S1 00:03 Welcome to the Sports Medicine podcast, brought to you by the Sydney and J.L. Huffines Institute for Sports Medicine and Human Performance in the Department of Health and Kinesiology at Texas A&M University. At the Huffines Institute, we're always working to facilitate, apply, and bring you the most up-to-date coverage of the wide world that is sports medicine and human performance, all in a language you can understand and share with your friends. And now, here's our host, the director of the Huffines Institute, Dr. Tim Lightfoot.

S2 00:32 Hello and welcome to the weekly edition of the podcast from the Huffines Institute for Sports Medicine and Human Performance. I'm your host, Tim Lightfoot. And I'm so grateful that you took the time to download us and that you're taking the time to listen. All of you know that have listened regularly, we work every week to bring an interesting person from the world of sports medicine and human performance to your podcast dial. This week, so you can listen to and find out the passions that drive what they do. And this week is no exception. We're thrilled to have Dr. David Threadgill with us here in the studio. Welcome to the podcast David.

S3 01:03 Thanks.

S2 01:04 And I'm going to tell them a little bit about you. Dr. Threadgill is a university distinguished professor. He holds the Tom and Jean McMullin Chair of Genetics here at Texas A&M in the Department of Veterinarian Pathobiology and the Department of Molecular and Cellular Medicine. He has a couple degrees here from Texas A&M. He got his bachelor's degree in zoology here originally and then his PhD in genetics. Then he went off and did post-doc work at Case Western Reserve University, did some time at Vanderbilt, worked at the University of North Carolina Chapel Hill in a variety of positions including a professor and department head of genetics at North Carolina State. And then he came back here in 2013 and we were glad to have him come back because he came back as the director of the Texas A&M Institute of Genome Sciences in Society. Dr. Threadgill is very much an awarded researcher, he has over 265 scientific publications. He has received millions in funding from various federal entities. He has many national awards, it would actually take us most of the podcast to describe all that. So we're incredibly thrilled to have you with us here on the podcast today David.

S2 02:14 So I've asked you to come on the podcast because you and I have been working together and known each other for a long time. And you currently work in cancer in a variety of different ways and how environment influences that. But I want to start off with your other passion, which is mice and the genetics of mice. And that's how you and I first interacted. And I want the audience I guess to understand a couple things and that is I want to ask you a little bit about some of the models that you have built over the last 15 to 20 years. In particular, this thing called the Collaborative Cross. And we'll get into that and talk about why it's important to health research.

S3 02:50 Yeah so actually, my background is actually a cattle ranch. I grew up on a cattle ranch. And so being a mouse herder is not sort of out of the ordinary.

S2 02:59 Just smaller pens.

S3 03:00 Just smaller pens. They breed faster, and we can get a lot more of them, and they're cheaper. So after doing graduate work at Texas A&M actually in cattle genetics, this is right when the ability to engineer the mass genome was just starting. And so I went and did a post-doc and learned how to do genetic engineering of mice. And during that time, we engineered one of the earliest mutations on a gene called epidermal growth factor receptor, which was a critically important gene in a number of cancer

types. But it also really revealed the background dependency or the dependency of the genetic context by which a mutation resides and how different the consequential phenotypes and/or diseases could be, depending on the genetics of the individual. And so over time, that got us into much more looking at how does genetic variability across individuals really contribute to health and disease.

S2 03:58 And there's a lot of genetic variability amongst humans.

S3 04:00 Among humans, there's lots of genetic variability. You can easily see it more philologically just by looking at people. And what most people don't realize is laboratory mice are no different. It's not your little white laboratory mice that you see in a pet store. But rather, there is an equally large amount of genetic variability in mice as there is in humans. And so we can actually model that genetic diversity in humans in a laboratory setting so we can understand how do the genes differ among individuals actually contribute to their differences in health and disease.

S2 04:30 So, that's a first question people say, "Well, how is a mouse similar to me?" And so you've just said it, that they are great models of human physiology in many ways.

S3 04:38 It's a mammal and so it has all the same organs. Around 98% of all the genes are identical. They function the same. They get the same diseases. They get cancer. They get diabetes. They get neurological diseases. They respond to environmental insults very similarly. And so it provides a stand-in in cases where we can't study humans for ethical reasons. We do it in mice to really understand the human condition.

S2 05:02 Right. Right. So you start to build these models using mice and that got you to a point in the early 2000s where you made a large proposal to the scientific community at large.

S3 05:14 Yeah. So in the late 90s, we got to thinking that trying to identify the genetic variance that actually contribute to how individuals respond differently to diseases was starting to be a challenge and we really didn't have the tools to very quickly navigate and get to the genes, underlying genes. So we thought, well maybe one of the problems is, is the mouse resources we were using. And so that led to a proposal to actually sort of rebuild the laboratory mouse in a way that much more accurately represents the human genetic diversity from a population standpoint. And this eventually led to what is now known as the Collaborative Cross, which is really a mouse population that is a stand-in for human populations. And so the genetic diversity present in humans is modeled or recapitulated in this mouse population. And so we can treat it just like a population of humans, but in an experimental setting.

S2 06:08 And you can replicate each of these animals intimacy to reproduce the same genome and so forth?

S3 06:15 Exactly. So one of the advantages is we can replicate the entire population. And so if we want to look at an environmental perturbation, we can take the entire population and put it under two different environments and ask which individuals in that population respond differently? And so by replication, it's basically like being able to clone a human population. So, that we have the exact same individuals within the population under different environmental conditions.

S2 06:39 And I think what I want our listeners to understand is this was a fairly bold and audacious plan when it was put forward. And you were the lead author on that proposal. But it also wound up involving centers in three different countries or four different countries and multiple places here in the United States. And this was not a small undertaking.

S3 06:57 It was a little bit ahead of its time from the perspective of getting funding lined up. And so we ended up sort of going after whatever funding we could obtain. And what most people don't realize, the actual initial funder of this was actually Larry Ellison and his foundation, the Ellison Medical Foundation, that provided the seed funding to actually get this project going in the US. And then we had two collaborators. one in Australia and one in Kenya that also were able to obtain some funding that initiated populations.

S2 07:29 Yeah. Now that resource, the collaborative mouse resource, is more or less established now.

S3 07:34 It's established. We probably have almost 100 research groups extensively utilizing it across the world. In fact, I just got back last week from our annual meeting where we had almost 150 individuals from every corners of the world sort of presenting their latest results on this population.

S2 07:53 Wow.

S3 07:53 And it's been used in already some human disease things. For example, I remember seeing the papers on Ebola.

S2 08:00 Yes. That was being used, the Collaborative Cross was being used a while.

S3 08:02 And so during the Ebola outbreak several years ago, there was a group at the University of Washington that obtained a population of these animals, and it turns out that just like humans, this population responds very similarly. We have some individuals that get very sick, they get hemorrhagic fever. Other ones that will eventually die, other ones that are actually somewhat resistant. And if you actually look at the proportion of individuals developing these different phenotypes, it was almost identical between the human populations that were being actively treated in Africa, as well as the mouse population.

S2 08:37 So the establishment of the resource has been great because it's already providing benefits for human health, not just mouse health.

S3 08:44 Right, and that's really the target, is human health and trying to use it as a stand-in to try to solve some of these challenges that we have.

S2 08:50 Yeah, that's what people ask me, "Do you really grow up to be interested in mouse exercise?" No, not really, I'm interested in human exercise, but this is the best model that we can use and it's the same way with this model. So, let's switch gears and let's talk about your particular research. You've done all this work to develop this model and so there are some particular areas that you are applying it to. Most recently, you've been doing some environmental work where you're looking at the environmental effects, especially on cancer. One of the things that's mentioned quite a bit on your CV is the herb gene. Tell us about the herb gene.

S3 09:22 So the herb gene is the epidermal growth factor receptor, that's sort of the prototypical oncogene or cancer-causing gene. There's a number of drugs on the market that target mutations in this particular gene. Individuals familiar with breast cancer may be unfamiliar with [inaudible]. It's an anti-breast cancer agent that is targeting a family member of the EGFR. So we've actually been studying this and using it as sort of a model in and of itself for many years because this is the one that it's very sensitive to genetic context. So some individuals that carry mutations, individuals in my case being mice, carry mutations in the epidermal growth factor receptor or EGFR, basically are perfectly normal, they really have no effects whatsoever. Whereas other individuals that carry mutations, even if it's the exact same mutation, can be very

severely affected. And so we know that there are other sort of natural differences among individuals that will modulate how severe someone is going to be when they have a mutation like an EGFR.

S2 10:30 And so you're looking at this mutation using the Collaborative Cross to determine how that works in humans.

S3 10:35 Well, one of the things we want to do is get back and use the Collaborative Cross in a way where we can identify what's called modifier genes. And so these are genes that don't really have an adverse phenotypic consequence by them self, but when you combine them with another adverse mutation or a defect in a gene, then they can exacerbate or they can basically lessen the consequences of that primary mutation.

S2 11:00 When you talk about these modifier genes, the work you've also been doing with environmental health influences. So the things that would trigger these modifier genes would probably be some type of adverse environment, like diet or what they're exposed to.

S3 11:17 Any perturbation, it could be a genetic mutation, it could be a change in the diet, it could be an environmental chemical, all of these can actually sort of reveal these modifier genes that are actually really the important ones for influencing how severe someone can be affected.

S2 11:34 You and I both know, in the early days of the excitement about the human genome sequencing, the idea was that we'd be able to sequence someone's genome and figure out what diseases they were probably going to get and it hasn't turned out to be quite that simple.

S3 11:45 Well, in fact, there's some papers that have just come out in the last two weeks arguing that point. That this massive search through what's called Genome-Wide Association Studies to try to find these genes underlying common diseases. For the most part, they've identified lots of genetic differences. But we really have no clue how these genetic differences contribute. And it's actually turning out that maybe the genetic differences in isolation are not what's important. But is rather, it's sort of an aggregate. The wiring of an individual and how all of these differences work together is what's really critical.

S2 12:20 And that would come into play with your modifier genes that you were just talking about. So I was wondering, do you anticipate a day in the future where someone would come back to that concept where you can do a sequence of someone and say, "Look, you need to stay away from red meat or you need to eat more..."

S3 12:34 I think that's still the sort of the Utopian situation from a geneticist standpoint, is being able to take a DNA sequence and having the ability to do more personalized medicine based upon an individual's DNA sequence. We're clearly a long way from that, but we're going get there eventually.

S2 12:53 Yeah, so this whole idea of a biomarker, we're not there yet, but hopefully down the road.

S3 12:59 There are a few examples of biomarkers, warfarin, anybody that's taken the blood thinning compound warfarin. That's a classic one where there's a specific genetic variant that influences how well someone responds to that. And so individuals are actually genotyped for that biomarker so they can determine what dose of warfarin they actually need to take. So there a few isolated cases where it has crept in. But high and large, at least for common diseases, it's not there yet.

S2 13:27 Yeah. And that'll release that idea of precision medicine.

S3 13:29 Exactly.

S2 13:30 Basing everybody's therapy on their [geno?]. So to switch gears one more time on you. It's great to have you in-house here because you have such a wide experience with all these variety of topics that face science in particular. And one of the things that faces science is funding. If we don't find the funding, we don't get to do the studies. Seems like the public thinks that we walk in the door and they shower us with money to do this stuff and that doesn't happen. And so you're one of the warriors in the war on grant funding or for grant funding. And you've got a couple recent large proposals in, you've had several large multi-collaborator projects that have been funded. So how do you think about this? If you were to talk someone on the outside of the university that doesn't know much of this and they're really questioning why the government is funding research? Research recently has been under fire.

S3 14:27 Well and I think most people have to realize that most of the research discoveries that lead to our therapies down the line, actually corporations don't fund that, pharmaceutical companies don't fund that. They actually take the basic knowledge that is generated by universities and actually then translates that into useful medicines and interventions. And so the government is really the only way that we actually produce that foundational knowledge. You think about the GPS. You think about the internet. All of these things came out of very basic foundational knowledge experiments that the government funded, that eventually led to new technologies. And biomedicine is no different. We know a lot about disease and disease processes, but there's still far more that we don't know. And the only way we're going get that knowledge is through basic foundational research that the government funds. That then eventually leads to the private sector picking these up and driving them to some type of useful intervention.

S2 15:33 What is the danger of the government cutting back on funding? I mean, it's difficult now to get NIH funding as it is.

S3 15:38 Yes. Well I mean, the danger is we're sort of stopped in our tracks. And any advances, it's going be marginal. And so whatever therapeutics we have now, this is probably where we will stop. And so you can imagine all the diseases that we still can't treat and all the mental illnesses that we still don't know enough about to actually develop proper interventions. How do we treat all the cancers that currently have no therapeutics that effectively treat them. We've made tremendous advancement, but there's still a lot of cancer types that we can't treat. How do we prevent the progression of diabetes in individuals that get very severely affected? All of these, we have to have additional basic foundational knowledge in order to be able to have an informed way to actually take those into productive therapeutic.

S2 16:27 And there is a time when research may not provide any results that we can immediately translate to humans. I mean, there's been this big drive for translational research, but sometimes that basic research is just foundational too. So many things that we don't understand at the time.

S3 16:40 And the vast majority discovers come out of unexpected areas that we can't anticipate what their uses would be. The most recent classical example is the CRISPR genome engineering technologies that are turning out to be extraordinarily powerful in a number of areas. It started out as a very simple foundational experiment trying to understand why was is it some bacteria were resistant to bacteriophages. And it turned out that there was this editing or this genome cutting ability that the bacteria had that now has been exploited to provide future therapeutics and in humans.

S2 17:20 And probably before the end of our lifetimes, all of us will deal with CRISPR at one point or the other.

S3 17:25 One point or the other, it's just a matter of time before we're going to start using that as a therapeutic tool.

S2 17:32 Fun stuff. David, thank you for being with us today.

S3 17:35 Glad to.

S2 17:35 It's been great. And as we do every time, we're going to ask you to give our audience a take-home message. What's the one thing you want them to remember from this podcast?

S3 17:44 Well, I mean, we really didn't touch on a lot. But I think what's critically important to remember is how important our genes are, but only in the context of the environment we live in. And as we hear about challenges to the environmental agenda, we have to remember that the vast majority of our diseases are actually driven by our environment interacting with our genes.

S2 18:06 Great take-home message. We'd like to have you come back. We can expound on that some more.

S3 18:10 Glad to.

S2 18:11 That's an interesting topic right now in the world, especially environmental health science. So I would also take the time to thank all of you for taking to be with us and downloading the podcast. Regular listeners know this is the time of the podcast when we usually have our podcast question of the week. And here with our podcast question of the week is our producer, Carlos.

S4 18:31 What is the herb gene?

S2 18:33 Great question Carlos. Be the first person to email us the correct answer to that question and you'll receive one of our nifty podcast t-shirts. Send that email to huffines@tamu.edu. That's huffines@tamu.edu. And we have been known to mail multiple t-shirts during the week. So don't think you're too late. Send us that answer. So again, thank you for taking the time to download us. David, thank you for being with us today.

S3 18:59 Glad to be here.

S2 19:00 And we hope that all of you tune in next week when we have another interesting person from the world of sports meds and human performance. Until then, we hope that you stay active and healthy.

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