

Ask A Biologist Vol 095 (Guest: Grant McFadden)

History, Rabbits and a Deadly Virus

This is the story of wild rabbits, humans, and a virus that might lead to a treatment for cancer. Twice humans moved wild rabbits from Europe to other parts of the world with dramatic consequences. It is also a lesson about learning from history and how a virus that is deadly to some rabbits could become a new cancer fighting tool for humans. In this episode, Dr. Biology has the opportunity to learn about the myxoma virus, its history, and the work of virologist **Grant McFadden**.

Transcript

Dr. Biology: This is Ask A Biologist, a program about the living world, and I'm Dr. Biology. Science and what we know today is often a result of earlier work or an event that occurred in the past. It is this history that often gives us clues to understanding how life works. One such event occurred in the year 18, 59 in Australia. It's a story of a British settler by the name of Thomas Austin and his hobby of hunting rabbits. The problem was Australia didn't have any rabbits, so Austin being clever thought he'd do something about it. He imported 24 wild rabbits. He thought, and these are his words. "The introduction of a few rabbits could do little harm and might provide a touch of home, in addition to a spot of hunting."

Dr. Biology: Well rabbits did what rabbits do well, they reproduced. Boy, did they reproduce. By 1920 there were estimates of more than a billion rabbits in Australia and yes, that's a billion with a "B". You can probably see where this is going.

Dr. Biology: With all those rabbits. They were displacing local animals and generally messing up Australia's ecosystem. How to control this rabbit population boom became a national project. Nothing really had much impact until the myxoma virus was introduced. This virus only affects rabbits and is harmless to other animals and in a few years the rabbit population dropped to a mere 100 million, but keep in mind we had more than a billion before. That's 10 percent of what it was before, but that's not the end of the story.

Dr. Biology: Fast forward to today where a research scientist at Arizona State University has been working with the myxoma virus and thinks he might have a future treatment for cancer. My guest today is Grant McFadden, professor in the School of Life Sciences and the director of the Biodesign Center of Immunotherapy Vaccines and Virotherapy at Arizona State University. He is the co-editor and chief of the journal PLOS Pathogens. If you're not familiar with that, PLOS stands for the Public Library of Science. And he is a senior editor at the Journal of Virology. If that's not enough, he is also a past president of the American Society of Virology.

- Dr. Biology: Welcome to the show Grant.
- Grant: I'm glad to be speaking to you.
- Dr. Biology: Before we jump into the story of the myxoma virus, can you talk a little bit about cancer cells and how they're different from normal cells?
- Grant: Yeah, so cancer cells are cells that have gone rogue in our body, and there are different ways that cells can go rogue, but in general, these are genetic things that happened to normal cells. The genetics can be caused by inheritance from our parents. It can be caused by environmental agents. Sometimes it just happens spontaneously, but the end result is that cancer cells pick up mutations that are changes in the DNA, in the genome of those cells. It changes the way they act, the way they operate, and if a cell picks up enough of these mutations and if it's the wrong combination then the cell can lose its bearings. It can forget who it is and what it was doing, so a liver cell can forget being part of a liver and start to grow and to spread through the body. The same thing can happen to any cell in the body, but some cells are more susceptible to becoming cancerous than others. That's why we have specific kinds of cancers. It's because certain kinds of cells are a little more prone to becoming cancerous than others. Technically, any cell can become cancerous.
- Dr. Biology: Right, and you say rogue - basically out of control.
- Grant: Out of control. It grows when it shouldn't. It runs to places that it shouldn't run to and sometimes it can hide from the immune system in ways that are very unique to it.
- Dr. Biology: Ah, the immune system, that's our defense system in our bodies and typically they would find these types of cells and say, you don't belong here and get rid of you, but if they can hide, that's a problem.
- Grant: That's part of the day job of our immune system is to look for things that are bad in the body that includes cancer, but also includes infections. It also includes other things, trauma that happens to the body, but cancer is one of them, and normally when our immune system is working, the immune system recognizes the cancer cells as being wrong or foreign and eliminates it. Eventually what we call successful cancers, even though that word is kind of odd applying to a cancer cell, but we say that when they survive and grow their successful as cancer, so all successful cancers have learned how to evade or get away from the immune system in some way and how they do that is actually a big field of study. How cancer cells trick the immune system into not recognizing them.
- Dr. Biology: Right. So when I opened the show, I was talking about the, the story of the rabbits in Australia. The billions of rabbits at one point and how trying to control them was not going anywhere until the myxoma virus was introduced. How did you learn about the myxoma virus?

- Grant: When I was a junior scientist in training, when I was a postdoc, after I finished my PhD, I went looking for a lab to train in an area that I thought I would want my career to go. So I did my training in a lab that studied a virus vaccinia virus, which is the vaccine that was used to wipe out a disease called smallpox. Many people have not heard of smallpox because it was wiped off the face of the planet in the 1970's and no case of it has been found in humans since 1978. Horrible disease killed literally billions of human beings until the worldwide vaccination program wiped it out. And it's kind of interesting. It's almost forgotten. And the vaccine field, for example, is under a lot of scrutiny and pressure from groups that call themselves anti-vaccine or anti-vaxxers. But one of the great medical triumphs of human medical health history was the eradication of that one disease, smallpox, from the human population.
- Grant: And that was done by vaccines. So at any rate, I went to a lab that studied vaccinia virus and got hooked on members of that family as something to study in my own professional career. So when it came time for me to look for a job as a professor and to look for what I wanted myself to work on, I went looking around for members of pox virus family that had not been studied before. And I was reading the literature and I came across these rabbit viruses and they were so interesting and almost nothing was known about them. I figured I got to study these guys. So that's what I set up my lab on, rabbit viruses, and for years I just studied them as biologic agents because it's really quite fascinating how any virus works in biology and these viruses are as exciting and fascinating as any of them.
- Dr. Biology: Actually, it's a really good point because there's applied research and there's basic research to relative terms we use. And basic research is what you were doing there. You were in the search to understand more about how this virus worked. You weren't necessarily on a quest to cure cancer...
- Grant: Correct.
- Dr. Biology: ... or to treat cancer, but that's why it's so important for basic research because in that quest, I'm assuming we're going to get, you know, in that quest, you actually come across a really interesting thing about this virus.
- Grant: So this is the way science works. So there are different kinds of science. There's what's called curiosity based science and that usually means someone is doing studies or investigating something simply because they're curious. There is no end game, there's no product, there's no milestone, there's nothing that you can tell someone - ah, if I do this experiment properly, here's the magic that you will get at the end of it. Here's the product. Instead, it's just merely to answer the question, how does, in this case, Mother Nature Work?
- Grant: So I was very fascinated how these viruses, these specific pox viruses, caused disease in rabbits. Why was such an extreme disease in rabbits and why it couldn't infect anything else? So both of those fascinated me and I

spent 15 years, uh, studying in my lab, just the basic biology of this virus family, how it infects rabbits. Why is it rabbit specific? What is it doing in rabbits? How does it tackle the immune system in a rabbit, et cetera? And only after about 15 years did we stumble upon the fact that this same virus that in nature lives only in rabbits if you put it into a cancer tissue, it treats the cancer cells in that tissue the same way it does rabbit cells, it infects them, it kills them, but it doesn't hurt the host unless it's a rabbit. So that's what got me into the whole business of developing a virus to treat cancer.

Dr. Biology: So viral therapy.

Grant: Viral therapy. So what the word means is viral is for virus and therapy just means it's something that we use to treat a disease. So viral therapy means using live virus to infect and kill and eliminate cancer cells.

Dr. Biology: How do you pick a virus for viral therapy? I mean, there must be some way you go about this.

Grant: In some ways. Picking a virus for viral therapy is a little bit of accident and luck and testing. So Mother Nature doesn't develop any virus as an oncolytic, uh, it's scientists who kind of study of virus, look at its properties and then wonder could we use those properties for something that Mother Nature didn't intend for it, but that we would use it for. So, all of the oncolytic viruses that are being developed were first studied in labs. Usually labs that were studying the virus for something completely different until they learned, or in my case, stumbled upon the fact that the virus has many of the properties we want for an oncolytic virus. And some of those properties are, for example, the virus has to be safe for humans. So if you put it into a human being, it can't cause disease. It can't kill the host because that's not a therapy.

Grant: So it has to be harmless for people. It also has to have the capability of seeing cancer cells differently and it has to have the capability of killing those cancer cells. And what we now know is that the best oncolytic viruses kill cancer cells in a way that wakes up the immune system. That gets the immune system to see the cancer cells again, the way maybe they once did and have forgotten how to do. So, you could think of oncolytic viral therapy as giving cancer a disease such that the immune system sees that disease and eliminates it.

Dr. Biology: You've been using the word oncolytic, which is so great word. Let's just unpack that just a little bit. Onco, by the way, it refers to tumors and lytic or lysis means to basically cause the cell to rupture.

Grant: Yes.

Dr. Biology: So it's basically a way of killing cells.

Grant: Killing cancer cells specifically.

Dr. Biology: Right?

Grant: For example, many people have heard of chemotherapy. So chemotherapy uses drugs to try and kill cancer cells faster than it kills normal cells. But the truth is chemotherapy is very toxic to all cells and it's a matter of dose and of timing and of speed of death. So some of the reasons that chemotherapy has so many toxic side effects is because it can kill and harm normal cells as well. But it tends to kill cancer cells faster

Dr. Biology: So let's talk a little bit more about the myxoma virus. Walk me through how it works and why it's so good.

Grant: So remember I got into this business because I was interested in pox viruses. So pox, viruses, I should step back and tell you that every virus, family, or group has its own properties, its own biology, its own history. So pox viruses are to me very fascinating because they are large viruses, at least in the virus family. They are one of the few viruses you can see with a light microscope. So most viruses are so small you need an electron microscope to see them. But pox viruses are a little bit bigger and you can see them with a good light microscope. They're very complex. So the genome or the DNA of this virus, it's double stranded DNA just like us. It uses the same genetic code as we do. But it encodes for far fewer factors. We call them proteins or genes that encode proteins and this virus encodes for about 160 of them.

Grant: So remember that humans have about 22,000 genes and their gene products. So you can think of the genetics of this virus as being comparable to about one percent of that, of a human being. It's a very simplified form of life. It's a parasite, but I'm really fascinated in how members of this family parasitize cells. How do they get in and kill those cells? So when I was looking for a virus to study in my lab, I came across these rabbit viruses and did a little bit of study about them and there was just such a fascinating history. Um, so I can tell you a little bit about that history because it fascinated me and maybe it will you.

Grant: So the virus that we end up studying called myxoma virus was discovered by accident. It was discovered in the late 18 hundreds when an Italian researcher by the name of Giuseppe Sanarelli, brought over some European rabbits from his lab in Italy to Montevideo, Uruguay and South America.

Grant: So he was a scientist. He was actually studying things like yellow fever, what caused it, uh, and he was a very well known in his day and he used rabbits in his lab, European rabbits. So he brought a bunch of them with him to Uruguay and housed them outside of his field station in Uruguay, in Montevideo, and went about doing his business. And then all of a sudden his rabbit started dying and all of them were dead within a couple

of weeks of a horrible disease. And he didn't know what it was. It was all a mystery. He was so amazed that he went into the veterinary literature and could not find any record of the disease at all. And he became so intrigued that he started talking to microbiologists in South America and went looking for someone to help him find what killed his bunnies, only because he was curious. It was just so unexpected.

Grant: So he met some microbiologists from Brazil and they spent 20 years looking for the bug. The thing they knew was infectious, but they didn't know what it was that killed all of his rabbits and they found it after 20 years and it turned out it was a virus. And viruses were being discovered around that time. They were able to show it was related to smallpox, the virus that caused that human disease. But it was a rabbit specific. And the reason these rabbits got it is because remember European rabbits are not native to South America. They only appeared there when humans brought them over. People like Sanarelli bringing rabbits there and it turned out that the virus was living in the Brazilian rain forest. And it was living in an animal called the tapeti and in the tapeti it was not a disease caused her.

Grant: It was just very quiet. It lived in the skins of tapeti and was spread from one to petty to another by biting insects like mosquitoes. So what happened and they were able to like do what we call this forensic microbiology. They were able to determine that mosquitoes that had just bitten a tapeti that had this myxoma virus when it now bit a European rabbit, this is what we call a species leap or hosts leap. The virus found itself in a host that Mother Nature had never put before it before. So whenever that happens, we never know what's going to play out. Sometimes the virus will vanish. Sometimes it'll do the same thing it did in its previous host. Sometimes it'll cause it to a new disease. In this case, it caused a new disease. The disease was called myxomatosis and they wrote it up, described it in the literature. It was an amazing killing disease of European rabbits, but it was just a curiosity in the medical literature and it sat there for half a century until Australians started reading these papers because something odd had happened in Australia.

Dr. Biology: Yeah, I just talked about it at the beginning of the show - billions of rabbits now. You just start with 24 and they're really good, aren't they there...?

Grant: Yeah. So when rabbits have a lot to eat and no natural predators, they do it rabbits do. And they bred out a control.

Dr. Biology: So we have our myxoma virus. We fast forward to your lab. Do you remember the day actually that kind of triggered, was it an Aha thing or was it just slowly just revealing itself?

Grant: It wasn't a single Aha thing, but there was one incident that kind of was an inflection point or a turning point in the story. So, uh, back around, Oh, 2000, 2001, I'd been studying the virus for about 15 years and I was interested in why it was so good at inhibiting the immune system of the

rabbit. And what those studies told me was that, uh, the virus itself is more complicated and sneaky than we thought when we first started studying it. So I was giving a seminar at the University of Ottawa and uh, what I was explaining in my seminar is that the virus, uh, inhibits elements of the immune system. And one of the ways, uh, that we learned that the virus could leap from one species type to another is if you inhibit the immune system or the immune signaling in the recipient cells.

Grant: It's a little complicated. But, the gist of it is a fellow came out of the audience and said, you're interested in putting your virus in human cells. And I said, yes, if I could find a human cell where the virus would grow, I could use these techniques. And he said, I've got a whole series of human cells that have got different defects in their immune pathways and would you like to test them? I said, yeah, that sounds exactly right for what we want to do. I said, "What are they?" And he said, "They're called cancer cells." So it turns out that all human cancer cells have defects, various kinds of defects in addition to things that they learn to become cancerous. And those defects, it turns out many of them are in pathways that protect the cells from virus invasion.

Grant: So when we got many of those cancer cells, the thing we learned was that our virus treated most human cancer cells exactly the way it does rabbit cells. It infects them, it kills them, it goes on to infect and kill new cells. So when we got that result, it wasn't quite the Aha, because it took many, many months and many testings in animal models and in culture before we realized that we had a virus that was very safe in mice and humans, but when it was in a tumor tissue, or in a cancer cell, it treated them the way it does rabbit cells in which simply means it infects and kills them very well.

Dr. Biology: Yeah, excellent. And you're not doing this in humans yet, right?

Grant: Not yet, although we're starting a biotech company right now as we speak to move this virus into human clinical trials.

Dr. Biology: And you've been studying the virus for 15 years before you even started in this path.

Grant: Correct.

Dr. Biology: Just to put it in perspective. This isn't happening overnight.

Grant: No. Uh, like anything else, things take time. And so developing new treatments for any new disease takes time. So there's a lot of research that we've had to do and so we've done about 15 years of that so far. Now we have to set up a biotechnology company because to get into human clinical trial costs millions of dollars. We have to find investors who are going to invest in it. We have to get the team and the expertise together. We have to learn how to make the virus in a way that's

consistent with clinical practice and we have to get the FDA to agree to our plan to put it into people. All that takes money, takes time, but I'm a believer and so we are launching a company, it's called OncoMyx and hopefully in 2019 it will be formed and then wish us luck and getting to human clinical trials.

Dr. Biology: Okay. I'm going to wish you luck right now.

Dr. Biology: Well, before we wrap up, one of the things I do with all my guests, I have three questions I asked them and uh, so we'll launch into these. Okay? So the first one is, when did you first know you wanted to be a scientist?

Grant: For me, I was a late bloomer. So when I went to university I did not know what I wanted to do. And a lot of things intrigued me. I was really interested in the time in a topic called cosmology. The word isn't used anymore, but it basically is like astrophysics. So it's the study of stars and galaxies and I thought that was so cool and I thought, man, if I could study that, it would not be so awesome. But at the same time I was at a university, it is called McGill University in Montreal and I was talking to people and I got some advice to say whatever you get interested in, try to do something that the place you're in is really good at. In other words, to get mentors who were the best in the world at what they do. And it's so happened that the program at McGill in biochemistry was very strong and world famous.

Grant: So a couple people recommended to me, why don't you go into something like that and study with someone who's like a world expert in something. So it ended up that I went to the biochemistry program and ended up doing my PhD studying what are called bacteriophage, which are viruses or bacteria. And it was fascinating. I was really interested in it, but at the end of it I thought that's cool, but I'd really like to study things that are related to us as opposed to bacteria. And when I went looking around for training, that's when I ended up discovering and stumbling into a lab that studied vaccinia virus. It was kind of a turning point for me in my career in the sense that by the time I was finished that postdoc, I knew I wanted to be a scientist and I knew I wanted to study pox viruses.

Dr. Biology: It's interesting because you started on a quest to study outer space.

Grant: Yep.

Grant: And where you ended up studying inner space.

Grant: Yes. And I sometimes wonder what would have happened if I had gone on to do a degree in let's say particle physics or something like that. My life would have been totally different. Uh, so it's amazing how our lives sometimes do revolve around very specific times and decisions.

Dr. Biology: Right. Well now I'm going to take it all away from you.

Grant: Okay.

Dr. Biology: You've had this great journey. You love what you're doing, but I always have a sneaking suspicion that a lot of my scientists have a secret that they could, if they had the abilities, what would you do or be?

Grant: So a hint of that comes from that choice that I made when I was young. So often when I'm at home I pick up books that are different than what I do. I often pick up books relating to quantum physics or black holes or relativity theory, just because I'm still fascinated by it. I don't understand it at the level that a professional does. I just finished a book called Einstein's Monsters and it's about black holes and it was fascinating and I just thought that was totally awesome. So if I was going to be a scientist, I probably would've said something related to particle physics or the nature of a, let's say dark energy or dark matter, or something like that probably would have interested me to no end. But if I couldn't have been a scientist, I probably would've wanted to be an explorer because I love traveling. I love seeing new cultures, I love eating new foods and seeing new vistas. So if I could have done something - like I would have loved to have been on the HMS Beagle and even just to watch Darwin and go to the Galapagos and travel through South America, I would have loved that. So, uh, if I could have figured out something to be a traveler and adventurer, that's what I would have done.

Dr. Biology: Ah, I like it. Alright, I have one last question. What advice would you have for a young scientists or perhaps someone who always wanted to go into science as a career?

Grant: You know, our lives evolve based on choices that we make, right? And uh, I was lucky in the sense that I was able to make some choices that I was able to end up with a career doing something that I ended up loving. So, investigating Mother Nature. It's just to me is there's nothing better, and viruses are the coolest thing on the planet from where I'm sitting, but I got there through a series of kind of accidental choices here and there and I ended up making what I look back on now are lucky choices. So if someone was to ask me, how do you make good choices, I would say that somehow you have to figure out what is it that you would do even if no one was looking, even if no one was paying you. So in other words, if you can pick things that move you down a path where you can do more and more things that make you happy, that feed your passion, whatever it is.

Grant: A musician understands this because musicians know they have to play to be happy and in some ways if you can pick things that make you happy, you're probably on the right road. And the way to know if it's true or not is would you do it on your own if no one was looking, if no one ever paid you? Is this what you would do with your time? And if it is, you're probably on the right road or on the right track to making good decisions for yourself. I always try and bug my kids to do things that they're natural passions would take them and it's okay to make mistakes and it's okay to

backtrack. When you try something you don't like it. You don't have to feel like you've made a mistake or you're a failure. You just backtrack and try another door. So, uh, that would be the only advice I would give is don't be afraid to go through a door if it's not right for you back out and try another door. But look for the door that opens up where you know on your inside, if it's making you happy or not, and listen to that inner voice. Listen to that little internal drive because it will give you better advice than anyone else will.

Dr. Biology: Well, Grant McFadden, thank you very much for visiting with me today.

Grant: My pleasure.

Dr. Biology: You've been listening to ask a biologist, and my guest has been Grant McFadden, a professor in the School of Life Sciences and the director of the Biodesign Center for Immunotherapy, Vaccines and Virotherapy. That's at Arizona State University. And you can read more about him in our story Treating Cancer with a Rabbit trick that's on our Ask A Biologist website. The Ask A Biologist podcast is produced on the campus of Arizona State University and is recorded in the grassroots studio, housed in the School of Life Sciences, which is an academic unit of the College of Liberal Arts and Sciences. And remember, even though our program is not broadcast live, you can still send us your questions about biology using our companion website. The address is askabiologist.asu.edu, or you can just Google the words, Ask, A, Biologist.

Dr. Biology: I'm Dr. Biology.