment that they were going into. They could have—we could have all done a much better job. And then once it started in Europe it spread around. So then activists in the United States started getting involved, and everybody is—they talk about risk and they're scared of technology basically.

And so they're—the activists are feeding on the fears of normal people who—one of the problems is we got the biggest gap in lay understanding of science that we've ever had in the history of humans. So your average person knows very, very little science and very little technology and they don't know how to judge things, and so they think of risk, but they don't think of benefit. And even in an assessment of a genetically engineered crop, you don't do a risk-benefit assessment. You do a risk assessment. And the benefits are huge, but they just don't think about what those things are.

Interviewer 2: Why do you think we have that gap?

[J.R.]: The gap in science?

Interviewer 2: Yeah, the gap of understanding of the public with science.

[J.R.]: Well, people are not—you know the schools the elementary—the primary schools are not teaching science and mathematics the way they need to. I mean it's been a dumbing down of the education process. People are not going into these fields as they did at one time. And I think it's a big problem and it's going to get worse.

I mean the whole vaccine issue, that vaccines are dangerous. Well, I'll tell you what's more dangerous is not vaccinating kids. It's vastly more dangerous not to vaccinate kids. A vaccine may have a risk, but these risks are generally they're like the thing where vaccines cause autism. Completely ridiculous. It doesn't cause autism to get vaccinated. And but there's a big belief among people that could happen because it gets into the public domain and all of a sudden I'm not ever going to have my kid vaccinated.

Well, now you can see the backlash because you start getting these diseases in elementary school because now you've got a substantial population that hasn't been vaccinated. But it's just this irrational fear, and they don't believe scientists who tell them there's no evidence about this.

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And then you've got guys that portray themselves as scientists and publish erroneous results, so the original vaccine publication was shown to be false. And it's been retracted. They disguise themselves as scientists, but they're not really doing science. So I think it's confusing for people and they're just not able themselves to work their way through the actual technology so that you get fear.

[M.B.]: So that fear is striking, because again, it doesn't seem to apply so much to genetic modification in pharmaceuticals or in health area. I wonder if you have thought—I mean you've worked in both areas and if you've noticed this phenomenon.

[J.R.]: Oh yeah, I mean look at cheese production. I mean there isn't a single cheese hardly produced in the world that isn't produced from genetically engineered enzymes. And beer production. You know it's all genetically engineered yeast. It's virtually everything you're buying is genetically engineered. But they—there isn't this fear about taking a recombinant insulin where of course that's genetically engineered. And before you had that they had to isolate it from pigs and it was immunogenics so type one diabetics could develop allergies against it and so it's vastly better having the engineered version.

But I mean I think people for some reason this frankenfood idea about it's crazy and they're poisoning the food that we have somehow hits a nerve with people. And they believe that, and it's hard once they believe it to get them to not believe it.

And I think one of the problems that we don't talk about the benefits that much. And the benefits can be huge, and we're using tons and tons less insecticides now that they're growing crops. The pesticide use has dropped off dramatically in the United States because we have genetically engineered solutions. That's a benefit because the pesticides they're known toxins. We know what they do. But they're still relative toxins. And so it's—they can be managed, their toxicity can be managed and for industrial scale agriculture there—you have to use them. So but you can cut down the use with genetic engineering, and that's just one benefit.

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And we talked earlier about the benefits of things like golden rice. And there's a friend of mine Ingo Potrykus that developed golden rice. He worked his whole career on trying to be able to engineer rice to where he could get vitamin A into it. And eventually he did, and the problem with rice is if you're in a subsistence agricultural situation and you're eating mainly a rice based diet you're not getting vitamin A, and you can't buy supplements because these are very, very poor people. And so they get into vitamin A deficiencies, and that leads to river blindness. And so kids are blind. And it's unconscionable that product has been kept out of the agricultural system as long as it has. But it's been fought by Greenpeace. They tried to scare everybody in Southeast Asia that it's genetically modified, it's going to cause harm, and in the meantime, a million kids have gone blind. And to me that's just a monstrosity of public policy.

We talked earlier, the US used to ship its corn, its surplus corn to Africa to Sub-Sahara and African countries that were subsistence living, and we would have a surplus and corn will go bad in a year or two so they would ship it as a—to donate it to people that were starving. And their governments wouldn't accept it because it was genetically engineered.

And that's crazy because you're talking about some remote idea that something might be dangerous which there's never been any proof for at all. And there's been a huge amount of study. And you're talking about that against the people starving. Well, we know if you starve you're going to die. And there hasn't ever been anybody get sick on genetically engineered corn. So it's crazy.

But I mean how do you get people in that kind of mentality? I mean for me it makes no sense. It's—I gave a talk one time at a conference on genetic engineering. This is in the early days when it was all blowing up. And there was a guy in England. His name is Sir David Sainsbury or Lord David Sainsbury. And Sainsbury owns the grocery stores so Sainsbury grocery stores in England. A very wealthy guy. But he was trying to promote these new technologies, and he formed this conference to discuss it all.

And so I went and talked there, and that's where I had met Ben Hareland from Green Peace. And he had really irritated me. And so because this political—his need to be paid for his political view was keeping a lot of this technology from being applied. And I think I made a point that—well I started talking about organic farming. And I said you know my grandmother used to practice organic farming and she did it in the cotton fields of Texas.

And she would as a kid come home from school with a tow sack and if you know what a tow sack is it's a big burlap sack that stuff comes in, and she would drag this sack through the cotton fields of Texas and pick insects off of the cotton plants. And she would have to do that after school until it got dark. And that's how they practiced organic insect control.

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And I just made the point that it's absurd—I mean it's immoral to deny a technology to people that can prevent a 12-year-old girl from having to walk through a cotton field and pick insects off of plants. We should be extremely proud of the fact that humanity has been able to solve problems like this. But instead, we fear it. Or some people fear it. And some people make money off of fearing it. And it's an industry. So they get jobs, and they get paid to create trouble. So I don't understand it. I don't understand why people are that gullible except that there's just this gap in scientific understanding.

[M.B.]: It's also true that very few Americans know what a cotton field looks like or have worked in a cotton field and that experience of agriculture is receding. In my case, my great-grandfather was the cotton farmer. And so experience perhaps had something to do with it.

[M.B.]: Oh, it's huge. I mean nobody understands food production at all. Back in 2000, I think when I was at Paradigm Genetics I got a call from the food editor of the Raleigh News and Observer. And at that point in time, there was a gene for a—that was in a fish that would keep the fish from freezing. It was called the antifreeze gene. And people were trying to put this gene into crops so that they would be resistant to freezing. I don't think it ever worked, but that was the idea. It was worth trying.

And they called me, and the lady asked me a question that was—I don't run from questions, and so she said well how do you think a vegan would feel knowing that there's an animal gene in a wheat plant. And now she can't be a vegan because it's got an insect or a fish gene in it. And so I started asking her questions. And I said well; let's talk about that. And I said, so you think bread doesn't have any animal parts in it? And she is like yeah. And I was well; I could show you a lab and I could in Michigan State ag department where there's a USDA scientist and all day long they're pulling bread apart, and they're counting insect parts in the bread. And what they're after isn't that if it is has insect parts they can't sell it. It just can't be above a certain level, right?

So there's a lab there where they're looking at tomatoes—at catsup. And you're allowed to have about one percent insect parts in catsup. I mean it's just hugely high. So you got a guy that sits there, and he looks at catsup under a microscope and counts all the insect legs because there's no way you can harvest tomatoes without having some of them infected with insects. And so you're just going to grind them up and eat them.
But people don't understand that. They don't understand where that food comes from. They don't understand how crops are grown. I mean there's less than one percent I think of the US public is involved in food production nowadays and so where do they get exposed to it?

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And the ability to industrialize food production we—over the past century we've brought the cost of food that Americans have to spend on their food down enormously. And the people required to produce that food have also dropped tremendously. So when my father—his parents were farmers. And back then 30 or 40 percent of the American public were farmers. You know people that you had small farms and people had to grow their own food. They understood these things.

Another story. My grandmother—I remember when I was a kid and she made great pies, and she made great apple pies. And one day she was making an apple pie, and I'm in the kitchen with her and I remember her saying I probably was 10 or 12 years old but somehow this stuck with me and she was cutting up the apples, and she said she talked to me and she said you know you're so lucky because nowadays apples don't come with insects. And she said when I was a kid if you bought an apple when she was a kid you wanted an insect hole on it because then you knew where the insect was. Because every apple was going to have an insect. And if you couldn't find the hole you didn't know where to cut out the piece of the infected apple or the insect.

But now with insecticides, we don't worry about that problem because it doesn't happen anymore. And she said I just love apples nowadays because you don't have to be afraid of biting into one and having—finding part of an insect knowing that you just ate the other part, right?

But people just don't—we're removed from the generations where they actually knew those things. And I think of our own children who have never experienced things like that for the most part.

[M.B.]: Well I want to ask you a looking back question. If you look back on your career, which of course is still underway, but if you look back on it what do you think are your most important contributions, or others would say are your most important contributions to genetic engineering in agriculture in particular?

[J.R.]: Right. Well, I think the work we did with acquired resistance has opened up a field of plant pathology and a way to protect crops from fungal infections and things. I think that's been a pretty big contribution. So having figured the molecular basis of how that all works that was—people that study it now I mean that was the work I did when I was much younger. So I think—a lot of people still remember that.

What we're doing in metabolomics now I think is groundbreaking. And it's—people still haven't caught on totally, but it's going to change everything. And I think—I mean I'm very proud of what we've done there. And very complex problems we've been able to solve it and now we can see how it's going to benefit science. And so I think those are the two really big things. I mean I've had fun my whole life, but those are probably the two things that I'm most proud of. Those two areas that I've done.

Alison Wynn: So it seems to me listening to the progression of your career that—I mean you have a very dynamic skill set. You're a scientist. You're an entrepreneur. You have leadership things. What drives you? What exactly do you think drives you and motivates you?

[J.R.]: Right. Well, it's always about the science and the technology. I mean the commercialization I'm less interested in most of the time. We hire commercial guys to build that, but it's really pushing the boundaries of the science and trying to figure it out. And now we're looking—I'm looking at okay, what's the next one that we're going to—that I might try.

And you know that discussion we got into the microbiome of the soil and that's how we started AgBiome and Eric Ward and Scott Uknes are the two CEO's of AgBiome. And now I'm very interested in the human gut microbiome. And so we have a lot of evidence that's involved in a lot of human diseases and in particular things like chronic fatigue syndrome.

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And yeah, I think it's going to be—nobody knows a thing about the—well, we know a lot about the human microbiome, but most people don't know how it relates to things like disease and what the microbiome is actually doing in the gut is that it makes small molecules and these small molecules get taken up by the gut, and they're in your blood. So you carry about 200 molecules in your blood that are synthesized by bacteria and not by humans, but that are maintained homeostatically. And that contributes to health and when you don't have them, or you have them at too high levels that can cause disease.

And people question that a lot and I use several examples of this and one is serotonin. So we know serotonin is involved in the sleep processes and things like that. It's a brain active compound. It's a neurotransmitter. Humans can synthesize serotonin, but it comes from tryptophan, so it's a one-step synthesis of serotonin. We can't synthesize tryptophan. So that's a molecule that comes through the metabolism of the bacteria either metabolizing your food or directly making tryptophan and when tryptophan gets at too high a concentrations, it can put you to sleep. And that's because you're making serotonin. And so when you eat turkey which is full is tryptophan you get sleepy, and so, of course, you can make brain active compounds and things. And then it works that way with disease as well.

So that's a new area I think that's going to be really interesting. And but you know I'm getting intrigued by it, and it's like okay, what can we do in that space that is going to be important? Because of that's—the thinking process about this is always kind of—you get intrigued by a problem, you try to figure out okay, what can you do that's unique that you're going to be able to apply and then how could you make money off of it? Because if you can apply—if you can do all three of those things then you can start a company and people will invest in it.

So yeah, I don't—it's fun for me, and it drives me. But you gotta be careful because standing on the edge of a cliff; some people don't like that. And so you gotta be careful of

what you wish for. Because at sometimes you may fall off that cliff. And I have done it before, and I have seen others do it before. And falling isn't such a fun thing.

Alison Wynn: But it didn't keep you from not climbing back up on the cliff, right?

[J.R.]: No. It's—you just keep doing it and you'll testing—I love the science, and so I don't see myself as doing anything other than science the rest of my life, and I'm not ready to quit. So I'll just have to keep finding things to do. And as Metabolon matures I'm sure I will move on and do something else. And I'm still wondering what that's going to be.

But there's areas right now that intrigue me because they're new. I'm the kind of guy—I get drawn to new stuff. Especially if I can see something in the new stuff. So I don't—there's scientists that love to just hit the same problem, and for 30 years they're working on the same problem trying to work to some deep, deep level of understanding. That would drive me nuts. So that's not me.

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And that's why I would never have done that well in academia because that's essentially what you have to do. I mean to be—to have the accolades in science and everything you have to have been in a field for many years and so it's kind of a system that keeps you in a box. And that—studying the same thing for 30 years would—I'd kill myself. Shoot myself. So it's kind of fun to change and do something totally different.

[M.B.]: So have you been—do you think that your experience in being driven by this intellectual curiosity, do you think that's true for broadly speaking the field of genetic engineering and agriculture?

[J.R.]: Yeah.

[M.B.]: I mean what are—what do you think really drives the changes in that field?

[J.R.]: Well, I think originally that's what it was. I mean the science got started that was—it was difficult to do. It wasn't like you could do it easy. People that had the vision and could understand what you could eventually do with it were excited. I mean it's terribly exciting. It's hugely exciting. It's one of the most exciting times of my life was going through that ten year period from about 84-85 to 94-95, and by then we had a lot of it solved. Well, I wouldn't say solved, but we were making huge progress.

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And I think people that get into it now they're driven by the technology, but they're also driven by helping farmers. So you have a lot of people in agbiotech that have a rural or farming type of background in their families. Because they become interested in the science and they, want to do something to help farmers and to help growers and that's what they choose to do.

So I think it's—it probably doesn't have the excitement in it as it once did but it's still pretty exciting if you get a gene and it gets into a crop and somebody plants ten million acres of it. That's pretty satisfying. And to see nowadays what 70 million acres of corn are planted genetically engineered corn seed are planted. Almost all the cotton is genetically engineered. Most of the soybean is genetically engineered.

So it has been amazing to see that happen and it's—I don't know what—we're over a billion acres now it may be two billion acres that have been planted historically. And so from having been in this for 30 years, it's fantastic to see what's happened.

[M.B.]: So what do you think were the most important issues in genetic engineering when you began working in the field and do you think those remain to central core questions today in agriculture?

[J.R.]: Yeah, I mean I think originally when we were trying to get a gene in a plant we had to learn all kinds of things. And one is that if you took a gene from a bacterium and just stuck it into a plant, it wouldn't work. And it's because the—what you call a codon frequency is not the same for bacteria as it is in plants. And so you had to take a gene, resynsethize it and make it look like a plant gene. And then it would express the protein.

Well it took the field several years to figure that out. And so people were putting the BT gene in and not getting anything out, and nobody could figure it out and eventually you—both Monsanto and Ceiba I think broke through on it. And guys at Calgene which now is owned by Monsanto. So we could—it took time to figure that sort of thing out. It took time to figure out how to transform some of these crops, so the elite crops are very heavily already bred. So they don't look like nothing their parents.

So if you look at corn, the parent of corn is teosente and teosente it looks like a little wheat plant, and it's got three seeds on it. It doesn't have a cob or anything, and that's teosente. Now you got corn with a cob—corn cob with a seed on it that's a foot and a half long and it's got 400 seeds on it. So that's a massively different plant. And in breeding, that over a thousand years or however many years corn has been cultivated we created a very elite type of plant which was very refractive to be genetically engineered.

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And so we had to figure all that out. I mean you had to figure out how to grow the corn in greenhouses and things because people don't grow corn in greenhouses much. And some of the original problems we had in genetically engineering of corn was that they couldn't get a nongenetically engineered corn plant to set seed in a greenhouse because the growth conditions weren't right. The soil conditions weren't right and just learning all those processes.

I mean huge barriers but everybody was so young because I mean aside from Mary-Dell almost every one of us that started there were in our early 30's and even younger if you got out of the Ph.D. guys they were 20-year-olds. So you were too young to say this is never going to work. Youth has a lot of ignorance, so we learned we weren't scared.

But nowadays I think the problem that limits the technology is finding genes that are novel and that are actually going to lead to new phenotypes and cause new things to happen. And that's limited a lot by our understanding of biology and in particular plant biology. So we've worked some with groups on drought because drought tolerance would be a great trait to be able to put into the field. It would have a huge—water is limiting you see that happening in California right now. But we don't really know much basic science about how a plant actually keeps itself from being affected by drought.

So there's basic science questions, and I think plant biology doesn't get a lot of funding. And most of the NIH funding and places like that are going into humans or other models. So I think that's a big limitation. But it's coming. I mean we're making a lot of progress.

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[M.B.]: One of the criticisms of genetic engineering in agriculture has been that despite all the possible uses of the technology it seems to have been commercialized in just a handful. And in particular in herbicide tolerance, in BT. And therefore some people have argued it really hasn't been that necessary a technology. That these are things that people just didn't need that much. How do you respond to that as someone who has worked in the field for all these years?

[J.R.]: Yeah, well, go talk to a cotton grower before he had BT cotton. And go talk to a corn grower before he had rootworm resistant cotton or corn. It's made huge impacts. Some things you can control with pesticides. Some things you can't. And for instance, corn rootworm at the time was extremely difficult to control with pesticides. And so the farmer would lose his crops. Well, it may not affect the person that's buying the corn cob except—or the corn—except it lowers the price of it. But the farmer was losing money, and so the grower's economics were getting hammered in times of high insect infestation or fungal disease.

So I think the farmer would say it's made—it's hugely changed their business. And it's—I think it will affect everything as we go. I mean we're trying to make more nutritious plants, there's stuff like that. But the economics of that type of work is hard to figure out. So making broccoli be more nutritious through genetic engineering we might know how to do that but who's going to buy it? And there's not a big market for broccoli—enhanced broccoli at the grocery store. So the value capture mechanism isn't there, and that's why people don't do it.

I mean that—where I've seen projects like that has mainly been in academia where they have growers groups or things like that that are very interested in having something happen. But part of the thing is we chase the big dollar problems. And that's what drives innovation. I mean the ability to do something that's going to be a big economic win that's why you do it. And so the smaller stuff doesn't get done. And I think there'd be a lot more small crops genetically engineered except that the regulatory pressure on this is so high that you just can't afford to do it.

For example, tomato. I thought the Calgene tomato was a fantastic product. We used—I knew Rodger Salk as well at Calgene, and he would send me a case of these and I would—the deal was that he would send—keep sending me a case of McGregor tomatoes that were genetically engineered not to ripen or not to rot and I'd keep them on my desk as head of research at Ceiba and show everybody and make a big deal out of it. You could store this tomato for months just right there, and it would never over ripen, and that was a great idea and a great technological win. Never made it economically as a big deal. And so—and people aren't going back to do it now because it's not a major crop. You can't make a huge amount of money doing it.

And I think—and then when you put the pressure—the cost of actually taking that through the regulatory systems you just can't make an argument as to why you would do that. So if the hurdles came down then, I think you'd have a lot more of these minor crops being—having technology applied.

And humans—and in human disease, they do this by—oh, I can't remember. The Orphan Disease Act, right? So if you have an orphan disease you don't have to go through all the same regulatory pressure that you have to do with something like a cardiovascular drug. So they lower the hurdles, or nobody would ever develop a drug for that disease.

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You take Shay's disease nobody would work on that. No pharmaceutical company would work on that except that they gave it orphan disease status and now all of a sudden your regulatory pressure dropped off 50 fold. And you can make money off of it. So I think there's a lot of that behind why it's not getting applied to a lot of the other crops. But I think it will. The regulatory pressures will come down in time.

[M.B.]: So given that kind of reality and the history as you've described it of genetic engineering in agriculture where do you think it is going and the policies associated with it are going in the future?

[J.R.]: Well, in the US I think it's just—it will continue, and it will still be a big deal. There's enough people that are farmers and that understand the food economics that I don't think you're going to outlaw the technology in the US. Can you restate the question?

[M.B.]: Sure. I'm thinking mostly about where you think the field might be going in coming years in agriculture.

[J.R.]: Yeah, well I think it's going to go to solving the next biggest sets of problems. So there's a lot of work now on drought tolerance. There's a lot of work now on salt tolerance, heavy metal tolerance because there's a lot of marginal land that if you had plants that could grow on it you could expand your growing areas. Yeah, I think that people will be applying and Bill and Melinda Gates Foundation is taking a big role in this and doing subsistence agriculture and trying to do projects that are going to help those people. AgBiome is actually working on projects with that group. They're determined to help the starving

countries of the world. So places like Sub-Sahara in Africa and Northeast and Northwest India where it's really a very poor area.

So I think those are areas that will get more and more applications. There's plenty of problems to solve. I don't think we're lacking for problems it's that we're lacking for good solutions at times.

And I think in agriculture, in general, you're going to have—it's a three component system. And you're going to have seeds and biotechnology, and so you'll be able to protect crops with genes. You'll be able to protect crops with pesticides, and you'll be able to protect them with microbes. AgBiome is on the microbe side, and in the end, you're going to have a multitiered solution. Because pesticide use will come down, use of GMO's will be there and then you'll be able to supplement that with microbes now and so I think those are all big trends that are going to be happening.

[M.B.]: What are your greatest concerns for the future of this technology?

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[J.R.]: Well that it does get—that the fear mongers do make progress, that somehow they're able to convince people that it's a dangerous technology. I mean there's—and that would be a pity because this technology is actually definitely changed the world and definitely changed how people get food and the price they have to pay for that food. So it would really be a pity if the activists were able to convince enough people that they somehow ban the technology.

[M.B.]: What about your greatest hopes?

[J.R.]: Well I hope—I mean I think at some point I do believe—we've now consumed billions of acres worth of corn. I know we've done the experiment, right? I mean it hasn't killed anybody. There hasn't been a sneeze from having consumed that much corn and corn products.

I think my hope is that eventually, people will accept the technology; it will be accepted as safe. The regulatory hurdles will drop and that you'll get the technology used in much more crops, much more applications of agriculture. I think that will happen, really. Technology that works and helps people rarely is excluded from being developed. I won't go into nuclear energy but...

[M.B.]: I have a big picture question for you. And it has to do with the way-- to go back to our conversation about the way people relate to or think about this particular set of technologies, genetic engineering in agriculture. What would you like the general public to know about that set of technologies?

[J.R.]: Genetic engineering?

[M.B.]: Yeah. If you could speak to the public in our time what would you like them to know and the policies that surround them?

[J.R.]: Well I think the… genetic engineering is a very, very precise way to do plant breeding, essentially. I mean we're not sticking in genes that we don't know what they do. I mean there wouldn't be any purpose of doing that. So it's an inherently safe process, and the testing—the amount of testing that goes into the products is huge. So they don't—you don't cause any health problems with genetically engineered products. And I think I'd love for the people in general to understand that.

And it gets back to one of the questions you had about food production and people being ignorant of food production. I mean people have been killed by plant breeding. I mean especially—there's famous cases of potatoes that have been—new varieties of potatoes that get into the market before they're—a normally bred crop doesn't have to be tested for anything. So we're only regulating the process of genetic engineering. We're not regulating the product. And I think because these things happen and they're just not talked about much.

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People just don't understand that the food itself—I mean even the normal practices of plant breeding are not that particularly safe. So you've got to be careful of what you do. When you bring a lot of variety of tomato and try to cross it with an elite tomato line, you don't know what you're sticking into that tomato line. And tomatoes were inherently poisonous when they first—we had to learn how to take the toxins out of them.

So I think that general ignorance of food production is a big deal. I mean I wish people would know more about what they grow. Organic farming—Pam Ronald would climb all over me for saying this, but I tell you if you look at the safety record of genetic engineering and the safety record of organic farming organic farming is vastly more dangerous than genetic engineering. And she would say well if it's practiced correctly it's safe. But the point is it's not practiced correctly.

And so people are using human waste as fertilizer. You know you get infections of E. coli in lettuce. You know this happens at least once a year or so. The perception that some things are dangerous while other things are safe is—it may make sense for somebody that doesn't understand the science, but it really is illogical.

[M.B.]: I have a big last question to ask but first I want to ask Alison if she has anything else she wanted to ask about?

[Alison Wynn]: I don't think so.

[M.B.: Katherine?

[M.B.]: Well then, it's a question I think you deserve to get asked and it is, are there any questions you expected me to ask and didn't? Or that I should have asked?

[J.R.]: No, I think it's been a nice conversation. And I think I've had my say.

[M.B.: Well thank you, John Ryals, for visiting us. I appreciate it.

[J.R.]: Sure. Excellent.