Cannon, Ronald 2003

Dr. Ronald Cannon Oral History 2003

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Dr. Ronald Cannon
November 14, 2003

It's Friday, November 14th, and I'm interviewing Dr. Ronald Cannon.

Sara Shostak: Dr. Cannon, you know that I have a tape recorder on.

Ronald Cannon: I do.

Shostak: Great. Thank you. I'd like to begin by asking you what your research focus was prior to working on transgenics.

Cannon: I came into a research program that was investigating the use of genetic engineered mouse models in toxicology. I arrived in '91-'92, so a couple of years before- '89 to '91 was about when these mouse models were starting to find some utility. Prior to that, I actually was working with EPA in identifying and characterizing molecules that cause male germ-line stress. Acrylamide was the chemical of interest. We were interested in it toxicity to sperm cells or to premature sperm cells and whether exposures to acrylamide could cause DNA damage or inheritance abnormalities in mice. I was a molecular biologist by trade, knew how to clone genes, how to express genes, how to characterize expression, and knew molecular genetics. I'd also worked with viruses…promoters and gene expression. NIEHS has just begun the characterization of a Ras and P53 KO mice. At that time they don't know much about them. So they needed a good molecular biologist to come in and look at expression patterns, to characterize the mice it a molecular level: That's when I came to NIEHS. When I arrived the toxicologists were asking, "Can we use these animals to identify a carcinogen or a toxic molecule, and how ?" And at the same time, while they were looking at that in toxicology areas, they needed a molecular biologist, someone who actually can look at the DNA level, the protein level, at the molecular level and characterize these animals. We were attempting to gain a mechanistic understanding: exactly how does this thing work from the bolts up? Okay? It's not just satisfactory to know a car runs; you've got to tell somebody, a mechanic, that actually knows every piece of it and how it's put together and how it functions.

Shostak: What made you interested in doing this research?

Cannon: Well, it was exciting to get back to an important and clinically relevant to cancer, one that was more *in vivo* and investigating carcinogenic pathways.. It has almost immediate application significance because transgenics were considered models for human health. Although, they do have shortcomings. But it was good to get to an *in vivo* model that might have direct application to humans and be more "translational". That was very stimulating. As a molecular biologist, sometimes you're abstract; you're dealing with liquids and things in test tubes that you can't see, you can only measure, or you have to see them in a special way. You have to use probes or markers to visualize them. Working with live animals that mimicked human diseases just seemed more clinically relevant. At the same time it was challenging. It's a challenge because you're dealing with *in vivo* mechanism s, so that's different than just looking at cells; as a reductionist, we take things apart and ask for it to work as a complex *in vitro*. Now we were investigating how everything worked together in a live breathing animal. Genetically altered in various cancer related signaling pathways

Shostak: How do they do that?

Cannon: If you remove a distributor from a car the car, it doesn't run, and you can determine why and how a distributor works. What is it contribution to a normal full functioning car. However, if you remove the compressor on the car's air conditioner, the car will run but you'll have problems keeping the car interior cool. Not that critical to running but if the temperature is hot outside it become pretty important. The same is true with genetically modifying mice. You can mutate or remove a gene and find out how and when it contributes to the wellbeing of a living animal? You may find the animal to be normal until it is stressed it a certain way, the analogy being until it gets hot and you need your air conditioner, you don't know your air conditioner's broken. So using transgenic technology you can alter single components and then search for the effect. And all this can be done in vivo. Chemicals are stressors too. You can raise or lower sensitivity thresholds. You can make an animal more sensitive to a particular exposure, stress or chemical. This allows one to test the validity of a model or hypothesis. If we hypothesize that a pathway important for tumorigenesis signals when exposed to chemical X , then activating it a high level will produce a tumor. Genetic modifications do allow one to increase the signaling level and alter tumorigenesis, give one the ability to produce more tumors. Conversely, if one blocks a critical pathway for cancer you may reduce or tumorigenesis. So now we can engineer mouse models and hypotheses and actually test in vivo. I find this pretty exciting! That just doesn't happen very often.

Shostak: Which were the first of the transgenic models you worked with?

Cannon: Tg.AC a ras model and some P53 were the first to arrive.

Shostak: You said that the models came into the institute. How did they come in?

Cannon: So there were collaborative efforts years prior to make a better mousetrap. NIEHS houses the National Toxicology Program which had invested many years in developing assay systems both *in vivo and in vitro* to identify hazardous chemicals, (carcinogens) to protect us and our environment. Chemical testing *in vivo* involves the "two-year bioassay". It was recognized early on that this assay could never test all the chemicals in question. There was simply not enough time or money to accomplish that feat. Dr Ray Tennant recognized this, and with the support of the Director, Dr. Ken Olden, was instrumental in investigation alternatives and/or adjuncts to the two year bioassay. Also at this time, the Leder group had developed a few genetically modified mouse lines. They were curious in evaluating its utility in the identification of toxic or carcinogenic chemicals. So two mouse line that showed the most poromise were brought in for consideration. The first, a ras transgenic was called Tg.AC. Tg.AC was almost a serendipitous finding. It turned out to be an interesting one with potential. And the p53 KO -- p53, was a hot topic. P53 was labeled molecule of the year. It's like the gatekeeper of the genome. I worked on Tg.AC and Jef French worked on the P53 model. Metaphorically, Ray thought of it as networks and hubs. If you want to alter something, you want to alter the hub, which will affect all the spokes in the entire network. p53 was clearly a hub. It was something that would regulate a multitude of genes and processes that deal with DNA damage, toxicity, carcinogenicity. It's truly a tumor-suppressor gene.

Shostak: And what does Tg.AC do?

Cannon: Tg.AC. Okay. So, back to the car now. If you think about cancer -- which is what these models are basically designed for. To investigate cancer and carcinogenic potential of chemicals to cause cancer -- you essentially have two things that happen. You must lose the break and press the accelerator at the same time. So there are a set of genes that we call proliferative genes that drive the proliferative process. Ras (Tg.AC) These are analogous to the accelerator. They'll make your car go.

Shostak: Okay.

Cannon: There are also a set of genes that are brakes. These are called tumor suppressors. P53 is one of these. -- so to get cancer, essentially you have to have the gas on and remove the brake, You if you accelerate with a brake intact you present with hyper proliferative diseases. In skin this would likely cause your skin to thicken and redden. But you wouldn't produce a tumor. But if you lost the brake, that is, if you lost the ability to become a normal skin cell and unchecked proliferation without differentiation is cancer. This type of growth in cells is genetically unstable and can give rise to metastatic events. The Tg.AC mouse has na inducible ras gene - a class of a proliferator. About 30 percent of all human tumors have been linked to mutations or aberrant expression of ras proliferator genes. Ras genes, normally, switch on/off very quickly. But mutations in *ras* basically don't allow this switch -- it's like the accelerator cable's been cut and you're at full speed. This molecular event is what we call constitutively activated, meaning it's on all the time and you can't turn it off. So now you're left with, just how good is your brake? The Tg.AC mouse is unique. It mutant ras gene is inducible. The animal develops normally, but when the gene is turned on, it expresses a mutant ras gene, constitutively. The ras protein is modified in such a way to send a constant proliferative signal, i.e., the accelerator is pushed to the floor, and now it's a question, can you stop it? Will the brake work? And in most cases, for a short period of time, the brake does works, just like in a normal car if you had the accelerator. . But eventually and additional genetic event occurs that disables your brake sending you into tumorigenesis. Knowing this, for any chemical to give you a cancer it must disable two mechanisms or hit two genes. Or you could have a genetic problem that you're born with. The aging process or going through normal life, could produce the mutations. This has been called two stage mutagenesis or the two hit model of cancer. Ok, back to Tg.AC. Tg.AC was actually designed for studying stem cell leukemia. The Leder lab was characterizing hemoglobin genes. They also had the oncogenic *ras* gene, a mutated form of the ras gene from a virus. They introduced the oncogenic viral gene into the mouse genome under the control of an embryonic hemoglobin promoter. The promoter regulates its expression in cells. They reasoned ras would be expressed in early progenitor blood cells causing unchecked proliferation and produce leukemia. And it did in a third of the animals, but it took a year out before it shows up. More interesting, a second observation was made in these mice. They noticed that the mice would sometimes over-groom. They'd scratch themselves. Or they would bite each other. Aya Leder - while managing these colonies and noticed that bite wounds sites were producing tumors. Now, historically, scientific studies of two-stage skin tumorigenesis had shown wounding was a promoting event and could cause tumors.

Shostak: It's very helpful, and I think I'm following you.

Cannon: The two-stage model of tumorigenesis describes the first "hit" as a mutation from chemical exposure and then a proliferative event from a chemical or wounding. Aya astutely recognized that the skin tumors were associated with bite wounds and also knew that mutant ras expression was potentially involved. She wondered if the mutated viral ras gene was expressed in these bite wound associated skin tumors." She tested it and found indeed it was. Next, she tested chemicals that were known to be promoters. The two-stage model characterizes the first mutation stage as "initiation" and the second proliferative stage as "promotion". Chemicals that cause proliferation are termed chemical promoters. She tested , TPA a known promoter some other classical ones. They all produced tumors in the Tg.AC mouse line and ras expression was positive in all.

She characterized the Tg.AC mouse to be "genetically initiated". Meaning if cancer required both a mutation (initiation) and promotion, this mouse model only required the second step, promotion, to get reach tumorigenesis. So, if cancer in humans is indeed a multi-step process and chemicals have to cause genetic hits more than once, then this mouse model reduces the number of hits, shortens the time and lowers the threshold to tumorigenesis.

Or restating- it reduces latency. Time to tumor or time to induction equals latency. So if you can reduce latency , the animal is more sensitive, but in a sense you're recapitulating what the normal process but in less time. I like to think of it as it's potentiated.

So this seemed like, on the face of it, a good model to test for carcinogens. Also since all the cells are genetically initiated in this mouse the process is more efficient, higher penetrance with a more homogeneous response. So next we sought to validate the response and standardize the protocol.

Shostak: How does a protocol become standardized?

Cannon: That's a tough one. We call it "the V word" – validation. Basically, you must know the animal and understand the process, the biological process. For example when using topical dosing, it's not reasonable to dose an animal at a dose so high that completely burns or blisters the skin or produces a wound or even kills the animals. We began by using toxicology studies that had determined the maximum tolerated dose and no-effect levels and modeled our studies to experimental paradigms similar to the two-year bioassay.

So our assay would be shorter, use less animals, and hopefully become a modified or adjunct to the two-year bioassay using a genetic model - Alternative models. Our hope is that these alternative models somehow have been genetically modified to either reduce latency, lower threshold, but do it in an acceptable, mechanistically or biologically relevant way. Using modified pathways known to be important for cancer. We know many genes that are mutated and/or overexpressed during a tumorogenic response. So our logic is to modify mice to contain these mutations to predispose them and expose them to known carcinogens for short times. And because the animals were genetically identical, we reasoned we could use fewer. Our hope is less time to tumor and fewer animals. That will allows us to test more chemicals. It also provides some mechanistic understanding. Now you know what pathway it activates. It is debatable whether it's actually cheaper. That is yet to be determined.

But getting back to your question, to validate this assay, you have to test a lot of chemicals, and so we've tested a lot of chemicals and we've published a lot of papers on it, and we've gone to a lot of meetings, and there was an international harmonization committee that was put together. There was the ILSI, International Life Sciences Institute....there were consortiums that were put together to come in and contribute to it. They began with basic questions: "Do you like these models? If you don't believe in them, what should we do? Give us a list of chemicals." So they all devised all these protocols and they standardized it, basically all came to an agreement, and then they contributed chemicals. It was unprecedented! Companies coming together. Previously they were competing in the marketplace now they were coming together as one. "I'll let you try this chemical and you try this chemical," They contributed and we tested against a bank of transgenics against selected chemicals. . There were multiple transgenics. I mean, there was one that goes through a DNA repair process, the XPA mouse. There's a *ras* H2 from Japan that is just now becoming readily available in the U.S. There's the Tg.AC. Larry Donehower and Alan Bradley had made the p53, so there's at least four, possibly five. I think there was a p53-XPA cross, where they put both of those in the same background. So there were a lot of these, and they wanted to see how they would do. Some liked the old model because they were predictable. They knew all the pitfalls. They knew what to look for. And let's face it, no one really likes change, especially if it impinges on your ability to get a drug to market

So that's basically how it was standardized. We all got together, we tested the animals models.. Then we came back and we presented the data and had an agreement on protocol with all the commercial companies and pharmaceuticals, regulators..

It took a lot of courage for those regulators to say, "You know, instead of doing the two-year bioassay in the mouse, you can use one of these alternative models. Do you still use a rat two-year ?." Prior to this, to get a chemical through, you had to have a bank of tests that said that your chemical would not cause a genetic effect. Then you had to put it through the rat as an *in vivo* in two year and a mouse two-year. So they basically said, "You know, the rat's probably enough. Let's use the alternatives to truncate the time," and they would get to market and test these chemicals faster by using an adjunct or a replacement model,

Shostak: One thing that I notice when I ask about which people in the regulatory agencies you all have worked with around the transgenic assays is that they're all at FDA, and I'm still trying to puzzle through what happened with EPA.

Cannon: I have no information on that. Only that the chemical tested were drugs not pollutants.

EPA has spent years, along with other scientists, to try to extrapolate risk to humans from exposure to mouse models. Humans don't line up to be exposed to bad chemicals -- right? -- so you do the best you can. It's not a perfect science. But they had gotten very good at it.

You'll have to talk with somebody from the EPA. But I would guess, my guess is, is that EPA thought that was a nearly impossible thing to do with an alternative model.

Shostak: Speaking of new paradigms, what kind of retooling or restructuring, if any, had to occur in your lab or in the labs in which you were working in order to do research on transgenics?

Cannon: For me it wasn't that big of a difference. For people that were used to studying in the two-year, dosing mice and having a two-year bioassay, there were many toxicologists, pathologists, that would perform necropsies and identify pathologies. The transgenics now said, "Well, you know, we have predisposed certain organ systems, certain tissues, certain cell types, to be sensitive to this chemical, so that we don't even think you need to look elsewhere. We basically are saying that if this animal is going to get a cancer, we've set up a pathway where it should happen on the skin or in the stomach or in the lung, organ-specific. That was the concept. And this didn't really change the lab, it changed the focus on the pathologies. Maybe we don't need to look at all the tissues.

For example, we've set the Tg.AC up where if you dermally treat with a carcinogen, you get tumors on the back of the skin. Dr. Tennant called this a "reporter phenotype", meaning it reports out on the skin. If the chemical is a carcinogen the mouse is staged for it to occur in the skin. Well, for a pathologist, he's probably a bit skeptical, "Well, wait a minute. You dose it, it goes through the skin, it goes to the liver, goes to the kidney, goes to the brain, goes to the heart, goes to the lung." So to him this is a big problem because he wants to know what the toxic effects are on all the organs, and we' re telling him, "Don't worry about it. If it's a carcinogen, we set up a molecular pathway that will fire off on the skin, and you should only look at the skin for the effect." Now, if you want to know if it's toxic to the liver, that's fine, but as far as its carcinogenic or oncogenic potential, the transgenic has been staged genetically to fire off in the skin.

That takes a paradigm shift for somebody that spent their whole life studying all those organs and the effects in all those, and integrating all of that into a nice story, "Well, it probably oversimplifies the process.

Shostak: I should have asked you this question earlier: Which laboratory were you working in when you arrived at NIH?

Cannon: It was called the Laboratory of Environmental Carcinogenesis and Mutagenesis, LECM. I was in a Gene Tox lab at EPA, where we were studying certain molecules that cause toxic effects and trying to come up with assays that would help you determine that. Here it was LECM, Laboratory of Environmental Carcinogenesis and Mutagenesis, under Ray Tennant, and Ray was bringing in transgenics and saying, "Will this one work?" "I don't know." "Will this one work? Is it too sensitive?" And the Tg.AC arrived, and we immediately recognized that it had potential, and from that point on we started doing molecular work trying to understand, " Why does this thing work the way it works?" And so that has been my job, is to figure out basically why does it work, how does it work the way it works, since it doesn't work the way it was originally planned. It's not a leukemia model, although it probably could be, and we published on it. But what's the mechanism and just how does it work? And because it was serendipitous and it's, if you will, an enigma, it wasn't originally designed to do what it's doing now, it's been not an easy thing, " it's been fun. It's a puzzle. It's a true puzzle.

Shostak: Do you feel like you've solved that puzzle yet?

Cannon: Oh, no. I don't think anybody knows the true mechanistic answer. We obviously know quite a bit about it, but to nail it to a true molecular mechanism of how the animal works has still evaded us.

Shostak: So, in regards to the Tg.AC mouse, research on the molecular mechanism has proceeded alongside research on its potential as a bioassay. Is that correct?

Cannon: That's probably not the total picture. The problem with molecular, it started at the same time, but it's much easier to do the empirically determine (testing) whether an *in vivo* model is acting the way it should act; that is, more consistent with a hypothesis. That is to say, to go in and clone a gene or to characterize something at the molecular level will take five, eight, 10 years maybe. It depends on what you need to do. Dosing the animal, if you have three, four, five, 10 commercial companies involved, two or three contract companies involved, you certainly could divvy out the animals, choose chemicals, judiciously choose chemicals, chemicals that should give you a positive, should give you a negative, so you can, known chemicals so you can test it, and just look for just the empirical results, just empirical observations. And what was found is that the animal behaved quite well. It could discriminate between carcinogens and non-carcinogens. So, presented with that data, even in the absence of molecular understanding, the regulators said, "This animal has utility in identifying non-genotoxic carcinogens."

And also, there was a need, there was a niche. This animal identifies carcinogens that don't necessarily mutate genes.

Shostak: I was going to ask you about that.

Cannon: Non-genotoxic. So one of the things that was discovered -- and Ray was instrumental in this discovery -- is that, again, there's a two-stage. There's things that mutate genes, but there's also things that just proliferate out genes that have been genetically altered or mutated, cells that contain genes carrying mutations mutated. And that proliferative component is important. Its essential. Without it, you don't get cancer. There are chemicals that do that, and those are called non-genotoxic carcinogens. So that was Tg.AC's potential utility. Now, some people call those promoters based on the two-stage model and initiation and promotion.

Shostak: Then that two-stage model is still dominant. Right?

Cannon: That two-stage model has been here for 40 years and is still being investigated. If you look up, I'm sure if we did a Medline search, just initiation promotion or two-stage model, you would find numerous papers, because there are multiple genes that control promotion. So the need for an *in vivo* model to identify non-genotoxic carcinogens and the fact that there were 20, 30 chemicals that were already known that had been well characterized through the two-year bioassay, some of which may have been called a positive, some of which may have been called a negative, but when they went through a Tg.AC, some people looked at it like maybe Tg.AC gave them a wrong response. And others that said, "You know, I didn't think that was a real positive in the two-year bioassay. The Tg.AC didn't fire off, didn't produce tumors." So that kind of makes me feel good.

So it had a good report card, basically. It was at least as good as or better than what people expected.

SIDE B

Cannon: What's the mechanism? How is this really working? Well, it's easier to drive the car and to know how the car drives than it is to take it apart when you've never seen the car and to put it back together, and so that's essentially what you have to do to characterize it. So that's what we' re doing, and we know there's a lot of papers out there and we've done quite well explaining it, but there are still some unknowns, and rightly so. We'll get to those, I hope. We're having fun doing it.

Shostak: I'm curious about the process of bringing a molecular focus or mechanistic focus into toxicology and what that process has been like for you.

Cannon: I think for most toxicologists, it's been a welcome change. I think we're all scientists and we all want to know basically how things work. We're just curious and we like to solve puzzles. That's what scientists do. We think we have the answer. We hypothesize. We build models. And then we got out there and try to put the puzzle together and we say, "Nope, we don't have the answer." Well, then we do it again, and that's why they call it re-search. Right? Not just search and find but re-search. So we do it over and over until we get it right, and then we alter our hypothesis and test. That' s the way it works."

So toxicologists are good scientists, but there had been -- and I think not rightly- a characterization about toxicologists that they were less mechanistic.

Shostak: Phenomenological?

Cannon: Yeah. Phenomenological, observational. They just looked at things and watched the dynamics of change and patterns and observed phenomenon, and characterized it as such. That's not entirely the case and I think that's an unfair. I don't think that's necessarily true. But some people thought that, nevertheless. So now, with the influx of the molecular tools, there were a lot of toxicologists that really supported a more molecular viewpoint because it moved them over in a molecular, more mechanistic and mainstream. if you will, more acceptable. The biochemists have been at the top tier, but then the molecular biologists came in vogue. And now we find that molecular biologists need biochemistry even more. The biochemists are basically the true molecular At least that's my opinion..

Shostak: Do you want to stop and get some water?

Cannon: Yes please.

[tape recorder turned off, then on]

Cannon: Then came the molecular evolution of nucleic acids, recombinant DNA -- this is in the late '70s -- biochemical protocols for molecular biology. So this was when the biochemists started learning how to manage DNA and RNA, this transition in the late '60's and '70s, and this is -- then the next generation of scientists focused on sequencing DNA and cloning

Would you like something? Do you need a drink maybe?

Shostak: I'm good, thank you.

When you were talking about the Leders, you mentioned that there had been some contention around the patenting. I'm wondering if that affected your access to the Tg.AC mouse in any way.

Cannon: It didn't affect our access because we were in the front side of the development, not necessarily design, but just the characterization and assessing the utility of things. So there were agreements, I assume -- and you'll have to speak with Ray on this -- there were agreements that were made with the government and/or with our laboratory and other laboratories that allowed us and the government and basic researchers, I think, to get these animals early on to use them, as long as they weren't used for commercial purposes. So for basic research, it's no problem because you could get them, I think, you can still get them. There was more of a problem for pharmaceutical, for commercial use. Screening for tumorogenic, carcinogenic potential, testing for regulatory purposes, because they were expensive. They're $300 a mouse. And some of these mice run more than that. I think the *r as* H2 was more expensive—When you use 500 mice at 300$/mouse. That can be a problem; It becomes expensive.

For commercial, I can see where cost could be a problem. But you have to also understand that the commercial companies in the drug development areas, could cut their time to market, and reduced time is money, a substantial amount of money. So these models might work for them.

Shostak: I'm curious about your opinion as to why so much of the Tg.AC research has been done here at NIEHS. What is it about the NIEHS that made this the right place for that research agenda?

Cannon: The initial characterization of the Tg.AC mouse -- and of other mice - the new mouse, were performed here at NIEHS.

Shostak: That's N-E-U, right?

Cannon: Yeah. That's NEU, and it's mouse mammary tumor models, I think, was where that came from. An earlier one that didn't work out. But because of the relationship between Ray and Phil.. You'd have to ask Ray, because I wasn't here in the early periods; the NEU work occurred prior to me coming here -- but I think that relationship just fostered an exchange of information.

Shostak: The relationship between . . .

Cannon: Ray Tennant and, I think, Leder, Phil Leder. Ray's a frontier man- a forward thinker in toxicology. He's looking for new methods, groundbreaking methods that will provide mechanistic understanding, less time, less money, less animals, no animals. He was willing to take a risk. And he knew that Phil, who was one of the earlier pioneers in transgenics, had potential models. So as those models came to be,Ray was willing to test them. NTP has the standard; National Toxicology Program is testing a two-year bioassay. Here's a group of people that are looking at alternatives, and that relationship allowed them to test in this genetically altered models. Some of the models worked, some did not work The first ones didn't. Then we came to Tg.AC and it did.

NIEHS has The National Toxicology Program. We have all these chemicals and pathologists. We have probably the highest concentration of pathologists in the world right here in this building. They can analyze all the tissues from these mice. So it's pretty obvious that this was *the* place for it to happen given the relationship and the early informational exchange about the models between Tennant and Leder.

Shostak: Dr. Tennant is now focused on Toxicogenomics. Is the transgenics research related to that in any way, or are these two separate trajectories that will move in their own path?

Cannon: Again, I think Ray is a forward looking person**.** I think that he's looking forward and trying to find assays that will move and benefit toxicology. And the microarray shows a lot of promise. It allows you to look at a lot of things all at once.

It's challenging because now you're asking . . . You know, it was challenging to tweak one little pathway and to study that pathway. Now you're saying, "Okay. When we took the distributor off the car, I want to know how it affected everything. When we disconnect the brake cable, what's not working? So let's track down every little wire, but let's do it in at one time point." So it's a challenge. A huge challenge.

Shostak: Just as a final question, are there significant parts of this story that I haven't asked you about that you'd like to comment on?

Cannon: I think that all should remember, that in this scientific arena we're using models, we're using mouse models, And by that definition, it's not a human. So there are going to be problems. There are going to be mistakes. There's no such thing as a perfect model

Also, this is a rapidly moving field. There's a lot of basic researchers that are involved. There's a lot of good scientists that are involved. And there's likely many good models out there that just have not made it to port. The ship hasn't come in because it takes a long time to validate in this system. It takes a long time to validate models, and it takes a lot of money,.

Shostak: That's just great. That's why I love interviewing you all. It's fun.

I'm going to turn this off.

END OF INTERVIEW