0:00:05.8 Sarah Crespi: This is the Science Podcast for October 22nd, 2021. I'm Sarah Crespi. For this show, every week, we feature the most interesting news and research published in Science and the sister journals. First up this week, we're gonna have staff writer Erik Stokstad. He's gonna talk about plans for a new deep soil observatory. Deep soil is like the dark matter of soil science, there's a lot of it, and we don't know exactly what's in it. Then we're gonna talk about why wood is a pretty good building material that could be made much better, so much better that one day, we might use it for making cars and planes.

0:00:47.2 SC: I talk with Liangbing Hu. He's a researcher at the University of Maryland, and we're gonna discuss moldable wood that's flexible and strong. And in a sponsored segment from our custom publishing office, Director of Custom Publishing, Sean Sanders talks with researcher Michael Brehm about the role of humanized mouse models in studying and developing treatment for Type 1 diabetes.

0:01:17.6 SC: We have massive telescopes that look far out into the cosmos. We have giant particle accelerators and gargantuan gravitational wave detectors. What about soil science? Where is the big science project on deep soil? Well, it's coming soon. Erik Stokstad is a staff writer here at Science, he wrote about plan for a new soil observatory. Hi, Erik.

0:01:42.3 Erik Stokstad: Hey, Sarah.

0:01:43.5 SC: As you write in your story, we know a lot about the top 30 centimeters of soil, it's for farming, it's for agriculture, we gotta know that stuff, but under that is this kind of secret layer of soil, the Mariana Trench of the land, the dark matter of soil. Why has this been hard to study in the wild?

0:02:04.1 ES: It has to do with shovels. As one soil scientist told me, the deeper you go, the harder it gets. Some other soil scientists said it's actually relatively rare to be down deep; like the deep ocean, it's often hard to get to.

0:02:19.8 SC: Do we have any kind of sense of a scale of how much soil we don't know about?

0:02:24.7 ES: Would you settle for a lot?

[laughter]

0:02:27.4 SC: Yes, I would.

0:02:28.3 ES: When you think about these layers, the upper 30 centimeters, give or take, that's really rich in life and in nutrients and roots, but it's a thin layer, so soils can go deep. It really depends what the local geology is like, but meters deep. And in some places, you know it's just really, really deep, so that's a lot of volume that's down below this thin vital layer of top soil.
The project you talk about in your story, the Deep Soil Ecotron, maybe I built it up a little bit in my intro, is it a big science project? Is it big, big?

Compared to astronomy or particle physics, a relatively little amount of money will go a long way in soil science. It's a mid-sized grant that they got. It's about $19 million that will fund construction. And the University of Idaho, where it's gonna be built, the university has a building to put it in and they've got money to build the equipment. People were describing it as hangar-sized, I don't know if it's gonna be sort of big enough to park a plane in, but it's a big lab that's gonna be in a probably one large room size of a lab.

What exactly is an ecotron?

The idea is to take kind of a replica of an ecosystem and put it into an experimental setting. It's sort of like a terrarium, and you measure various aspects of the ecosystem, but you do that multiple times so that you're getting this combination of some ecological realism, but also, the benefits of a laboratory experiment where you control the setting and you have multiple instances so that you can start to say with some statistical certainty what the patterns are.

Is there a set size already for the ecotrons that are in there? Or is it gonna depend on the project?

You've got this whole range of sizes and questions. And one thing that's been missing up to now is really sort of manipulating the deeper part of the soil. That's where this Idaho lab comes in. And the design there is that they'll have 3-meter columns of soil that are placed in metal cylinders, and on the top, they can plant vegetation that will be sealed airtight, so that they can measure the gas that is to come in and out, they can control all the rain that happens inside, and they'll have a look with much greater access because you'll be able to walk around these columns of soil. There'll be little ports to look in and there'll be sensors plugged in at various depths.

You could wrap your arms around it, I'm sure many soil scientists will be hugging them when they first meet them, right. So it's kind of the diameter of a manhole cover and 3 meters tall, so they've opted to go deep and to have a lot of them. So that's what's different, they'll be able to heat them from the outside or cool them off, all the way down to create freeze-thaw cycles or have the water come up from the bottom. If you imagine water upwelling, that's a new capability that this lab will have.

How hard is it to get 3 meters of soil into a tube without disturbing it so much that you're mixing those different depths?

That's a great question, Sarah, and that's one of the things that they're working on and this won't be built for five years, I think there'll be a lot of experimenting how to make this happen. There are already devices that you can go out and sample soil, and typically what they'll do is they'll take a big steel tube and they'll pound it down to the ground, and then they will dig out around it, and then you can slice the bottom and pull it up, but that's gonna be really hard to do, something that's 3 meters tall. But it's really pretty important to get the soil out as intact as possible because it's
a deep part of the ecosystem and it's got a structure.

0:06:48.7 ES: One thing that's different about the deep soil is that compared to the topsoil, where you might have plowing, where you might have lots of organisms digging in the soil or worming their way through it, so you've got a lot of, relatively speaking, turnover in the topsoil. In the deep soil, everything is happening at a much slower pace. Particles are moving much more gradually, things are moving down through little channels in the soil that the roots have dug out, but there's a much more layering and structural element to it. And you wanna keep that as intact as possible, because if you jiggle it and everything gets loose and wobbly, then the gases are gonna behave differently, the microbes might behave differently. You'll have exposed it to oxygen or lots of oxygen for the first time.

0:07:38.1 SC: What about the big questions? What don't we know about dirt, Erik?

0:07:43.2 ES: One of the soil scientists said to me, "We know just enough to know it's really important and not enough to predict how it's gonna impact the fate of the planet." As climate changes, as precipitation changes, as these soils warm up through the rest of the century, we know that there are a lot of important things going on down there. So top of everyone's mind is climate because there's carbon stored in the deep soil, almost as much or maybe more than in the topsoil because it's such a large amount. Already, there are indications from experiments in the field that the rate of carbon that's emitted from the microbes in the deep soil, that's gonna increase. But more carbon might be stored down there as plants grow and as more roots make their way into the deep soil.

0:08:35.9 SC: Speaking of microbes, is that something they're gonna be able to monitor in this lab?

0:08:41.0 ES: What they'll be able to do much more easily is measure their activity by sampling the gases that these microbes take in and emit. It would be easy to go in and take a little sample of it, and then sequence all the DNA there and identify exactly which microbes are present.

0:09:00.3 SC: You also talk about watching the birth and death of soil, which I thought was very poetic. So what kinds of factors are important for that cycle?

0:09:09.8 ES: Where does soil come from? Soil comes from rock that's broken down. And that's happening down where the soil meets the rock, where roots are fracturing it, where roots are emitting compounds that will slowly dissolve the rock, where microbes are doing the same thing. That's where nutrients come from ultimately, right, on sort of a geological timescale. They'll have a much better view of that process. And if you ask how much topsoil is it safe for us to lose through soil erosion? No more than is being made. You wanna keep the same amount of soil. So calculating that rate is, it's actually a pretty important thing to know.

0:09:51.2 SC: You mentioned that soil is created at this interface between the soil that is and the rock that will be soil; is part of it coming from the surface where things are degrading, like in the forest?
0:10:02.3 ES: That's part of this incredible cycling of soil. The leaves that fall, that's a hugely important process. The leftover parts of the plants after crops have been harvested, these will get broken down by microbes and by insects, and then pulled into the soil. Those particles, they will go down deeper, yes, and all the enzymes that are being released in the topsoil and further down, these things move. So understanding how things go from the top down to the bottom, that's a really important process. These elements fundamentally, they're coming from the bottom up, 'cause it's rock is what Earth is made of and it's life that is enriching it and modifying it.

0:10:53.7 SC: And you got to think about weather too; weather, how it works now and how it's gonna change in the future, 'cause that has an influence on where your soil goes and how it's being created.

0:11:03.7 ES: So one example is, if you think about nitrogen pollution, and that's coming from power plants, it's coming from tailpipes of vehicles, it's coming from livestock manure. This nitrogen pollution, that reactive nitrogen compounds that then settle out of the air onto soil, when that gets wet, if there's an increase in precipitation, then that's gonna release a greenhouse gas called nitrous oxide. And there are all sorts of questions about how that's going to change and how it works. These mechanisms are known and a lab like this can really help scientists figure out what's really going on, what the mechanisms are in this ecosystem. And then they take that knowledge, and they can better equip these big computer models to simulate what's gonna happen over the coming decades.

0:11:55.8 SC: We talked about soils, rocks, microbes, a little bit about plants, roots and gases. What about bugs, invertebrates, all these critters that live in the soil? Will they also be in the ecotrons?

0:12:07.6 ES: I think all of us, even if we don't remember it, some of our first impressions of soil, besides it getting between your toes and eating it, is turning over a log and seeing the creepy crawlies, right? That's the way that all of us first realize that soil is alive. And what's astonishing is that life goes deep. Earthworms aren't just on the top part of the soil. There are giant earthworms a meter long that will burrow down deep. That's really important 'cause they changed the structure of the soil, they move particles and nutrients around, they process the soil. I don't know if there's room for a meter long earthworm in these columns, but...

0:12:47.4 SC: Right. That one really did trip me up there for a second, a meter long earthworm. Let's go a little bit smaller. How about regular scale earthworms, isopods, they'll make the soil...

0:12:57.1 ES: Springtails...

0:13:00.6 SC: Springtails, other things that make the soil so alive.

0:13:01.5 ES: Springtails, mites, right? All these little guys, that's part of having a realistic soil ecosystem. So what they'll be able to do much more easily than the field is monitor where they are, 'cause there are certain organisms prefer to be at certain depths. They could put probes in. People have already developed sampling chambers for soil organisms. You can listen for earthworm
activity with microphones.

0:13:31.6 SC: Will this project, looking at these deep soils over time, all these different aspects of it help study wild soils?

0:13:41.0 ES: One of the payoffs is they're hoping is to be able to have a useful testing facility for new kinds of measuring devices, that you could then insert more easily into deep soil and in the field, the modeling is another big component, trying to figure out how we can approximate the behavior of this deep soil.

0:14:00.7 SC: Here we are talking about plans. There's a grant, there's a five-year schedule. What happens when the facility opens?

0:14:06.4 ES: The vision is that when they have this facility and you can imagine that there are 24 of these steel columns, 3 meters high and catwalks and probes coming in and out of them, there'll be maybe a zoo for soils, right? That they'll capture some of the diversity of soils. It's hard in a quick chat to really convey how different all the soils of the world are and the fantastic names that they've been given when scientists classify them. Alfisols, ultisols, I'm probably butchering it, but Idaho has a great diversity of soil, so they'll be able to go out and try bringing in a diversity of soils. So this facility, ideally, it'll have many kinds of soil in it; easily accessible, highly instrumented. So, scientists from all over the country, their collaborators from other countries will be able to come and ask questions, maybe bring new sensors and plug them in. So it really will be kind of a testing lab for soils.

0:15:10.7 SC: Thank you so much, Erik.

0:15:12.1 ES: Hey, pleasure to be here. Get our fingers dirty.

0:15:14.6 SC: Thank you so much. Erik Stokstad is a staff writer for Science. You can find a link to the article we discussed at science.org/podcast. Next step, we have Liangbing Hu, we're gonna talk about making moldable wood.

[music]

0:15:28.0 SC: Wood is, in some ways, an ideal building material. You can grow it out of the ground. It's not very heavy. It's strong, but materials like metal and plastic have one-up on wood in terms of flexibility. Plastic and metal can be melted and molded into complicated shapes. Could wood ever do this? Well, we're not gonna melt wood, but Liangbing Hu and colleagues wrote about making moldable wood in a different way in this week's issue. Hi, Bing.

0:16:09.8 Liangbing Hu: Hello. Hi, Sarah.

0:16:11.3 SC: So what do you see as the big strengths? The big pluses of using wood to build things or to make things?
Yeah. So wood is a natural material, is naturally grown. So it can actually store carbon dioxide, one of the major topics these days. So if we can engineer wood to replace plastic and metals, it's gonna be a big deal in addressing the global warming issues.

Let's get right to it here. How can you make wood more moldable, more shapeable like plastic or metal?

So what we did is we soften wood by breaking down the lignin in wood, which is the rigid component. And then we shock the wood in water, so that you partially open the vessels while keeping the fibers closed. And this these partially opened vessels gave you space to mold the material. And then after you dry the wood, just like you cool down plastic or metals, you fix the structure at room temperature.

Delignification, taking the lignin out, is not a new process, right? That's something that people have done. What's different here is the way you shock it with water treatment?

Exactly. Yes. That's the new twist in this process.

What do you mean when you say you're "shocking the wood"?

It basically means remove the lignin, make the wood soft and then you completely dry it. Then you put this very dried water-thirsty wood into water, so it can absorb the water very quickly. Now you have the big vessels, you have small fibers. The big vessels are what tend to absorb the water much faster so they will swell. Then you take it out before the fiber is actually swelled because of the time is very short, like 3 minutes process, you put a lot of water into the wood and now it become a very soft, foldable material.

Now the vessels that are in the wood, are they the vessels that move water up and down the tree?

Yeah.

So maybe that's why they're particularly good at getting water in fast?

Yeah. And as you do this process, the vessels actually form this very interesting wrinkled structures and this wrinkled structure, as you are trying to bend it, the wrinkled structure gave you fibers, gave you space to expand without breaking it.

Yeah. You have a little give right there.

Yes.

And when you dry it, you have your shape. Well, what happens if it gets wet again?

If you put them in water again, the structure will lose the shape, but you fix this by
adding some hydrophobic coating. So this becomes a irreversible process.

0:18:57.6 SC: Okay. So if you seal it up, the water won't get in there and take away your shape?

0:19:02.4 LH: Exactly. Yes.

0:19:03.2 SC: What are some of the shapes that you are able to make with this process?

0:19:07.0 LH: We demonstrate like tubes, corrugated structures, honeycombs, and in principle, you can make into any kind of shapes you want because the extreme case is you fold this 180 degrees.

0:19:20.1 SC: Like fold it in half?

0:19:21.6 LH: Yes. We demonstrated that and that is the dream case of folding and molding. So because of that demonstration, we believe we can basically process into pretty much any kind of a shape that is required for applications.

0:19:35.4 SC: Right, there were spirals, there are honeycombs. And the other thing you show in your paper with folding it in half is you can do that a hundred times, but if you fold aluminum in half five times, it's not gonna recover, it's gonna tear.

0:19:48.7 LH: Yeah, that's actually a very interesting aspect. So if you think of wood, it's actually made of fibers. You're actually folding a lot of tiny fibers back and forth, back and forth, and because it's a one-dimensionality, with excellent flexibility of the individual fibers, you actually can achieve much better folding capability.

0:20:10.0 SC: How do moldable woods properties compare with plastic and metal?

0:20:14.7 LH: Well, we mainly compare with metals because our mechanical strength is much better than plastic's, so we want to compare with materials that has similar mechanical strengths for more advanced applications, such as aluminum. So even compared with aluminum, the metal, the widely-used lightweight metal, this material is even lighter, two to three times lighter, with almost identical mechanical properties such as mechanical strength. Lighter means you can save more fuels in transportation, in flying objects.

0:20:48.0 SC: What about strength? How does it compare with aluminum?

0:20:51.4 LH: Yeah, so they actually show very similar mechanical properties. That's actually why this is extremely interesting. And people have actually done 3D wood before. You can imagine that you can use some steam to make the wood soft and you can fix the structure. People show some 3-dimensional chairs, but the mechanical properties is like five times worse than what we reported here. So, only by doing this simple, but a very... To traditional wood processing people, this process is actually very complicated. It involves a lot of chemicals. But only by doing so we can change the shape, make it moldable, at the same time, increase the mechanical strength by 5 to 6X compared to natural wood.
0:21:40.3 SC: One thing I was thinking about when I was reading this is that I'm not saying it's infinitely large, but you can mold out a really big piece of metal meters meters wide, whatever. Is that gonna be a limitation on this because trees are only a certain width?

0:21:57.0 LH: Trees have a limited dimension but if you do the rotary cutting, you can actually kind of unroll a tree from a cylindrical shape into a thin veneer, up to like hundreds or even 1000 meters long.

0:22:14.0 SC: So you cut it like a scroll, like you kind of un-scroll the tree?

0:22:19.1 LH: Yes.

0:22:19.8 SC: You keep your vertical fibers just the way you want them. Is that something that we already do to trees?

0:22:26.3 LH: Yeah, this is actually when you buy veneer, some of the floors are actually using veneers, that's actually done by rotary cutting. It's actually a common practice. And the folding molding process works the best for thin veneers. And after that you can really make honeycombs and this is really the way of using this lightweight, strong and thin veneers, that which is very similar to aluminum films that people use for this kind of honeycomb structure.

0:22:56.5 SC: So honeycomb is used to give strength without adding a ton of weight to different molded things?

0:23:03.3 LH: Exactly, yes. And coming back to your question, trees and the woods indeed have major limitations compared to metals and plastic which can be molded into very large format. So that's actually exactly the motive... One of the motivation of this particular work is that, can we use wood in other kinds of shapes that is not like wood anymore, but is taking advantage of wood as a sustainable material? That's the honeycomb structure, right? You make it into a honeycomb, now you can actually make infinitely large honeycombs like what you can do with aluminum foil.

0:23:40.8 SC: This kind of gets at the lifecycle analysis that you did in your paper. Were you trying to just show that wood, even with this additional processing, has lower energy consumption, lower carbon output?

0:23:54.6 LH: Of course, wood itself is porous, it actually stores CO2, instead of, for example, processing aluminum, you emit a lot of CO2. So, potentially, this wood-based product can become a carbon-negative material. But of course, as you mentioned, we indeed process wood-based chemicals with drying process that can consume electricity. So that's why we did that lifecycle analysis to include the process steps to see how, what is the impact of, for example, the environmental impact, the CO2 emission.

0:24:38.0 LH: In the end, even when you include all these steps, the material still shows significant advantages in terms of environmental sustainability. In the initial demonstration, we used 30 hours
to process the wood; now we can use a few minutes to process the wood as we've recorded in the paper. So by this kind of further improvement of the process, by the recycling of the chemicals, we believe we can make this material, including the process, even greener.

0:25:07.5 SC: I started talking about buildings and you kinda mentioned airplanes. Do you really see using this moldable wood in all these different areas?

0:25:16.7 LH: Saving weight is the most efficient way of improving fuel efficiency. And in all these vehicles, structural materials is commonly used. So for example, honeycombs, in the doors, in the roof, and all these components potentially, you can use this kind of 3D wood to replace whether aluminum or steel are used.

0:25:37.6 SC: Are you imagining a wooden car?

0:25:40.6 LH: Yeah, actually that's something we're very interested. Actually, we have a project funded by the Department of Energy for using this so-called super wood for vehicle applications. That's actually exactly the purpose there, trying to explore this material for lightweight vehicle applications.

0:25:58.7 SC: What do you see as some applications of this moldable wood that people might not think about as they're reading this or listening to this?

0:26:05.6 LH: Molding wood, folding wood, right now, what we demonstrated is like positive way. We mold it, we fold it into the shape, we fix it. I can imagine that in the future for buildings. For example, people created origami buildings. Buildings can be responsive to temperature and the sunlight. For example, in the very hot summer, maybe your building component, because it can be bended, can actually be responsive to sunlight, to humidity, so that you can make an entire house, entire building more energy efficient.

0:26:41.1 LH: Or you can use wood even for robots, for structure of robots, because now, certain component can be now it can also be five times strong, as strong as aluminum and steel, at the same time, it's very lightweight. You can think of lot of possibilities beyond the vehicles, beyond just positive applications. You fold it, make the shape and it just stay in the shape. Once you can make wood processable, affordable as plastic and steel, anything people are doing with those two materials, now you can use wood as a choice.

0:27:16.5 SC: Thank you so much, Bing.

0:27:17.8 LH: Thank you for having me here.

0:27:18.8 SC: Sure. Liangbing Hu is a professor in the Department of Material Science and Engineering and the Center for Materials Innovation at the University of Maryland. You can find a link to the paper we discussed and the beautiful image of molded wood on the cover at science.org/podcast.
SC: Up next, we have a custom segment sponsored by the Jackson Laboratory, Custom Publishing Director Sean Sanders chats with researcher Michael Brehm about the use of humanized mouse models in his research on Type 1 diabetes. We're running a survey to learn what you think of these sponsored segments. Listen to the interview, then go to bit.ly/podcastsurvey2021. That's B-I-T-L-Y/podcastsurvey2021 to share your thoughts and for a chance to win a prize.

[Music]

Sean Sanders: Hello to our podcast audience and a warm welcome to the sponsored interview from the Science AAAS Custom Publishing Office brought to you by the Jackson Laboratory. My name is Sean Sanders and I'm Director and Senior Editor for Custom Publishing at Science. Today it's going to be my honor and pleasure to interview Dr. Michael Brehm. He is an Associate Professor in the UMass Diabetes Center and Co-Director of The Humanized Mouse Core Facility at UMass Medical School, as well as an investigator in the JDRF Center of Excellence in New England. He uses humanized mouse models to investigate approaches from modulating the body's immune system to treat Type 1 diabetes. Michael is going to be sharing some of his work on these mouse models, including talking about recent successes and some of the challenges that he and his team have overcome. Michael, a very warm welcome to you.

Dr. Michael Brehm: Thank you, Sean. It's great to be here and I'm looking forward to discussing some of our projects with you.

SS: So Michael, let's start with a little background. What are some of the major immune cell types involved in Type 1 diabetes or in other diseases like cancer?

DB: Right. So all these disease processes in the human context are generally fairly complex, involving numerous immune cell subsets. One of the primary goals in my laboratory has always been to focus on human T-cell responses and that's one of the key aspects that we look at in both Type 1 diabetes and cancer, but the overarching theme of that is really understanding dysfunction of human T-cells. So for example, in Type 1 diabetes, you have activation of T-cells that like to attack itself. Pancreatic beta cells make human insulin and regulate glucose levels, so those remain overly activated.

DB: In cancer, the T-cells are generally thought in many instances to have a reduced overall level of function, unable to respond to this growing malignant tumor and control it. And understanding how both of these contexts, either in an overactivated Type 1 diabetes T-cell or in cancer T-cells where they're not as functional is really the focus of my laboratory to get that balance and understand the pathways which might be unique or overlapping in both of those contexts. But that's only the tip of the iceberg. There are other immune cell subsets, B-cells, innate immune cell components that are also involved in these and we're actually working on projects involved in all those areas.

SS: Now what are your thoughts about the availability of mouse models for the study of human immunology since you're deeply involved in using humanized mouse models for this work?
Right. That's really an important question. Much of what we know about human biology has stemmed from experiments done in traditional standard mouse models. I did my PhD thesis and most of my postdoc working with a mouse called the C57 Black 6 from Jackson Laboratories, and these models have laid the foundation for our basic understanding of biological phenomena and have translated in many cases to humans.

The problem is that there are specific instances where you have human specific characteristics that aren't reproduced in those mouse models. So there are a number of aspects that don't translate well from the traditional mouse to what we see in humans. And I've been working with my colleagues here at UMass, Dale Greiner and at the Jackson Laboratories, Lenny Shultz, who are some of the pioneers in this humanized mouse field, and the ultimate goal is to be able to make a mouse model that gives us a better reflection for what happens in human-specific context. And we're really focused on the immune system, but these models have applications well beyond that.

Can you talk a little bit about how you in particular utilize these mouse models in your experiments?

So again, we're really interested in T-cells, so a lot of our experiments revolve around how do we get functional human T-cells to survive and engraft in these mouse models? But we're using them in a wide variety of contexts through a number of collaborations as well. For example, in the Type 1 diabetes field, we actually work really closely with the Harvard Stem Cell Institute, Doug Melton and a variety of other investigators in our JDRF Center of Excellence, and there, we're actually trying to recreate human Type 1 diabetes in our humanized mouse models.

This approach really involves the use of induced pluripotent stem cells from Type 1 diabetic individuals where those populations can be differentiated into those pancreatic beta cells and into immune cells, and into other pieces of the immune system which help to educate those immune cells. The ultimate goal is then to engraft those cell populations into our mice, watch a diabetic immune system develop in vivo, in these models and see then if we can recreate that attack by the immune system on the growing pancreatic beta cells in the animals, and be able to study that disease process. That's really an exciting field and I think it will actually allow us to almost create personalized mice, depending on the specific donor, where we get those pluripotent stem cells from to create the other components that are critical for generating diabetes.

On the flip side, going back to where we have suppressed immunity in the cancer field, we've worked with a colleague here at UMass, Giles Whalen, to create an Avatar Institute where we actually are able to collect specimens from consented cancer patients, both tumors, peripheral blood, and these can be engrafted into immunodeficient mouse models where we'll have mice growing a human tumor and then engrafting with the matched human T-cells from the peripheral blood, and study how they interact. It's actually a pretty powerful model then to come in and test some of the groundbreaking immunotherapeutics that have been developed over the past few years to study if we can reactivate those T-cells now to find that tumor and to kill it.

How has the field progressed in, say the last five years, in terms of what types of
models have become available and how this has impacted the drug discovery field?

0:34:24.3 DB: Yeah, so it's actually interesting, and this is a pretty hot field, as these immunodeficient mouse models continue to evolve. Right now, there is no perfect humanized mouse that will reproduce all aspects of human biology. It's almost an a la carte kind of approach. There have been a number of models which have been created to specifically improve various aspects of either immunity or how tumors grow, or how these can support other human tissue engraftment protocols. So for example, we've been working on a mouse that expresses a specific cytokine called IL-15 of human origin, which is a critical cytokine for the development of human NK cells, which have never been that great at developing in our traditional immune system engrafted mouse models. And specifically, we use this NOD-scid IL2 receptor common gamma chain or NSG mouse, that was developed by Lenny Schultz up at the Jackson Laboratories.

0:35:22.4 DB: So, Lenny actually added IL-15 back to that animal and now, we get really robust development of human natural killer cells or those NK cells in these animals, and we're doing a variety of studies understanding what regulates NK cell development, its functionality, how they respond to tumors and what their contributions are to diabetes as well. So, as these models continue to evolve, we would hope to have a selection, this tool box, if you will, of a model depending on your specific scientific question of, is there a mouse tool in that tool box you can take out and do your experimental studies with? Ultimately, one day we would like to get a model that reproduces all these aspects in a single mouse, but that's still an effort that it's being worked on.

0:36:10.0 SS: So I'd like to talk a little bit more about the humanized mouse models that are currently available to study human immunity, can you talk about some of the strengths and weaknesses of these models?

0:36:20.7 DB: So historically, there are a few issues with these animal models, of course. And one that is getting close to, maybe if not solved, getting very close to having reasonable utility to answer questions is looking at human innate immunity, so things like natural killer cells, as we already discussed, monocytes and macrophages, dendritic cells, which are always... When you engrafted human immune systems into our animal models, their level of maturity, functionality and development were always less an ideal. But a number of groups, including ours, and these are a number of laboratories here in the US and internationally, have gotten really good at adding back growth factors for specific innate immune cell populations to improve their overall development, their functionality and their maturity level.

0:37:10.8 SS: So historically, there are a few issues with these animal models, of course. And one that is getting close to, maybe if not solved, getting very close to having reasonable utility to answer questions is looking at human innate immunity, so things like natural killer cells, as we already discussed, monocytes and macrophages, dendritic cells, which are always... When you engrafted human immune systems into our animal models, their level of maturity, functionality and development were always less an ideal. But a number of groups, including ours, and these are a number of laboratories here in the US and internationally, have gotten really good at adding back growth factors for specific innate immune cell populations to improve their overall development, their functionality and their maturity level.

0:37:08.7 DB: Two of the other areas we're still struggling to make good mouse models is one, development of lymphatic and lymph node structures in these mice, because of the common gamma chain mutation on most of these animal models, you lack the cells which are critical for development of lymph node tissues, the lymphoid tissue-inducing cells. So with that, these animals really don't have great peripheral lymph nodes, lymphatics are a little questionable, so it's hard to get a completely functional immune system without having good lymph nodes, or you have T-cells and B cells all communicating to generate good, robust immunity to antigenic or infectious challenge. There has been some progress in that area, either by adding back cytokines or specifically expressing molecules to improve those LTIs. But it's still kind of a work in progress to get robust lymph nodes structures in these mouse models.
The other area, and I kind of consider this the Holy Grail, are using these mouse models to look at immunogenicity. So for vaccines, we're looking for immune responses to any kind of immune challenge. It's extremely difficult to get good antibody responses generated consistently in these mouse models. So for example, if we wanted to evaluate a COVID vaccine, these models probably won't work very well in their current state, and that's why I consider it kind of the Holy Grail, 'cause if we can get a mouse model which will induce robust antibody responses against something as an mRNA vaccine, we'll have a variety of tools at our disposal to look at immunogenicity and look at efficacy for testing these vaccines or other immune-inducing agents.

So I have just one final question for you, Michael, and that's looking forward to the future, where do you think the field is moving in the next 5 to 10 years and what role do you think humanized mouse models might play in future advances?

Really being able to get robust immunity generated in these mice would be a game-changer. The other aspect for this, and I think we're still in that 5 to 10 year range is, again, kind of a personalized mouse model, where you would engraft mice with cells, whether they be from stem cells or from the peripheral blood to develop patient-specific therapies in a patient-specific manner, evaluate how they respond to a vaccine, an inflammatory agent, a treatment regime, where they reproduce a patient's response completely inline with what the patient would actually do, and then use that as a screening tool to identify the best treatments in a personalized way.

Michael, thank you so much for taking the time to talk with me today. I've very much enjoyed our conversation.

Thank you, Sean. It's been a pleasure.

Our thanks to the Jackson Laboratory for making this conversation possible and to the Science Podcast audience for your interest and attention. Until next time.

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