

Donna Gulezian

December 22, 2003

Sara Shostak: You're aware of the fact that I'm recording.

Donna Gulezian: Yes.

Shostak: Great. Thank you.

Gulezian: You bet.

Shostak: I was wondering, at the most general level, if you could help me understand Taconic's role in the production and distribution of transgenic mice.

Gulezian: Sure. Taconic has been a longtime player, if anybody is a longtime player, in transgenic models since their fairly recent development, now, I guess, approaching two decades. Taconic's first interaction, in fact, with scientists in the transgenic field was with the NIH, and, in fact, with four of the models that you're particularly interested in talking about, that of models that were developed at Harvard, one of which was called the Tg.AC mouse, which is a model for skin carcinogenicity. And it was used in collaboration with Philip Leder and Ray Tennant to have a look, to evaluate that model to see if it would be useful as a predictive model for potential human carcinogenicity. Taconic raised that model in a contract for the NIH, for the NIEHS specifically, and that was in the late 1980s. Following that, Taconic began to do contracts like that for other institutions and companies. One of those companies that Taconic did such

a contract for, which was using their expertise for the production of transgenic models, was a company called GenPharm. GenPharm International was a company in the San Francisco Bay area in California that was founded on the use of transgenic animals, primarily for producing products, like human monoclonal antibodies based on immune-deficient mouse models, but there were other . . . And those immune-deficient mouse models were transgenic models. But there were a couple of other areas of application for the transgenic models, and one of those was for, in fact, producing transgenic models to make them commercially available for both drug discovery and safe testing purposes to institutions all around the world -- academic and for-profit. GenPharm had on its board of advisors many of the prominent scientists in the field of transgenic technology, one of those being Alan Bradley from Baylor College of Medicine, who worked with Larry Donehower to create the knockout model, the p53 knockout. So that model, through Alan Bradley and Baylor University, because of his association with GenPharm, was licensed to GenPharm exclusively for all testing purposes. GenPharm came to Taconic at that time to produce the model. It began using their expertise for production of that model and to be able to have access to investigators, again, worldwide, There are very few animal vendors in the world. There are really three large ones. There used to be many small, regional suppliers, but as the restrictions on sharing -- let's not say sharing of animals, but as the need for a greater and greater health status and better

and better definition of animals has grown over the last 50 years, let's say, there have been fewer and fewer companies who have been able to meet those specifications and be an approved vendor so that animals can't be received by that many different vendors anymore. So, again, GenPharm needed to find a contractor, and that contractor was Taconic, to produce the animals so that the animals could be delivered to anybody who would want to have access to them. Taconic subsequently purchased this business from GenPharm, all of the rights and licenses for the production and the right to various models -- p53 was one of those that was included - - to the specific technologies as well as some of the platform technologies that were needed to create those animal models. And from that time of purchase, Taconic has become really the leader in the commercialization of transgenic animal models to the research community, has actively sought after new models as they're emerging, to bring them into Taconic's production facilities, to bring them to the status of the specifications for the health and the genetics and the genotype that need to be done in order - - and the intellectual property is another piece of that -- to make them available worldwide, as well as Taconic has participated with all of these different groups who are doing this evaluation to be part of the builders of the information, of the networking of the information, so that it would advance the knowledge of the technology and the use of the technology. So I hope that answers your question.

Shostak:

Yes, absolutely.

Gulezian: Okay. Ask me questions anytime.

Shostak: Thank you. One question that occurred to me, listening to you, is what is the mechanism for a model coming to Taconic? How does that proceed?

Gulezian: Right. There are a couple of different pathways that it might proceed on. Often, investigators would come to Taconic. In fact, this still happens. Sometimes it can be very humorous, in fact, really, that sometimes an investigator will come before ever even having created the animal model and just will say, "I've got this model and it's going to be better than any model that's been created. It's going to be used like this. It's going to sell millions and millions and millions, and you're going to become rich, and I'd like to become rich, too." And usually -- so it might be that someone comes to us. And in some cases, they really may have a great idea. But when it's just an idea, it's very unlikely that it would be something that we would say is ready for this sort of mainstream commercialization. In the case of the Tg.AC model, which I think is a particularly unique case, the way that that one happened was that the model had been in, let's say, development in Ray Tennant's group. They had done several testing of, you know, testing with several different compounds with the Tg.AC, had done quite bit of publication. There was, you know, continued to be further and further advancement, and it looked like the NIEHS and the NTP were wanting to consider... I can't remember exactly the time line on all this, but considering the incorporation of the Tg.AC into the NTP testing program as one of the alternatives. At that point, the model was not

available outside of the NIEHS because of the intellectual property around the model. So Taconic, at that point, because we'd been participating with the PIM -- we had the PIM model. This was from GenPharm as well as the p53 model for carcinogenicity testing. We understood what the needs were for the Tg.AC model, so Taconic went out and proposed at this point to Dupont to license the model to Taconic. So it will sometimes go that way that Taconic will identify the need, and we will go and specifically make a proposal to solicit, to bring the model, and to license it to Taconic to put it into production. There will be other times that investigators will drive, you know, will let us know that this is something that is really needed. So it really comes through communication with our clients of, one way or another, understanding that need, and we may see it as a way that we can meet it or an investigator may come to us and say, "Would you consider this?" and we will look at it. We'll judge it on a number of different criteria to say if we think that it would be ready for such kind of distributions.

Shostak: What are those criteria?

Gulezian: Yeah. The criteria would be, are other laboratories interested in using the model? Has it been published? What are going to be some of the concerns and considerations about actually producing the model, the health of the model itself? Are there aspects of its phenotype other than, let's talk about right now, other than its propensity to developing tumors that would be needed to consider before being, putting a model into

production? You don't want to put a model into production that is only going to survive for 12 weeks, something like that. So there would be, it could be a myriad of other things, but you'd want to consider as much of that as you could. You'd have to know that you could have some way of testing to be sure that you could reproducibly produce that model. That would be another criterion. But the main ones are that it receives some degree of acceptance by the community for a given application.

Shostak: You mentioned the licensing of the Tg.AC model to Taconic from Dupont. Can you help me understand the intricacies of that process?

Gulezian: Yes. Let's see. The Tg.AC model is both -- there were . . . Let me see if I can, how best to do that. Give me just a second here.

Shostak: Of course.

Gulezian: Yeah. The Tg.AC model had, as you know, been made available to the NIEHS through collaboration with Ray Tennant and Phil Leder, and so was able to be developed in Ray Tennant's laboratory, but not beyond. Dupont had also contracted Charles River Laboratories, who is in fact the largest of all animal breeders in the world. They're located in Wilmington, Massachusetts, back almost, I think, simultaneously with Phil Leder's sharing of the model with Ray Tennant. So the model was created at Harvard, but the patent, and was patented at Harvard, and the rights were all assigned to Dupont. So Dupont had the exclusive rights to the patent for the Tg.AC model. And beyond the Tg.AC model, there were five other models created at that time, but the patent was a very broad

patent, as I know you must have read now in some of the background that you've done, very broad patent, in that any animal model that, any genetically manipulated animal model that had a propensity to develop tumors was covered by that patent. It was called *Oncomouse*. So it was very, very broad in its reach. And Dupont had contacted Charles River to produce that model similarly to the way that GenPharm had contracted Taconic to produce animal models. But one thing that was very different about what Charles River's contract with Dupont was and the way that Taconic goes about licensing models was that Charles River was really just contracting the breeding of that animal model. When they sold the model, the end user, whoever wanted to use it, needed to obtain a license from Dupont in order to use it. In the early stages of the use of that model, licensees had to sign on to reach-through agreements with Dupont. So, in other words, any discoveries that were made with the use of the model would be subject to royalties on drugs sold. So there were very few, as you can imagine, licensees that were up for that, future sales of drugs that might have been discovered using the *Oncomouse*. So it was not a success at all at Charles River. So that is, one of the important points of negotiation that Taconic does whenever we license in a model is that we ensure that we are obtaining the rights that not only allow us to produce and commercialize the model, but that we can pass through a right to our end users that allows them to actually use the model. So that's an important major distinction, and that's a part of every license that we do

with any model that we include as part of what we call our Taconic transgenic model.

Did I send you a product guide with our different transgenic models listed in it?

Shostak: No, not yet.

Gulezian: No, not yet. Okay. I will take care of that right away.

Shostak: Thank you.

Gulezian: You'll see in there what our label license says. We sell models with a sub-license to use under a label license that's very similar to a software license. So when you kind of break the seal on software, you're agreeing to not duplicating and not commercializing what you just bought, but it is for your use, and that is a similar approach that we've taken with animal models, to not have executed material transfer agreements, but to have a label license, sort of informing that this is what you've agreed to on the purchase of. So the intricacies of trying to . . . Try and ask me another question so I can get at what level of intricacy you want to talk about when we talk about doing these licenses so that I'm not talking about something you're not interested in.

Shostak: Sure.

Gulezian: You can direct me in the right way here.

Shostak: Since I'm still learning this, my question might be more general than would be helpful, but essentially what I'd like to understand is the process from product development in a university lab kind of through the moment

when one of your end users breaks that label

Gulezian:

Right. I will. There are some things that I've got written up that I can send you to kind of follow up on this conversation, and I'll do that. It takes a long time. That's one thing that's for sure. In the investigative lab in some university, it usually takes or can take as long as two years to go from that idea of, I've got a great idea, let me make a construct, to then do the work in the stem cells or in the blastocysts to either insert this gene or to knock out this gene, and then to do the subsequent breeding that has to take place, and then to do the preliminary tests of the phenotype of the animal. That could take anywhere from two years, you know, from one and a half to two and a half years, let's say. Then it would take typically another year or so for those preliminary investigations and that first publication to be done, and then other investigators would start to say, "Gee, this looks interesting." Or it might have been sponsored research somewhere with a drug company, let's say, and that company then wanted to further develop that model. But say somewhere in that first three to four years after the model has been created, several other users may pop up that are interested in using the model, and that would be the time that Taconic would get involved, typically get involved with the investigator to begin talking about negotiating a distribution pathway or the production and commercialization of the model. It would then need to come to Taconic, to one of Taconic's campuses for production, and would need to go through a derivation. So we go through this license negotiation. And we can -- do

you want to stop there and talk more about the license negotiation?

Shostak: Sure.

Gulezian: Or do you want to talk a little bit more about what the process would be after it arrives at Taconic?

Shostak: I would be interested in hearing about the licensing process.

Gulezian: Okay. So then it would typically be, we would make a proposal to this investigator to say that we would like to bring the model in under our commercialization program, which we call Taconic transgenic model. One of the important criteria that I had mentioned before, which is a distinction, I think, among most others, is that we would be providing our end users the right to use the model so that there would not, so that there wouldn't be further obligation on the part of the end user to go back to the licensor -- let's just say it's Baylor University's again -- to get any additional licenses. The other thing that we would do at Taconic would be due diligence to learn if there are any other patents or intellectual property licenses that might apply to that model. So in the case, let's say, of p53, which is not a Harvard model or a model that was owned by Dupont, the *Oncomouse* patent still applies to the p53 model even though p53 locus itself was created and knocked out at Baylor College of Medicine. The *Oncomouse* patent, which applies to that model because these models have a propensity to develop tumors, is owned by Baylor. So Taconic needed a license from Baylor in order to sell that model in addition to the p53 gene locus license. You following that?

Shostak: It's incredibly complicated, and I think I'm following it.

Gulezian: There are other technologies besides the two that I just mentioned. There's the technology that was used to create the model itself. There's a technique called positive-negative selection. This is homologous recombination technology that's used to make the animals or to make knockout animals, and that is technology that was created and patented at the University of Utah, where Taconic has to have a license to that in order to distribute the p53 mouse. So the p53 mouse would be covered by three patents in this case: the positive-negative selection, the *Oncomouse* patent, and the patent on the p53 mouse itself. Let's say that there were another patent on it for -- you've heard of the CreLox technology, which is something that says that a gene would either be turned off or turned on at a certain time of development, or it's a technology that allows for that or a technology that allows for it to be only expressed in certain tissues. And Taconic does not have a license to that technology, so we would not be able to go forward on a license for something specific if there were a broader, what we would call a platform technology that also applied to that animal without negotiating that license as well. So that would be another -- that would be something that we would be needing to do inside at Taconic in order to have something fit that program of distribution, the commercial distribution for us, because we have found that it's very important to have all of these licenses covered so as to enable the evaluation and the development in the field.

Shostak: So, following up on that last comment, I've looked at your web site, and it looks to me like Taconic does a tremendous amount of in-house research. Is that correct?

Gulezian: We do a limited amount of in-house research. I'm not sure just what you saw that prompted that. We do research projects often with animal models that we have commercially available for our clients. That might be what prompted that.

Shostak: Yes.

Gulezian: Yes, we definitely do. We do behavioral studies, we do all kinds of phenotypic characterization of models, we'll do diet-induced studies, we'll do compound administration. Those are sponsored studies.

Shostak: Okay, so . . .

Gulezian: We do some research to better characterize models that we have so, again, that we can provide more information. But most of studies we do research to develop new processes and technologies that are going to better allow us to do what we do, you know, developing our own skills for animal production as an increasingly sophisticated science.

Shostak: That's helpful. Thank you. Going back to the first moments of our conversation, could you talk about the ways in which the intellectual-property issues pertaining to transgenics have shaped the development of the models?

Gulezian: Definitely. Let's talk now specifically about the carcinogenicity models, the ones that you've been talking about at the NIEHS?

Shostak: Yes. So, p53 and Tg.AC.

Gulezian: Absolutely the Tg.AC. So what has happened there is, we first talked about, you know, Charles River had a contract for the sales of the Tg.AC following commercializing that, but couldn't provide the end users with any, with a license to use them. So what effectively happened there was that it slowed down the evaluation tremendously, by several years, because investigators couldn't access the animals. The NIEHS had been using them, I think, since 1988, and it was in 1996 that Taconic negotiated the agreement with Dupont, so in that intervening time, there was no access to that model as it was getting developed. So it got developed, I think, in some ways without as much -- I don't want to say without as much peer review, but without the same kind of evaluation, because nobody else could get their hands on it to use it. So it was just done in a single laboratory. It wasn't a multi-lab effort. Have you spoken with the group at ILSI or anyone from the group at ILSI?

Shostak: Not yet.

Gulezian: But you understand that process, or what went on at ILSI?

Shostak: I've read about it. I would love to hear your perspective on it.

Gulezian: ILSI -- in fact, I went to ILSI before I was at GenPharm before I came to Taconic, just trying to get anybody to listen to anything about the use of the models. We at GenPharm had been working with the NIEHS because at GenPharm we had two models, and the NIEHS was very interested in them. One of them was the PIM1 model and the other one was the p53

knockout model. Both looked like they would be useful in carcinogenicity testing. You know, there I was marketing for GenPharm and trying to get interest in the models, and there were many investigators in companies who were very concerned about the use of the models, fearing that they would be too sensitive to carcinogens if they were used. But, you know, here we are trying to make them more sensitive by putting in either an inducible oncogene or removing the tumor-suppressor gene. They were very concerned that models tested with compounds would be starting up with tumors all over the place, and they didn't want to be having false-positives. That was the biggest concern. And they also didn't want to be testing any proprietary compounds with something that they might then have a false-positive with. So I'm backing myself up here and this was because -- let's just see if I can remember why I was saying that.

Shostak: Talking about the . . .

Gulezian: The access.

Shostak: For Tg.AC.

Gulezian: To Tg.AC. Yes. So, and then I started telling you about ILSI a little bit. So I went ILSI, because -- this is a sideline on ILSI just because I want to say that Tg.AC and how it shaped Tg.AC is that much of the early work was just done in one laboratory, and that's different from some of the other models . . . Let's say the p53 or even the PIM had multi laboratories doing the evaluation, so there was different kind of consideration given to the protocols than there were for the Tg.AC. So

maybe they got a fuller appreciation of what their use might be because many labs were able to use them, and that was because of the difference in the licensing, in the license that was available from the start. Part of that evaluation or much of that evaluation with the p53 model . . . Well, let me just tell you about the ILSI project because I think it actually does explain pretty well some of the things that have gone on. There have been four models in the ILSI project that have been being evaluated for further use for carcinogenicity testing. One of them is the Tg.AC, another one is the p53, and another is the rasH2 model from Japan. As I'm saying these things, are you aware of any of them or . . .

Shostak: So far, yes.

Gulezian: You are. Okay. And the third is this model called XPA.

Shostak: That's the only one I don't know.

Gulezian: Okay. So those four models were all in this ILSI evaluation. ILSI is an organization, it's the International Life Sciences Institute, and there's a group within them called HESI, which is Health and Environmental Sciences Institute, which is just a consortium of pharmaceutical companies that come together, sometimes to just articulate issues, but sometimes, in fact, to sponsor studies, and in this case they did sponsor studies on all of these different models to, in fact, try to evaluate them in multi-lab protocols, looking at several different compounds across all the different models.

Shostak: And did Taconic supply the animals for all of those?

Gulezian: No. Taconic supplied the animals that we produced, which were the Tg.AC and the p53 models. At that point in time, Taconic had licenses for Tg.AC and p53. Taconic did not then have a license for the ras H2 model, which was being produced in Japan. There were some very intricate details, which would take us the next three hours to try to explain to you exactly what the process was for the licensing of the ras H2 model, but Taconic now does have a license for the ras H2 model from Japan. Okay? The limited access to the ras H2 model during the time of those evaluation studies has impacted how quickly the ras H2 model was or was not accepted. All of the evaluation studies were done in Japan. Very, very few were done anywhere else outside of Japan. Only in the past year or so have the models been available outside of Japan, and that was because the licensing hurdle had to be overcome. Once they were overcome, it is now being used in other places. I'm just going to give you some round numbers -- I think like 60 to 70 protocols have been approved by the FDA for the use of the p53 model; maybe 35 to 50 -- and these are big ranges, I know -- protocols approved by the FDA for Tg.AC; and I think three or four have been approved because of the ras H2. So the ras H2 was created prior to, in fact, the p53 model, but it was that limited access, and access was mostly limited by licensing that prohibited it from being further developed. And now the more interesting part of it is, is that the XPA model has never -- we've never been able to successfully negotiate a

license. And, again, it's a lot of ins and outs, and I'd have to pull all my files to really re-create the history.

Shostak: I promise not to ask you to do that.

Gulezian: But it was one of the ones that we had hoped to be able to license for further use, but we were -- it never was accomplished. And it would look, because of that, that the XPA model is pretty much falling by the wayside. There's never been a study approved at the FDA, and no one could use it, in fact, if they wanted to. It looked like there was quite a bit of promise in combining the XPA with the p53 model, putting those two together to really make them a useful and valuable model, and that won't happen. I mean, in the foreseeable future. I can't say it will never happen. We've tried to do everything we can to be able to make that available. So that's what happened. For all the intricacies there, the bottom line is it's pretty cut-and-dried. You know, companies will not use models that don't have the appropriate licenses associated with them. It's way too risky for them to do, and so they won't do it. We are now at the point. The license that Taconic negotiated with Dupont at the time that we negotiated the license for the Tg.AC permitted us to do this commercialization necessary to license for use with the Tg.AC and for four other models. We had to nominate those models within a year of the negotiation, and we did. The models that we nominated were the ras H2, subsequently licensed; an XPC model, which is very similar to the XPA, which we do have a license. The reason, so this is another reason, and it's not a licensing reason, but I think

it's interesting for you to understand the fuller picture -- is that, again, it's that that multi-lab use of a model is so important in its evaluation, and the XPA was the model that was first promoted through this ILSI group for further evaluation. And the ILSI was trying to do all, select models that had been developed all over the world, you know, cannot be U.S.-centric in their sort of evaluation and progress. This XPC model is created also in Texas, at Baylor, and has not gone on for further development. I can tell you that what may happen in the future is that if there's a lot of promise for one of these XP knockout models, that it may be because of licenses that the XPC model will become a model of use and not the XPA model due to the inability to obtain the needed access. So that's a way that the shaping could definitely happen. Another model that was one of these is the model called the K6ODC model, was another one that we nominated and subsequently brought in under this license from Dupont. It has not taken off, but it is in use, and it may or may not be a successful model. But the fourth model that we had nominated was the XPA, but we weren't able to do it within the time lines, and then Dupont withdrew its willingness to license it to us. So that's kind of the short story on all the back-and-forth on the XPA. We are now at the point of, in time, we have now used all the options that we had negotiated for in that Dupont license. The PIM and the p53 were other licenses from Dupont, not done at the same time, but individual licenses done with Dupont back at GenPharm, prior to Taconic. Taconic would like to negotiate another license with

Dupont for additional models under similar or the same terms as we have done these previous ones, and Dupont does not want to further license Taconic or anyone, as far as I know, to commercialize any additional models. So as near as we can see, what is going to happen is that this is going to be it. The NIEHS has had long-term hopes and goals of developing other models or developing other tissue-specific, especially tissue-specific. They want for us to have prostate- and mammary-specific and lung-specific tumor models, and those -- there's no way, at this point in time, that we can see a way to provide those models because of the issues with the inability to negotiate a license, so that, as you can see, already it's having a huge impact, because, since we don't have anything in the pipeline right now that we even are working on. I didn't finish that time line for you before of what happens after a model comes to Taconic, but we kind of stopped short with what happened with the licensing. But even after a model comes to Taconic, we're talking about another year to 18 months for the first animals, by the time it goes through all the steps it has to go through before it can be commercially available. So we're right now, since I can't even tell you that we've got something in the pipeline, we don't have a license in negotiation, we are probably more like, even if we were able to do something with Dupont tomorrow, which I can tell you that we're not, we are two to three years away from being able to get another model out there for evaluation. So this intensive process that has brought us sort of from 1988 to 2003 is, you know, I would say at risk of

coming to a screeching halt as far as being able to get, again, outside of the NIEHS, because the NIEHS, within the NIEHS, seems to be developing models for their use and for further evaluation, but to get those beyond the NIH, we don't know what the future is. So that's how the licensing shapes the field.

Shostak: Now, the NIEHS can develop these models because it has memoranda of understanding with Dupont?

Gulezian: Well, no. I think that Dupont just probably sees it as politically not wise to really jump on NIEHS too much, and that the NIEHS does have an understanding with the NIH for *Oncomouse* technologies and for use by not-for-profit research, so that's something actually that's new in the last three years, is that not-for-profit research can use. The NIH can do it, and academic institutions can sign a memorandum of understanding or further agreement with Dupont that will allow them, not-for-profits, to use of the *Oncomouse* models.

Shostak: Okay.

Gulezian: But they can't go into any further development, which is really where it's going to happen.

Shostak: And I realize that I'm asking you to speak for Dupont, and that may not be fair, but can you help me understand why Dupont is not interested in issuing further licenses?

Gulezian: Yeah. Well, just like you said, it's not that it's not fair, it's just it might not be accurate. All I can do is say what I think that they're about and

what they said that they're about. I think they just have a new strategy about intellectual property. It's not a new strategy. It's even, I think, the strategy at the time that we did the license with them to provide the models. They believe that they can obtain much greater revenues from doing license deals directly with companies, so that they would like to go and license all the end users themselves.

Shostak: Okay.

Gulezian: I do have a perspective with individual models, and it's unlikely that all of the players that are needed for doing evaluation would be able to enter into these licenses with Dupont. They won't. I mean, that's just all there is to it. They won't all enter into these. And so even if that were to be accomplished, if Dupont licensed every last for-profit who might have interest in accessing the models, it will slow down development of the models. But that, I think, is the strategy for them to do direct license deals where they can achieve much greater revenue.

Shostak: When we first began talking, you made a comment about how NIH's access to these models has affected the access of other biomedical researchers. I'm not sure if I heard that exactly correctly. But is that consequential beyond your comments about the NIEHS being the sole site of the development of the Tg.AC model?

Gulezian: Let's see if I can remember what I was saying. The NIEHS was able to develop the model, and especially now, the Tg.AC model, for a number of years where nobody else, no other entities other than the NIEHS could get

their hands on it unless they did it in collaboration with the NIEHS. There were a couple of those going on. So I guess it caused a lot of furor, I think, that the NIEHS was doing this and that the National Toxicology Program might adopt it and then begin to in fact require it, this as a test, where, however, companies wouldn't be able to use the tool themselves.

Shostak: I understand.

Gulezian: Is that what you were asking?

Shostak: Yeah. That's very helpful.

Gulezian: Okay.

Shostak: And has that furor changed over time?

Gulezian: Yeah, it did I think, because we were able to achieve that license and the license to bring in the ras H2, and so, you know, I think that right now there's probably not a very good awareness of what the situation going forward is, as right now there's been such a major effort. There were some 30 pharmaceutical companies that were involved in this development through the ILSI project together with the NIH, and the NIEHS played a big role in that as well as governments in other government-funded institutions in other countries. So right now, I think that what's going on is the sorting of the data and the sharing of the data and the evaluation of the data that came out of those studies because it really is immense. There's a lot there. And protocols that are being proposed to the FDA are all with the models that are currently in use. These aren't facts that I'm telling, those are facts; now these are sentiments. So I go and I hear people

talking about the consistent last slide that people would ever put up when they talk about one of these presentations is, you know, the future and future models.

Shostak: Right.

Gulezian: What they think would have to be done next, and then new models would be tested against this sort of matrix of compounds. They've already been tested against the four models that are available, and I think that people just don't know that, no, that's not going to happen.

Shostak: Right.

Gulezian: So do I think there'll be a furor again? Yeah, and I think it could be worse this time because there's now been a major investment in the idea, in the use, that, you know, I'm of the mind, and I think everyone else who's participated, was that these models were really just prototypes in many ways, and they were what was available now to understand could it be useful, and now what needs to be done is to develop, to use and develop better models, and I think that they just don't know yet.

Shostak: And it's interesting both to think about the development of another furor about this, and then also in what directions it might go. Right? So I can imagine a sense of outrage being directed towards Dupont. Are there other ways in which you could foresee that?

Gulezian: No. I think it would be towards Dupont. You know, one of the things that I think has floated down that it probably would, there would be more of an outrage right now, but this understanding that Dupont reached with the

NIH on access for not-for-profits to these models have. It hasn't divided the community, but it's kind of taken away a big part of the voice of the community, because now it's not like the academics and the for-profits are in it together. Before it was, nobody could use it, and now it's, what happens to the academics is that they aren't -- they could be in the position of not being able to license the models, which is an important source of revenue for some universities, and even for the NIH, that's an important source of revenue, is licensing models and the royalties that they receive on those. But that's really where it's affecting academics now, is more in their tech-transfer groups rather than in their resource groups. And so they're all part of the same community, but right now, who might have been the most vocal, who would have been on really the leading edge of the research, they're enabled, and it's sort of that next tier, they're not enabled. They probably just don't really know it yet and don't have the strength that they had the last time around, when the academics were -- it's really in the same boat.

Shostak: I got an article that you wrote about transgenic animals and intellectual property rights off the Taconic web site, and you conclude that by emphasizing the importance of partnerships between academia and industry that facilitate the sharing of intellectual property rights. And we've been talking about some of the challenges to those partnerships.

Gulezian: Right.

Shostak: What are some examples of successful partnerships?

Gulezian:

Ah, sure. Well, I think we've talked about several. Right? The p53 is a tremendously successful one, and Tg.AC as well. I mean, those are the best examples, I think, right now in the world of success. P53, and those partnerships were academic, NIH; Taconic as a provider; pharmaceutical companies as evaluators, and happening all over the world, you know, providing, developing protocols and testing according to those protocols and really being able to evaluate and move something forward. I'd say that that is the best model that there is. In other fields of research where these have been overcome, just to kind of give you a parallel, because I think we've seen the carcinogenicity testing field is one of the primary, is one of the first applications where transgenics started to move and shape, shake up this field of getting models out there and commercializing them. But following that is the neurodegeneration field, the APP mouse, the Alzheimer Precursor Protein mouse, where there's been a lot of controversy and inability to get access to that model for use in investigating Alzheimer's disease. That's another one where partnerships with academics and industry have allowed the model to be shared and evaluated, and now has really expanded its use to far areas of the world. So I was talking with someone today about use of the model in Taiwan and how they might do something else to modify that model of transplantation and vaccine development. There are a number of good examples there, too. And I mentioned the neurodegenerative disease and other disease areas. We're seeing that happen to the cardiovascular

atherosclerosis area. A company that was primarily involved in creating transgenic animal models, the company that was once called DNX and has now been bought by Xenogen Biosciences, DNX had developed models for studying atherosclerosis back in the late '80s, and they had developed and wanted to maintain them exclusively for their own use for testing for clients, and then in the mid-'90s, joined a partnership with Taconic to begin to make them available. It took quite a while. But through the access, other companies began to use them, and these models are now being used quite routinely by a number of academics and for-profits for these purposes. So, again, it takes a long time, and it really takes that combination of basic research that comes out of academic labs to feed the industry research, and it takes that use and evaluation by the industry research to warrant putting something into commercial production so that it can be produced at levels that make it marketable for a company, you know, reasonable for a company like us to market. There are thousands and thousands of transgenic models, and we have maybe a hundred that we provide in this way. So, obviously, not every one can be done. It's just not economically feasible. So it really takes that commitment by pharmaceutical companies to do the evaluation to make it worthwhile, and they wouldn't be doing it without sort of the basic information, characterization, and gene knowledge that's coming out of the academic labs. So I think that those are some of the best examples of the success of it. It really does require that. It does not happen if it's in just one sector

alone. We couldn't see it. It just doesn't happen. It really needs that sort of constant cross-dissemination.

Shostak: I'm wondering about the economics of this aspect of the industry.

Gulezian: Sure.

Shostak: And it might actually be easier for you to send me information about this. But I'm wondering things like, roughly speaking, how much it costs to develop a transgenic model for commercial purposes.

Gulezian: Right. You know, it's hard to answer that, and it would have to be a range, and I think you're probably talking about, there are two different aspects. What does it cost an academic lab in terms of research monies to in fact create a model, and I think you probably have to look at that and say, what are all the ones that failed and what's the one that was successful? And probably if you took a look at it like that, you're probably talking about a quarter of a million to a million dollars, probably, when you talk about the range of, you know, again, all those that are not hits for the one that's a hit. And then, once you talk about bringing a model to a company like Taconic, there's a range, I would say, of, again, depending on what some of the characteristics and so forth of the model are, another \$100,000 to \$200,000 investment in a model sort of up front for getting that model produced, and then models may or may not get to a break-even point. So you could be in production with a model for many years where it's not at a break-even point. Again, you'd have to take a look at a whole portfolio of models to look at the financial side of it.

Right? Some of them will be profitable, and some of them will just never even be break-even, and it's really more about looking at it as providing a whole portfolio and a service to a community, because some of those that, because, you know, you've kind of gotten a sense of how long it takes. You can't say, "I'm going to put something out there for a year," or even two years and then say, "Oh, this is not catching on." It takes longer than that. So there's a long time commitment before you can see a return.

Shostak: And can you give me some sense of what the trend has been in the demand for these models, specifically the models that are used to study carcinogenicity?

Gulezian: Sure. Let's see. I can do that, I can do that. It's gone from, let's just take over the last five years, and one way to do this, instead of talking about absolute numbers of animals, it might be a better way to do it would be in terms of number of studies. So let's say a typical study size of animals would be about 200 animals in a study, and maybe five years ago there were big studies, and that has now, that's more than, I would say it's about five times the amount now, so more like 30 studies now for any one animal model that we're talking about. So more like 30 studies in a year for p53 as opposed to five or six five years ago.

Shostak: Okay.

Gulezian: So it's not quite 10 times.

Shostak: From your perspective as the producer and distributor for these models, would you say that they're becoming standard instruments or standard

tools in carcinogenicity research, or are they still kind of cutting-edge?

Gulezian: I think it's got to be somewhere in between. So if we looked at that as cutting-edge as a 1 and a standard as a 10, I'd say we're probably around an 8.

Shostak: Okay, okay. And what steps do you see as necessary before they became more a standard tool?

Gulezian: Right. You know, the evaluation studies uncovered some questions and concerns with the model, so even though they're now being accepted for protocols by regulatory agencies like the FDA, there are still some outstanding questions, so further research needs to be done. But it's a smaller degree of research than has been done before. Some of those have to do with just responses to certain compounds and questions about those responses, other reference compounds and what the response might be if it were to other reference compounds. Those have yet to be done. And there is work afoot to, again, a partnership of the different groups here to support some of those studies and to get this done. But I'd say it's another two to five years.

Shostak: You mentioned that protocols for studies using transgenic models have been approved by FDA. Are you aware of protocols approved by any of the other regulatory agencies?

Gulezian: I am not.

Shostak: Neither am I.

Gulezian: Yeah. I know that the EPA, just like the NTP, has used the models. But,

of course, NTP is not regulatory. EPA I think did a set of studies on byproducts of water. I don't think just chlorination, I don't think I can remember the whole project, what it was called, but it was water treatment. So whatever the water treatment was, it was byproducts of water treatment, and I think that there were concerns about those and there was some testing done. But as far as regulatory agencies, not that I know of.

Shostak: Okay. I appreciate just being able to check my perceptions against yours.

Gulezian: Yeah.

Shostak: Two more quick questions, if I may. Three, the first being possibly somewhat less quick. I'm wondering if there are important aspects of this general story that we've not yet touched on. Are there things that you think I should have asked you?

Gulezian: I'm thinking here. No. I think there are levels of detail, of course, but I don't think that those are critical to what you're trying to do. I'm certainly happy to answer them as you kind of take a look at it and if you want to get further into understanding something but we hit the important ones. It takes a long time; it's expensive; it takes multi-laboratory evaluation; and it takes participation from all sectors. The characterization of the model is important in access; it's important in licensing; it's an important part of the access. It is a global community. This is not just the U.S. And any time you ignore that, you'll also run into trouble, I think, with really getting development of a model if you just look at it from one geographic

center or another. I think we touched on that. And I think we've touched on what the, what we see about the future that's known it's not known, of course, but what we might expect to happen, and we don't know what will happen.

Shostak: Thank you. And that's incredibly helpful.

Gulezian: Okay.

Shostak: Then the quick questions. Are there other people who you would suggest I talk with?

Gulezian: I think you probably ought to talk with someone from ILSI. Do you have some names at ILSI?

Shostak: I know Denise Robinson is no longer there.

Gulezian: She's at Pfizer now. Actually, Denise and I are friends. She's out of the office for a couple weeks. But Amy Lavin. Do you know Amy?

Shostak: I know her name actually, but I don't know her well.

Gulezian: I'm sure that she'd be happy to talk with you. I thought I had her number. Let's see. I'm sure I have her number here somewhere.

Shostak: And they have offices in D.C., correct?

Gulezian: D.C.

Shostak: That's great.

Gulezian: Yeah. Let's see if I can find it for you. I know I have that.

Shostak: Would it be helpful if I just sent you an e-mail about that?

Gulezian: Yeah. If I don't find it in a second, we'll do that. Yeah. Why don't you go ahead and send me an e-mail, and I'll get that back to you.

Shostak: Thank you.

Gulezian: She's probably the best one, and then she might be able to tell you who there, if not her. She did come in on the project there at the end but still would have probably good historical information and a different perspective.

Shostak: That's great. Thank you. And then, finally, I realize that from the different things that I could gather from the web site, I nonetheless failed to gather what your exact title is at Taconic.

Gulezian: Right. So I'm director of product management.

Shostak: Okay. And just quickly, if I can ask you what your educational background is?

Gulezian: Sure. Its biology, and that's then I've kind of taken it from there into molecular biology and spent years in research in the laboratory and then went into sales and marketing in research tools.

Shostak: Great. That's also very helpful.

Gulezian: Okay.

Shostak: I appreciate your time and all of your insights and your willingness to help a novice learn this field.

Gulezian: Yes. Well, I like this stuff, so it's fun for me and it's always intriguing for me when someone has picked up on, you know, kind of from the outside, come out there and picked up on this. Like what was it that made you think this was interesting? And so you shared that with me, and so that was neat, too. You said you'd share the transcript with me once you've

kind of got things down. Are you going to have a final product yourself?

Shostak: There'll be at least two final products. One will be a lecture given at the NIH sometime in the summer, which should be available over the web as well as on campus, and I can certainly send you the details.

Gulezian: Oh, that would be wonderful. I would love to come, and I think others from my company would like to come as well.

Shostak: I would love for you all to be there. To have another opportunity to engage with you around these issues and your perspectives on them would be wonderful.

Gulezian: Yes, that would be great.

END OF INTERVIEW