This Week in Virology

with Vincent Racaniello, Ph.D. Alan Dove, Ph.D, and Rich Condit, Ph.D.

Episode 154: Symbiotic Safecrackers

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Vincent Racaniello: This week in Virology, Episode 154. Recorded Oct. 20, 2011. Hi everybody, I'm Vincent Racaniello and you're listening to TWiV, the podcast all about viruses. Joining me today from western Massachusetts is Alan Dove.

Alan Dove: Good to be here.

V: How you doing, Alan.

A: Doing all right.

V: Nice day, isn't it?

A: Yea, yea, cleared up nicely after buckets of rain and uh, things look good.

V: Yea, we had a ton of rain this week. This morning, it was pouring. Beautiful, beautiful now. really nice. Also joining us from north central Florida is Rich Condit.

Rich Condit: Hi fellas.

V: How you doin', Rich?

R: I'm doin' well. This is good. I'm having a good time. Everything's good.

V: The weather is beautiful down there.

R: Yea, there's a clear blue sky, it is 64.

V: Nice.

R: It was 47 this morning.

A: Wow.

R: Yea, how 'bout that? We could use some of your rain, though, we need some rain.

V: We have a lot of rain up here. Currently, it's 61 here, which is of course Fahrenheit.

R: Yea, I dunno what any of that stuff is.

V: I can tell you that it's 18C, which I just read off my new iPhone 4S.

A: Aaah…

R: Oooh! You got an iPhone! Wooooooooooooow! I'm gonna go out and get one this weekend.

V: First one.

R: I mean, I gotta get an upgrade.

V: I've never had one, so I figured this was the time.

R: You digging it?

V: It's really cool.

R: Good.

V: I can do stuff when I'm at a faculty meeting and it's boring, I can do email. [laughs]

R: Yea. You need to uh, download "Vaccines".

V: "Vaccines"?

R: Yea, the app.

V: I got Health Map, that was cool.

R: There you go.

V: I should just go back through all the TWiV picks and get all these…you should get one, Alan. It's really cool.

A: Well, I have an iPod Touch.

V: Yes, that's cool too.

A: Yes, so as long as I'm in range of Wifi, I've got most of the iPhone features.

R: It's getting so that you're almost always in range of WiFi.

A: Exactly, but I'm not paying the digital rates.

V: Yea, so I know that the temperature in New York City today is 18C. So there you go, all international listeners. Today, we have two cool stories and I want to begin with them right away 'cause Rich has to leave in about 30 minutes.

R: Yea, Rich's heart is nearly broken here. Actually, the meeting is right across the hall, so I got 40 minutes.

A: Great.

V: If you finish early, come back.

R: Ok, that's unlikely, but…

V: Yea, these student meetings go on. Before we start, a few weeks ago, we said we're going to give away a free Drobo. Well, hardly anyone responded. Hey guys and gals, free Drobo! I'll make it simple.

Go to bit.ly/drobotwiv. Just fill out that form and you'll enter the contest. You don't have to do any Tweets or anything like that, ok?

R: I probably can't enter, right?

V: I dunno, just enter. Everybody enter. See the thing is, if we get a lot of response, Drobo will go, "Oh, they have a good audience. We should advertise with them again."

R: Right, and you get a Drobo!

A: If you don't know what one of these things is, it is THE backup solution. I've got one, and it's great!

R: How bad can it be? This is easy! There's like 10,000 people out there. Do this.

V: Hey, there's a lot of you guys out there, and gals.

R: Piece of cake.

V: It's good for us, we're not asking for any money, and maybe Drobo will give us some in the future so we can get better equipment and I can sound better.

R: Good for us, good for you. It's a win-win situation. Go for it.

V: Thank you. Ok, today we have two stories which just came out in Science and they're both about how viral invaders get help from your gut bacteria. This is really cool.

A: Thanks a lot, gut bacteria.

V: Just amazing! The bacteria are letting us get infected with viruses. How 'bout that?

R: I don't think they're doing it consciously.

A: I think they're not given any choice in the matter.

V: It's evolution, it just got selected this way.

R: I mean, that bacteria probably don't care unless we get killed. Actually, you know, if you wind up with gastroenteritis or something like that that might even be good for the bacteria.

A: Or bad.

R: Or bad.

V: You mean viral gastroenteritis?

R: Yea.

V: It's a very interesting symbiosis. I don't know if the bacteria get anything from the virus, ok?

R: Well, that's what I was just wondering about.

V: The viruses have clearly co-opted something out of the bacteria, but who knows. It remains to be seen.

A: Yea, I suspect it would be bad for most of these, um…you get a viral gastroenteritis, it kind of cleans you out.

R: Yea, but you get to spread.

A: Um, yea.

R: These are commensal bacteria.

A: These are commensal bacteria, so we don't have a problem with that.

R: But we're getting ahead of ourselves.

A: Yes, we're getting ahead of ourselves.

V: Yea, you're not gonna be here for the fun part, Rich, when we speculate, but…

R: I'm already having fun. We're already speculating.

V: [chuckles] The first paper has to do with mouse mammary tumour virus. It's called "Successful transmission of a retrovirus depends on the commensal microbiota." By Kane, Case, Kopaskie, Kozlova, MacDearmid, Chervonsky, and Golovkina and this is in Science. They're both in Science.

R: One of my immunology friends walked in on me while I was reading this paper and I was telling them about it and he said, "That must be by Golovkina, right? From Chicago." He was really impressed that I was saying stuff like IL-6, IL-10.

A and V: [laughing]

V: Very good. Well, on Monday, Dickson comes in and says, "Oh, you have to look in the latest Science." There's a cool paper on microbiota and I looked and he was actually referring to a paper that came out a few weeks ago where they look at diet and enterotypes. So I picked that for TWiM this week and then I saw these two papers and I said, "This is TWiV." And that's how I found these.

A: Yea, and actually I found these independently and I put a link in the Google Box.

R: Dickson would've liked this, it's got, you know, it's got germ-free and specific pathogen-free mice in it.

V: Yea, I dunno why he's not joining us, he's sitting outside, but we just did a TWiP. Maybe he's had enough talking.

R: [cracking up] Not likely, not likely!

V: So I don't think we've ever talked about MMTV on this podcast have we?

R: No, I don't think so.

V: Mouse mammary tumour virus. It's a virus of mice, as the word, as the name indicates. It causes mammory tumours and is often spread from mother to offspring via milk and milk has virus in it.

R: And it's a retrovirus.

V: It's a retrovirus, so it integrates and, in fact, it's sometimes spread vertically by, from mother to offspring in the genome, but also by spreading in the milk. So do we need to know anything about this before we get into the paper? Is that enough?

R: I guess that's probably enough.

V: Spreading in the milk, retrovirus. So basically, these viruses establish chronic, long-term infections. The mice are fine. They might get tumours from time to time, but these viruses exist in mice for long periods and, of course, to do that, the virus has to somehow evade immune responses and that's where this paper begins because it's previously know that, in order to persist in mice, this virus needs to produce a cytokine called IL-10. And, in fact, even more specific, it has to be dependent on the Toll-like receptor 4, so it's called TL[R] 4 dependent production of IL-10. You don't get that, the virus is cleared.

A: Right, and IL-10 is an immunosuppressive cytokine.

V: Yes, which makes sense, right?

A: Damping down the immune system and the virus somehow trips this TLR4 to trigger the IL-10 and damps down the immune response so that the virus can persist.

V: That's right. And in fact, to illustrate this, they feed adult animals MMTV-laden milk.

R: So they infect them orally.

V: They infect them orally. They infect them when they're born and when they're adults, they still have the virus but they don't have the antibodies against the viral proteins because the virus has suppressed the production of antibodies by this TLR4-dependent IL10 production.

R: Yea, they actually take the adults and basically try and immunize them with MMT proteins to see if they get an antibody response and the mice don't respond.

A: Right, they appear to be tolerant to this antigen. They treat it almost as if it were self, so they don't respond.

V: But they do respond to, say, ovalbumin or different protein antigen.

A: Right, they're immunocompetent, but to this particular antigen, they've got a blind spot.

R: And as a control, it's interesting because it's specifically oral tolerance. Because if they take mice at birth and inject them intraperitoneally, inject them that way instead of orally, and then come back later, those mice, I think, clear the infection and they can mount an immune response to the antibody. So specifically, virus acquired through the oral route. And this, I, you know, I'm naïve to a lot of this stuff, ok? This oral tolerance is a big deal because we encounter a lot of antigens by eating stuff and if we mount an immune response to all of those, we're going to be in big trouble all the time. So we have to have mechanisms to tolerate some of this stuff that goes through our GI system. So there's immunity from the oral route, oral tolerance is a special deal.

V: Of course, when we're born, we're sterile and immediately, we start eating and one of the first things we eat is mother's milk. So this virus has sort of taken advantage of that, gets in there, makes it tolerant, makes the animal tolerant right away. Very interesting. Now this TLR4, Toll-like receptor 4, is one of the many Toll-like receptors. There's also the RIG-I-like cytoplasmic receptors that all sense foreign proteins or RNAs and TLR4 is known to sense bacterial lipopolysaccharide, LPS.

A and R: Right.

V: And that gave them some clues about what this virus might be doing, at least what pathway to go down to figure it out. They say, well, it could trigger TLR4 itself, the virus, or maybe it uses some part of the microbiota.

R: So for the otherwise uninitiated, LPS is a long polysaccharide attached to a lipid that exists on the outer membrane of Gram-negative bacteria. So basically, a lot of bacteria out there are coated with this thing. So it's basically something that identifies bacteria.

A: Right, and this comes up a lot in the innate immunity because the immune system obviously has been encountering bacteria for as long as there's been an immune system and, as a result, there's a lot of machinery in the immune system that's built around detecting and responding to lipopolysaccharides in various ways.

R: Responding or not.

A: Yes, depending on the context. In some contexts, it should not respond, for example, gut tolerance. In other contexts, if it's floating around in the blood stream, that's probably a bad thing and it should respond.

R: Right.

V: So when LPS binds TLR4, this starts the innate immune response. You have cytokines produced and cells are brought into the area where this interaction occurs so it's a very important trigger. So they did an experiment where they basically treated mice with antibiotics to drastically reduce their gut flora and then see if they can respond to viral antigens and what you find is that, if you deplete the gut microbiota with antibiotics, the virus can, the mice can respond to viral antigens.

R: So same experiment, you've got the infected mice, but now you don't have any bacteria and now they cleared the virus rather than the virus persisting and they can make antibody to it. I mean, you know, those two are obviously related.

V: Right, treat them with antibiotics, reduce the flora, doesn't eliminate it, but it reduces it substantially and now the virus, the mice make antibodies against the virus. So that's one cool approach that suggests that the bacteria in your gut are important. The other one is to use germ-free mice and ask whether germ-free mice, which don't have bacteria in their gut, are able to produce antibodies or, even more than that, be infected with the virus.

R: So do you know how you make germ-free mice?

V: They say we produce them. Um, I don't know how you produce them. I know you can buy them and you have to put them in your germ-free facility.

R: And you gotta assay them all the time. So these have, like, no bacteria at all. At least undetectable.

V: Right, as opposed to specific pathogen-free, which have, some microbes are missing, but others are still present.

A: Right, and the germ-free mice, as I understand it, are difficult to maintain, not only to maintain germ-free, but also because they're not especially healthy in that condition.

R: I can imagine. That must be both expensive and difficult.

V: Is that equivalent to gnotobiotic?

R: I do not know. See? Vincent ought to be here. He would know.

V: Vincent is here. Dickson, you mean?

R: Ah, Dickson.

V: Gnotobiotic.

R: Looking it up.

V: He said it's, only certain strains of bacteria are present.

R: So that sounds more like SPF.

V: The germ-free are very difficult. I know Julie Pfeiffer, who's the PI on the next paper, collaborates with someone at her institute who has a germ-free colony and I dunno how you would make them because just treating with antibioitics isn't enough.

R: Well, I read something about how birthing them by Caesarean section, to start with.

V: Yea.

R: Ok, so they don't encounter any bugs from mom so they do that in a sterile environment and then obviously you have to rear them in a germ-free environment.

V: Anyway, so you make germ-free mice and you infect them and what they find is that most of these germ-free mice don't pass the virus on to their offspring. They make an antibody response which clears it, alright? So no germs, virus doesn't succeed at multiplying in these animals. It's not 100%, it's interesting and they suggest that it might be LPS in the animal feed.

A and R: Right.

V: So, I dunno what's in animal feed, mouse feed, but apparently there's some LPS which comes from bacteria.

A: Yes, because even if the mouse feed has been sterilised, it probably was not produced exclusively from things that were bacterially sterile.

V: Yes, and the bacteria are broken, they're killed, but they still have LPS in them. So they, in fact, find some LPS in these germ-free females, in the milk of some of the females, which presumably comes from the feed. So can you imagine doing this experiment and you go, "What's going on here?" It's kind of like, one day it's this, one day it's that and someone thinks of the feed? I dunno if I would've thought of that. That's why you have to talk to people. You go to someone and go, "What's going on here?" I go across the hall with a cup of coffee and go, "Condit, what's going on here?"

R: Condit would said, "I dunno, go away, don't bother me."

V: He's say, "What about the feed?"

A: That's the kind of thing you'd probably need to talk about your veterinary staff about because they'll often have a really good idea of, they obviously know what's going on with everybody's animals and

they're in touch with all these aspects of animal husbandry and so the veterinarian who's in charge of the mouse house might be able to come up with something like that.

R: Well, you can imagine these guys would've been totally focussed on LPS, so if you've got something that doesn't fit your hypothesis, you would be thinking, "There must be some LPS in here somewhere", ok? Then you start wondering about the food and that kind of stuff. I spent forever on this table in 2C. For some reason, this is one of these double and triple negative type experiments.

A: Oh, the mouse genetics thing always take me and…

R: I had a real problem with this but it was fun because it was something, all of a sudden, it clicked and everything made sense and it was ok. As a matter of fact, it wasn't until I got to the nice figure that they buried in the supplementary data that it all really started to make sense.

V: So the figure, the table that we're just talking about shows the different kinds of mice they test and whether they're germ-free or SPF.

A: Right, so that these mice that they're testing, they're trying to figure out what is connecting LPS, that is apparently involved, to viral pathogenesis to mice that are lacking different parts of this TLR4, IL-10 chain.

R: Right, so if you've got germ-free mice that don't have the TLR4 receptor, ok, then even if there's any LPS there, it's not going to be sensed and all of those mice clear the virus.

V: Yes, 8 of 8 families. So that's compared to wild-type, 5 of 7, and that's because of the LPS in the feed, right?

A and R: Right.

V: Why don't you go on, Rich because you got a handle on this.

R: Then they've got this, well, I may fall flat on my face here, then they're got mice that are missing MYD88, which is a, I would say, a ubiquitous intermediate in all of these signal transduction pathways.

V: Most of them, not all, but most.

R: A lot of them and in particular in the TLR4 pathway. And if you don't have MyD88, then you can't do, um, any of this immune response and the virus persists, even in germ-free mice. And then they have, they do specific pathogen-free mice, both wild-type and MyD88, and the, none of those mice can clear the virus. So the specific pathogen-free mice are really no different than regular mice because they do have bugs, they've got LPS. They've just got a subset of the normal bugs. There's good correlation, in the end, there's a good correlation between bugs and an LPS receptor and whether or not you can clear the virus.

V: So MyD88 is an intermediate between TLR4 and what goes on in the nucleus in terms of transcription.

R: Right, so it ultimately generates all these interleukins.

V: In fact, TLR4 can signal either through MyD88 or another protein called TRIF. The cool thing about this table is that, in a MyD88 deletion, none of the families of mice are virus-free, even though they're germ-free. Because, apparently, MyD88 is needed to clear the virus, so even if you can't, if you don't have TLR4-stimulating LPS, the virus is not cleared because you need MyD88 to do that. And the other

protein that can signal from TLR4, which is TRIF, they say that doesn't matter for clearance of virus. So this is kind of a side issue, but it threw me for a while.

R: Oh yea! Like I said, it wasn't clear to me until I got to this Supplementary Figure 7 that has this nice cartoon, shows all this and what they show is the anti-viral immune response. They don't even talk about TLR7 in this, but the anti-viral immune response, the thing that actually clears the virus infection normally, is done through another Toll-like receptor, TLR7, that's also mediated through MyD88. So if you don't have MyD88, you can't mount the anti-viral immune response in the first place, so almost everything else is irrelevant.

V: Yea, so there's two things going on here. One is that TLR4 interacting with LPS seems to be important for keeping the virus around but clearing it depends on MyD88. And so MyD88 knockout, no virus-free families.

R: In the last few minutes, I have said, TLR4, TLR7, MyD88, and IL-6. It's incredible.

V: You're an immunologist, man.

R: Uh, no, not quite. I'm trying to learn, though, vocabulary.

V: Well, you could say, some few other markers, and then you'd be there.

R: You think so?

V: Ok, so now we see that LPS and TLR4 are important. So basically, they show next that LPS binds the virus. It binds the particle directly. They can add it to virus and, even in a germ-free mouse, that virus can infect those mice, just by the fact that LPS is present. So they do physical, biochemical studies to show that LPS interacts with the virus particle and that interaction allows the virus to infect mice, which is amazing. So I guess the idea is that you stimulate TLR4, which makes IL-10, and that allows the virus infection to proceed. And only if LPS is present, which is a component of your microbiota, of course, can this happen. Alright, so it's not that this virus can't infect, but it can't persist without this immunosuppressive IL-10.

R: So what strikes me about this is that it's not just LPS. It seems to me that it's LPS, 'cause there's LPS everywhere anyway, it's LPS in the context of the virus, it seems to be.

V: Right, it's the two of them together.

R: So it's more complicated than just tweaking the TLR4 receptor, it's tweaking it with LPS that's in the context of the virus. I'm thinking there's probably components missing here, like coreceptors or something like that triggers this tolerance.

A: Right, and because the virus does not induce a general immunosuppression, these mice don't respond to other things. In fact, it would be detrimental to the virus to do that because it could kill off your host too soon.

R: Likewise, LPS doesn't induce generalised immunosuppression.

A: Right, but the two together…

R: LPS in the context of the virus.

A: Right, LPS in the context of the virus is triggering this LPS tolerization pathway TLR4 and IL-10 and something else, as you point out, is going on that is specifically tolerizing the host to probably viral antigens, so saying, “Hey, this is self!” and then, the host immune system assumes that for the rest of its life.

V: Rich, they do say that binding of LPS by the virus enhances its ability to induce IL-10 compared with LPS alone. So yes, the virus is doing something and there must be some other receptor or protein involved.

R: I have to believe that these investigators must be looking for that. I would because that would be fascinating.

V: Absolutely.

A; And they make an interesting point to here, the end of the paper, that this isn’t necessarily a mechanism that’s gonna be exclusive to the gut. So viruses that go through other mucosal surfaces with bacteria, in our noses and in our throats and all other sorts of places, something similar could be going on in this routes of transmission too.

V: Yep, absolutely. I’m sure people will be on it. I like this statement they say, so basically, they say, “LPS induced signalling, of course, together with MMTV, drives a viral subversion pathway via IL-10 production that promotes viral transmission to successive generations.” That summarizes it really well. So I am really amazed or curious about how this evolved, right? I mean, the bact…who’s there first and how did it evolve this way? Could the virus infect but not persist and then one day it picked up a little bit of LPS and it just boggles the mind to try and go through the scenario.

A: Well, and this is not something I would expect evolved with MMTV and mice.

R: Well, this all has to do with MMTV taking advantages of the probably pre-existing oral tolerance. Oh, you’re saying evolutionarily, it goes back.

A: Evolutionarily, I think it probably goes way, way back and when I figure saw this paper, “That’s a…”, I was just flipping through abstracts and I looked at that and I thought, “Wow, that’s cool, I wonder how many other viruses do that?” and of course, we’re going to talk in a moment about exactly that question.

V: I think you’re probably right, it goes way back. It’s an ancient thing because a virus and bacteria probably coevolved.

A: And the immune system.

V: Right, and this probably happens in everything with a gut.

A: Right, and you get a gut and you’ve got commensal microbes living in the gut from the earliest stages.

R: You have to have oral tolerance.

A: You have to have oral tolerance and as soon as you have a security backdoor like that, something’s going to take advantage of it and here you go.

R: It’s the safecracker thing again.

A: Yes.

V: So here you have an abetting role for a microbe and a viral infection. We did a paper on TWiM a couple of weeks ago, where eliminating gut bacteria makes mice more susceptible to respiratory infection with flu. So there, the bacteria protect the mouse against viral infection, but at a different site.

A: Damned if you do, damned if you don't.

V: Can you imagine all the different scenarios, something with the skin, there's going to have to go be something going on there with viruses that infect maybe even mucosal surfaces, like HPV.

A: Yea?

V: It's just amazing and just to think, it's a mouse virus that people are working on. Hmm, that's not really translational research, is it?

R: No, that sounds like basic research to me.

V: Sounds like curiosity.

A: Yes, that is curiosity driven research.

V: And look what happens? Hmmm…

R: But certainly has brought application.

V: Yea, I think it's fabulous. It's a great story. I actually heard about this a couple of weeks ago. I was very happy when it came out. Anything else about this before we move on?

R: Well, I'm not saying that, when you first brought the paper to my attention, I was going, "Oh, Vincent, this is immunology!", alright, but I'm really glad you're making me do this because I'm learning a lot.

V: I hope we didn't confuse listeners with all the abbreviations. It can be daunting.

R: I think we did ok. We'll put this cartoon from the supplementary figure, ought to be maybe the image for the episode. The one on the left that shows that actual IL-10 thing, summarizes it, 'cause that maybe makes a lot of it clear, I think.

V: Will do. You wanna bow out now, Rich, before we go on?

R: Ah, no, I'm gonna hang in there til the last minute.

V: Alright.

R: Even if I have to bail out in the middle of this next story.

V: Got it. So the same issue, in fact, the following paper is a paper entitled, "Intestinal Microbiota Promote Enteric Virus Replication and Systemic Pathogenesis" and this is by Kuss, Best, Etheredge, Pruijeer, Pruish....Alan?

A: Pruijssers?

V: Pruijssers, Frierson, Hooper, Dermody, and Pfeiffer. And I know there's some TWiV listeners in the Pfeiffer lab. This has to do mainly with polio and also with reovirus. Poliovirus, which is of course the virus that Alan Dove did his thesis on, remember?

A: Yes.

R: You got a PhD for it, right?

V: Yes, he did! He actually worked on polioviruses, we had done in the lab for many years. And in this paper, they are using a mouse model for polio infection, a transgenic mouse model where you take the poliovirus receptor, identified in my lab by Cathy Mendelsohn, and you make a transgenic mouse, which was done by Ruibao Ren in my lab, and those mice, you can infect with polio. And so they begin by saying, you know, when polio infects your gut, it's a lot of bacteria there, so what do they do? Do they interfere? Do they help? Do they hinder? So why don't we treat some mice with antibiotics and see what happens when you infect them with polio? So, this is one of those experiments I wish I had done.

A: Yea, it's a simple enough experiment.

R: Except you're trying to do plaque assays on feces. It strikes me, that could be a problem. You've got enough antibiotics in, I guess that's ok.

V: Yea, you could filter it, I guess, 0.2 micron filter ought to do it, 'cause polio will go through.

A: You could flocculate it.

V and R: [laughter]

V: Yes, floculate it. So they use transgenic mice expressing the polio receptor. Now, when we made these mice, we used to feed them polio and nothing ever happened. You could inject the virus in their brain, or IP, or intravenously, or the muscle, they would get paralyzed, but if you fed them, nothing would ever happen. And many years later, Satoshi Koike in Japan found that, if you don't take away the interferon system, nothing happens, but if you take away recepters for interferon, genetically, then the mice become orally susceptible. So, that's what they use in this paper.

A: So these are mice that are transgenic for the poliovirus receptor, the human poliovirus receptor gene, and they have had their interferon receptor gene, one of their interferon receptor genes knocked out genetically.

V: Exactly. So they don't respond to interferon and apparently, that's important in the mouse gut. Now, all of us, of course, have interferon receptors, as far as we know, and we can get polio, so our guts are clearly different from the mouse gut. And why that is, we don't know, but that's another story. So basically, they find that if you treat mice with antibiotics, very similar to what was done in the previous paper, untreated mice succumb more often than mice treated with antibiotics.

A: Doubles the mortality.

V: Doubles it. So you get rid of the bacteria and polio doesn't kill them as well and it also doesn't replicate as well in their gut. And this is only by feeding the mice. If you inject it, say, IP, no difference. Antibiotic-treated or not.

R: They have a cool control where they take the antibiotic-treated mice and recolonize their guts with what, antibiotic-resistant bacteria.

A: Right, and when you do that, you're back to the situation that you would have, it's like the untreated mice.

V: Now, just measuring virus in feces, they found, wasn't very informative, so they actually do a very cool experiment which happens to be ancient, well, maybe not ancient, but many years old. And that is, you can grow poliovirus in cells in the presence of a compound called neutral red. And the neutral red gets packaged with the RNA genome in the virus, ok? So if you take neutral red virus and you shine light on it, it knocks out the infectivity. So that's how you can tell what comes out of a mouse is what you put in or if it's replicated. Because really, when you think about it, you feed mice polio and then you take the feces and do a plaque assay, you don't know if that's the inoculum or if it's replicated.

R: Right, so you might just have a high background of unreplicated virus that just passes through the gut.

V: Right, and they had some issues where they use the neutral red virus to show that, in fact, if you deplete the microbiota, the virus doesn't replicate as efficiently as in wild-type mice. So that, we don't actually have to talk about that, but I thought it would be an interesting aside for our listeners because it's a really cleaver trick that you can find in the literature 40, 50 years ago and some old techniques are sometimes still useful.

A: I remember people using that in the lab when I was in your lab.

V: Yea, I think, was Cathy Mendelsohn around?

A: Cathy was not there, um, who was doing, I think Sa might have been doing something, Sa Liao was doing something where she needed to distinguish inoculum from replicating virus and did it that way. You know, she would have her plates covered with tin foil and everything in the incubator so they could grow without light.

V: I remember when Cathy used to make her neutral red virus, she would turn the lights off to check the cells, you know, see if they were infected. Someone happened to come and turn the lights on and she would scream at them, "Turn the lights off, you're going to kill my virus!" Anyway, so, getting rid of the microbiota for polio, as well, seems to harm its ability to infect.

A: Right, so the untreated mice or the recolonized mice die. The antibiotic-treated mice survive and the virus that you're getting out of the antibiotic-treated mice is mostly what you put in.

V: Ok, so then they get the idea that some component of the bacteria might be involved. So they have an assay where they simply incubate poliovirus in vitro, in the absence of cells, at various temperatures, and they add stuff to it and they quantify the infectivity. And they show basically that virus, if you treat virus with just a buffer, you lose infectivity, but if you incubate them with feces of mice or germ-free feces or components of bacteria like LPS, you can restore or enhance the infectivity. So LPS is, in fact, one of the most potent enhancers.

R: Oh, I can think of times where I've been so frustrated and I've wanted to defecate on my experiments.

[everyone cracks up]

V: Hey, woulda helped.

A: Yep!

R: God…that's pretty amazing. You can actually mix the virus with poo and…

A: And it makes it more infectious.

R: And it makes it better.

V: Yea, so here, polio incubated with PBS, feces from antibiotic-treated mice, and germ-free feces, you lose viability. But, if you incubate it in untreated, or germ-free feces supplemented with bacteria, you improve the viability. Bacteria don't have to be living and LPS turns out to be one of the best stabilizers, if you will. They show the virus actually physically binds LPS and that's about it. They don't go beyond that, we don't know if it's binding a particular receptor in the gut or what, so that remains to be seen. What LPS binding is doing, maybe it's simply stabilizing it.

A: But it seems to improve the virus' ability to get into cells and, for distinction here, we're just looking here at viruses getting into cells, it's not to do with the immune system. So whereas MMTV was using the LPS as a way to bypass the immunity, in this case, poliovirus appears to be using it as an entry assistant.

V: Or a stabilizer. So maybe you get more virus infectivity and therefore a better infection and that's all it is. It could be as simple as that.

A: Right.

V: Right? So I like their conclusion, "Our work implies that antibiotic-mediated microbiota depletion can have anti-viral effects, although we do not advocate the use of antibiotics to prevent viral disease." I'm glad they added that, otherwise…

A: They also did they with another virus too, so after finding this with poliovirus, they looked at reovirus. So they're another enteric virus and they did a similar set of experiments, antibiotic-treated vs. untreated mice and looked at pathogenesis in these two and you find, once again, and did the follow up-type assays and, once again, the virus appears to use LPS as some kind of stabilizer or entry-type assistant.

V: Right, here, of course, reo is a natural virus of mice, so one could argue that it's kind of an important experiment to include to show that it's not a specific phenomenon to polio. I like the phenotype to reovirus.

A: You don't often see pictures of poop in scientific papers.

R: Right.

V: And the description. "Feces from untreated mice were yellow, oily, and hardened, typically of biliary obstruction from viral replication and damage." Excellent.

R: And with that, fellas, I'm outta here.

V: Hey, we did the two.

R: We did the two, not bad. Sorry to miss the rest. Have a wonderful time. I will listen to you on TWiV.

V: Have a good meeting.

R: Yep, see ya.

V: Bye.

A: Take care.

V: Ok, so, two papers, an enteric, two different enteric virus, or three. Their infection is facilitated by enteric microbes.

A: Yes, and by different mechanisms.

V: One involves immunosuppression, right, to allow persistence, and the other may be just enhancement of infectivity. So I think a lot of people are now going to be looking at this, right?

A: Yea, I think this is gonna turn out to be a general story, that viruses have, particularly enteric viruses, they're in this milieu where they have all these bacteria around them and they're adapting in different ways and, you know, polio and reo are pretty much guaranteed to end up in this environment with this LPS floating around. They might as well use it for something.

V: Yea.

A: And they might get some kind of advantage, maybe if they had to stabilize themselves, rather than relying on LPS, it would require more energy or they'd have to have a different shaped capsid, whereas LPS provides this or it could even be that this helps to concentrate the virus somehow in the areas where it's most likely to be able to infect.

V: Do you think that the stabilization by LPS, years ago, allowed this to be a site of infection?

A: Maybe…

V: Or did it happen later?

A: Or it may have been the other way around, that this was the site of infection and it's an advantage that LPS is kind of an indicator, "Hey, you're in the intestine. It's time to infect a cell." Rather than trying to infect cells in the esophagus, which wouldn't be productive.

V: So we have a gut microbiome which can influence virus infection. We know that there's a skin microbiome. Where else are microbiomes in and on us that could participate in infection?

A: Any surface, certainly any mucosal surface, your skin, of course, is contiguous with your mouth and your gut, so you follow all that through.

V: How about the lung? Is there a..

A: I would assume there is, I don't think there's been a lot of work on it.

V: There are calls for proposals from the NIH to study the lung microbiome, yea, because it's not sterile because you're breathing in.

A: I don't see how it would be.

V: So that could influence infection. So I guess there's an eye microbiome.

A: Yep, there are penile and vaginal microbiomes.

V: It's very cool.

A: Any surface of us that's in contact with the world.

V: Mouth microbiome.

A: Absolutely, that's huge.

V: A number of viruses infect there. Wow, this is going to be fun. And look at this, if we had eradicated polio 10 years ago, this work would never have been done.

A: You'd have to use some other enterovirus.

V: I guess the field would have turned toward another entero and there are plenty of those that do replicate in mice, but the polio system is so compelling because you have so much information and so many reagents and you have this mouse, the genome cloned and sequenced.

A: Yea, and you have a half-century of classical virology that's been done on it. It's very hard to take an established system like that, it would be like if we'd all of a sudden, I dunno, we're going to eliminate mice and now all work that's been done on mice, stop, you have to get rid of all of them, you have to switch to rats or pigs or whatever else and you wouldn't be able to refer to this vast resource of the model which you'd built.

V: So kudos to the Pfeiffer lab for continuing to work on polio.

A: Yea.

V: In the face of difficult times, it's not easy to get funded on polio.

A: No, I don't imagine so.

V: There's some sentiment on study sections that, well, "Oh, it's going to be eradicated soon."

A: One of these days.

V: Yes, as you know. Ok, nice papers.

A: Yea.

V: Let's do a few emails. First one's from Gabriel, who writes, "I just finished listening to TWiV 152, in which you spent quite some time discussing the death of Steve Jobs the past week. Though this mention is certainly well deserved, I thought it was an oversight not to make any mention of the outstanding immunologist and fellow New Yorker Ralph Steinman, who also passed away due to the same disease that same week, only days before being awarded a Nobel Prize for the discovery of dendritic cells. I know you guys are not the greatest fans of immunology, but I think that it deserved at least a mention, especially given the huge importance of DCs to the way our immune system senses and responds to viral pathogens.

A: Absolutely correct.

V: I agree, we should have mentioned it, but we are fans of immunology, don't you think?

A: Yea, absolutely. I have the greatest respect for people who work on immunology and it's just, they've discovered so much that it's often hard to get my head around all this stuff.

V: Well, we too, from time to time, cover immunology. It would be good to have someone here from time to time who knew more and maybe someone will show up. Yea, we should have mentioned Steinman and Bruce Beutler, who also co-won the Prize. But in fact, we are going to do a show on Ralph Steinman in a couple of weeks, Jeremy Luban work in his lab.

A: Right.

V: He's going to be in New York in a few weeks and he said, "Let me come by and I'll reminisce about Ralph. I'll tell you what it was like to work in his lab and what he was like."

A: Outstanding.

V: So Jeremy understands all that. So we'll do it then. But that was quite the story, that he was awarded the Nobel Prize and had died a few days before, right?

A: Yea, they don't award posthumously , but they made the decision and they just hadn't announced it, and they announced it and then they found out that he died a few days before and I gather the Nobel Committee said, "Well, you know, we would look like total jerks if we rescinded it now", which they would've, not that that's stopped them from some earlier decisions, but in this case, I think they made the right call.

V: So yes, you're absolutely right, Gabriel, we should have mentioned it and we will make up for it in a couple of weeks. Alright. Alan, why don't you take the next one.

A: Falaeh? Or Faleieh? Or Falei? Uh, sorry I butchered your name, I probably just mispronounced it three times, so I'll stop now. Anyway, he writes, "Hi TWiV crew, I'm Faleye Temitope from Nigeria. I finished a Master's Degree in virology in Nigeria and will be convocating in November 2011.", which I guess means graduating?

V: Sounds like it.

A: "Though I've been offered a PhD position in Nigeria, I'd love to experience education in another part of the world. I've been searching for what do for a PhD and in this light, I went to this meeting in Sapporo, Japan, IUMS and it was mind-blowing. It was my first time at an international meeting and a virology meeting at that. I learned a lot and just assumed that the TWiV crew would be there. I was, however, not very happy to not see you guys there."

V: [chuckles]

A: Well, they didn't offer us a ticket. We absolutely would've gone. "At the meeting, I learned about Saffold virus for the first time. Saffold virus is a human cardio virus, first identified in 2007 by Morris Jones and his group in California. Virus is isolated in 1981 from an 8-month old female child with fever of unknown origin. On returning to Nigeria, I downloaded everything on Saffold virus listed on PubMed and am churning through it all. I'm surprised to see the likes of Eric Delwart, Howard Lipton, Don Ganem, Joseph Derisi and Nathan Wolfe already neck deep in the field. What was more surprising was the fact that I have no memory of Saffold virus being discussed on TWiV."

"The way you guys covered XMRV has built in me a level of trust in your judgement as a team and I will so appreciate you guys discussing Saffold virus on TWiV. Should I venture out to work on, for PhD, Saffold virus in Nigeria? Please, i will appreciate it if you can, in additon to your opinions, also add the opinions of David Baltimore, Karla Kirkgard, Ian Lipkin and any other individual you feel is well positioned to inform my choice."

"You guys have constantly been a source of strength and support to me. I'm glad to inform you that I finished top of my M.Sc. class." Ah, congratulations. "And I have to confess that TWiV and Prof Racaniello's virology lectures played a big role in my education. You guys thought me a sizable chunk of all I know today about virology. Thanks guys for all the effort you put into educating me and everybody

out there who, in one way or the other, has benefited from TWiV. Look forward to hearing from you." And here he's sent some pictures.

V: Yea, he's got some pictures from this meeting and he's got one with David Baltimore.

A: Ah!

V: And others with other virologists and he said, "Feel free to post" so we'll post them.

A: Yea!

V: And Saffold is an interesting virus.

A: Aren't they all?

V: You know, you're right. Every one of the millions and millions of different viruses out there. And we should do a show on it, so we'll put that on our list. There is a review about to come out in the Journal of Virology on Saffold, actually, Faleye, and you might want to look out for that. So thanks for that.

Next one's from Dan:

"Hello, I'm a second year medical student and was turned on to your podcast by my medical microbiology professor." Alright. "I love listening to your shows because they integrate the often dry, tedious, concepts and "bugs" that I'm learning about into relevant, amusing, and easy-to-follow stories. You make learning entertainment." What did someone call it once? Edutainment?

A: Edutainment. Yes.

V: "A few episodes back, you mentioned that you were looking for a 'Virology for Dummies'-style text book for amateur enthusiasts. While, not specifically virology oriented, I've found the book 'Clinical Microbiology Made Ridiculously Simple' by Mark Gladwin and William Trattle to be a great resource. It takes a humorous and lighthearted approach to a fairly complicated and, as I said before, often tedious subject. Through humour, cartoons, mnemonics, and other imaginative "study tricks," it's a great way to understand the basic concepts of medical microbiology. Since I've been completely immersed in all things medicine/science for the past few years, it's hard to judge just how "ridiculously simple" the book may appear to a complete lay person. However, for someone with basic science knowledge (e.g. knowing the difference between RNA and DNA), and trying to get more insight into the world of microbiology, I highly recommend it."

"The best part about this book is its knack for juggling basic concepts with just the right amount of detail, without overwhelming the reader with technical jargon or complicated, seemingly random, facts. It is able to integrate and link concepts without coming off as a "bug parade" as most micro courses/books often do.

"Besides a few chapters on viruses (classification, life cycles, structures, specific viruses, etc.), it spans concepts of microbiology from differentiation of gram stained organisms, to specific organisms to parasites, fungi, prions, and even mentions some pharmacology. Definitely worth $25. Please keep up the good work."

A: Cool.

V: Thank you, Dan, so we'll post it and people can check it out. Alan?

A: So Ricardo writes:

“Hello Vincent and the rest of the TWiV gang. Congratulations for the three years. I haven’t writen much but you can be sure I’m there, listening every Monday on my driving to the University, talking back to you as if I was there. One of your listeners said it seems like you are our friends. Well, it sure fells like it. I can see a tertulia about Virus with all of you siting at a café table.” A tertulia?

V: I dunno what that is.

A: Tertulia?

V: You don’t know? Let’s Google it.

A: It’s some kind of an event, I think.

V: It’s a, well, it’s a café, bar, or restaurant.

A: A tertulia, ok, a social gathering.

V: Ok, yea yea, got it.

A: In Spain or Latin America, with an academic overtone. Ok, ok.

V: I’ve learnt something there.

A: “I’m giving a little bit back with this video, once again. You might use it on a public TWiV event while you wait to start the show, so people can see a little bit of the TWiV history. Best regards, Ricardo.” who is at the Fernando Pessoa University in Portugal. And he sent a video, it’s a computer-generated video of a timeline of TWiV. The episodes starting from number 1.

V: All 150. Thank you, Ricardo. Alright, and the next one is from Geoffrey, who writes:

“Doctors and Alan (I don’t remember mention of a PhD for you).” But we did today.

A: I do have one.

V: Yes, and you got it in my lab.

A: That’s right.

V: So yes, Alan should be included there. PhD, in fact, working on poliovirus.

A: That’s right.

V: “I don’t follow these matters closely but I have a point that I feel probably confuses a lot of people and probably contributes heavily to rumours of continuing US offensive biological weapons programs.

As pointed out in episode 151, there are now quite a few defensive programs in place in the US. As part of their research, some of these programs actually do weaponize biological agents. This is not because they are, necessarily, looking for the next best weapon nor because they think defenses against these will be of direct use in the future. It is, rather, because weaponizing (indeed any genetic manipulation) has unpredictable (at our level of technology) system-wide effects and they are creating these agents to gain insights into how weaponizing might make biological agents more or less susceptible to established

defenses. Sure they keep these creations around for future study and that is, I believe, what causes many rumours of weapons development.

However, the difference between defensive and offensive development is mainly in quantity. A few vials of a weaponized strain, while dangerous, is not a weapon. A few tons of micronized smallpox or anthrax ready to be distributed to warheads is a weapon (as was the case before the disbanding of the Soviet Union). To the best of my (the public's) knowledge, the US is not stockpiling biological weapons and is not, therefore, engaged in any offensive programs. This does not mean that the US does not have some gems in a freezer somewhere that they are prepared to produce in quantity should the need arise but that is not an offensive program."

A: Good point.

V: Ok, thanks for clarifying that. And the last one.

A: Ok, Timothy writes:

"Dear TWiVers, I'm responding to your discussion about MD.-PhD. training in your email-only episode #151. You got it mostly right, but there are some nuances that were missed. While M.D.s can do basic research, and PhD.s can partner with MDs to bring clinical translation to their work, we clearly need people at the interface who do both for a more seamless transition. The two pathways for a person to reach the point where they take care of patients and conduct bench science are, as you said, (1) the combined program or (2) an MD who trains extensively in the laboratory. Many of my colleagues that have taken the latter route received their laboratory training during their subspecialty fellowship years and stayed under their mentor's wing until they were able to procure their own K- and then R-level grants." Those are different levels of NIH grants.

"They learned to do science by apprenticeship, however, without the rigorous oversight of a thesis committee or completing the academic requirements of a PhD training program. I believe that the PhD training equips the individual with a more robust toolset for conducting research, and ultimately they are better poised for success. There is a downside, of course, in that the training is long during years of being a student and going further into debt. I myself essentially was in school for 17 years after high-school before my first real job. Of course, talented individuals will be successful no matter which route they take. I do want to emphasize how important it is for there to be people that do both, because they can get things done or see insights that two people from the different spectrums can't appreciate."

Ah, Tim is, as you probably figured out, an MD/PhD and he is at University of Cincinnati. That's a good point.

V: Yea, that's good. We didn't get that advantage as we talked about it previously, so thanks for that. Tim is also the author of 'This Week in Pediatric Oncology'.

A: Ah, great!

V: TWiPO. So check that out if you want to learn about cancers of kids.

A: And I think for the MD/PhD discussion, we're going to bring somebody on who is an MD/PhD and can talk about specifically their trajectory.

V: Yea, we have one coming up in a few weeks and you know, everyone has a slightly different view but we're getting a bunch of different ones, so it's good, so if you're out there and you have an MD/PhD, add to the conversation for sure. And let me just do the last one which is short, from Georganne.

“Has Ila Singh made a statement about whether XMRV is still a player in prostate cancer? I’m surprised I haven’t seen a statement from her regarding this issue. Have I missed it? I would think she would go with the latest studies that show XMRV is a contaminant in prostate cancer. Thanks.”

Well, I was at a meeting in Chicago called ICAAC and I heard Ila Singh give a talk and she is still detecting some antigens in prostate tissues using antisera she prepared against XMRV. Now she said she realises XMRV itself is a lab contaminant but she’s leaving open the possibility some related viruses might be involved in prostate cancer.

A: Or some other antigen.

V: Some related antigen, yea.

A: Because it’s not necessarily an infectious virus antigen that she’s detecting.

V: Yes, unfortunately, all she does is, she takes tissues and sections them and probes them with antibodies.

A: Right.

V: Yes, so it needn’t be a virus antigen that’s there, cross-reacting with the antibody. And she admits that her antibodies are a bit dirty. They do detect cellular proteins. So, she said she’s making monoclonals, at the moment, to XMRV and will be using those to look at her tissue sections. So I don’t know, I’m very sceptical that a retrovirus is involved in prostate cancer. As I’ve said before, to think that a contaminant would point you in the direction of a bonafide retrovirus infecting humans seems unlikely.

A: Yea, it would be completely random that you’d get a useful lead off of…

V: Yea, exactly, it seems weird. So she’s still pursuing that. She’s doing a lot of work. In fact, now she has moved to New York City. She’s here at Mt. Sinai and we’ll be hearing more from her. So she still thinks there’s some connection with some infectious agent so stay tuned. She hasn’t published any of that yet so I don’t want to talk about it, but I’m sure we’ll see it eventually.

A: Great.

V: Alright. Let’s do a few picks of the week. Alan?

A: Well, my pick is, I actually had something else and then this discussion got more interesting, so my pick of the week is this post that Seth Mnookin put up on his blog. He’s calling it SciWriteLabs [spells it out] and it’s an experiment in communication between scientists and writers and Vincent and I are participating in this. Vince, you just had a post up that was quoting you and we’re now talking with Seth back and forth over email and this all grew out of a discussion about fact-checking for scientific articles. It’s an interesting debate/discussion about when and under what circumstances should science journalists run their articles or pieces of articles past sources or independent scientists to check the facts and this is actually a discussion that grew out of TWiV, from your episode in Chicago because it was something that Trine Tsouderos said that really brought this about.

V: Right, and so I’ve picked a blog called Take As Directed, which is written by David Kroll, who did the original post about Trine’s statements on TWiV in Chicago. He did a very nice blog post a few weeks ago and there were lots of writers commenting there. So Seth took off on that and he’s continuing it. But Take As Directed by David Kroll, who is a professor of pharmacology in the US and he’s very interested in communication, hence his participation in this. It’s a very good blog, covers a wide variety of topics,

not only pharmacology, but professional development of scientists and so forth. So I thought I would add that in because it's relevant to what Seth is doing there.

A: Yep.

V: What do you think about Seth's SciWriteLab?

A: I think it's a great idea. I think this was a discussion that, obviously the time was right to have it and Trine kind of touched it off and now there's a lot of discussion back and forth between scientists and writers, which is always good. Talking about, you know, obviously there's this tension between journalistic independence and making sure that the facts are carefully check by somebody who knows what's what. And it varies from publication to publication and depending on your, on the topics that you're covering, obviously there's some topics where it's gonna be much more technical and much more difficult for a general journalist to get everything right. And so I think it's a really good conversation about where do we find that balance. And I'm sitting right on the fence. I see, as a scientist, it's crucially important to get the correct information out there to the public. As a journalist, I see that it's crucially important that the press be independent from influence by the people that they're covering. And that's scientist or politicians or business people or whoever they're covering. So, you can't just send your articles to the researchers that you're writing about and have them vet them and rewrite what you wrote. I don't think that would be appropriate. I think that would compromise the independence of the journalistic coverage. But at the same time, journalists just writing it up and not bothering to check any facts is not really the way to go either because obviously a lot of wrong information gets out that way.

V: I think Trine's point, as you know, was to get someone else to check, not the person you're writing about.

A: Ideally, yes.

V: Which is what you said in the discussion, it's not always possible. You gotta find a Racaniello somewhere.

A: Exactly. You made the assumption that all researchers behave as you do and…

V: I did.

A: ..requests quickly and reasonable and that's just, unfortunately, that's just not the case, if I send something to a researcher and say, "Hey, I'm writing this story about somebody else's work, can you check it over?", they're, I'll never hear back.

V: Yea, I made that assumption and it was an error and didn't realise how, but, you know, it's worth trying at least because you might be able to identify a number of people in different fields who are cooperative, right? They're out there. So this is an interesting conversation and check out both of these blogs for more on this. You'll see it's testy at times because people are sensitive about what they're doing for reasons that Alan has just said.

A: There's a lot at stake on both sides but I think, overall, it's a case study in how to have a discussion on the internet. There's been a little bit of this and that and some silly things said but the overwhelming majority of it is a bunch of people who are genuinely interested in doing the right thing and figuring out what the right thing is and they're just having this honest, intellectual discussion.

V: There are a few people who said, "No, I don't check." And that's the end of that story, and that's not really useful. And those people kind of tainted my view of the whole conversation, you know? Those are

the ones that stand out in my mind when I think back on it. Not the ones who were reasonable, unfortunately. But the whole issue, the whole issue of science writing is very interesting because it's difficult because you have often people who are not scientists writing. So you are unusual because you are one, but not everyone is one and not every science writer needs to have a PhD, right?

A: No, and in fact, for general publications, most of what they're going to be covering is going to be stuff that an ordinary person ought to be able to understand from the outset and ought to be able to get the straight story direct from the researchers and not have to do a whole lot of back and forth. But there does need to be a lot of care about getting the story straight because when you screw it up, it can have real implications.

V: So your view is that a good journalist should be able to a, say, string physicist and inquire enough so that they can write a reasonably informed study that is correct. They don't need to know the field in order to be able to do that.

A: Yes. Now they're not gonna write a description of string theory that a physicist would read and say, "Oh, my gosh, I've never looked at it that way." They're gonna write a summary that a physicist would look at and say, "Well, hmph, doesn't everybody know this?" but the average person, the average biologist would pick it up and say, "Wow, I never understood this string theory thing and now I know something about it." So a good journalist, a good general journalist, science journalist should be able to do that with any topic but it's a question of talking to the people involved and really just kind of going around and around with them about, "Does this mean this or that?" and really just nailing it down in your own mind.

V: So Seth teaches in a graduate program in science writing at MIT. So are those some of the skills that would be taught in a course like that?

A: Yes, in fact, I taught in the graduate program, the journalism school at NYU for a number of years before I moved out of the area and the commute got too extreme.

V: I remember...

A: That's right, I remember I had you come and talk to them at one point and they came to your lab and interviewed to the folks in the lab, too. So yea, there are a lot of exercises like the one that we did, having scientists talk and having people interview scientists as a practice and also lots of discussion about how do you figure these things out and how do you set up an interview and how do you really kind of delve into a topic like this.

V: I'm sure it's a skill because you may not understand something. Someone's talking and you don't want to keep hammering at the same thing over and over again because they'll get pissed off and not open up so you have to have ways so that you can figure it out.

A: Yea, you kind of, although, as a journalist, it was one of the hardest things for me to learn when I started out, I did not go to journalism school. I did an internship at the Nature offices, which was very helpful, and figured out most things out myself. But early on, I discovered, "Yea, I gotta make a real pest of myself" and it's just part of the job. You talk it through with people. And I actually found, once you get a hold of a researcher, particularly if you're talking to them about their own work, they're usually pretty willing to take things down to the necessary level and simplify it and talk you through because they really do want people to understand. And I think, particularly in recent years, there's been an even greater appreciation of the importance of that, so if I do cover a story, I have done a couple of things on

nanotechnology and those sorts of physics and engineering fields that I'm just not really well-versed in and I just pick people's brains.

V: And they don't mind if you go back a few days later and say, "You know, I wrote this up, but I don't get this part. Could we go over this again?"

A: That, I've never had a problem with, with a source, recontacting them. If it's about their own work, people are willing to put in the time for that.

V: Yea, when it's someone else's, it's less likely.

A: When it's someone else's, they're not even gonna call you back unless they're a Vincent Racaniello.

V: That's unfortunate. Well, I was told, as I wrote online, Rebecca Skloot emailed me a couple of years ago and I, "Why not, you want to send me your book about HeLa cells? Sure." Now if someone did that with string physics, I'd say, "No, I don't know the field, I can't do it." But I figure, in your field, virology, is a pretty circumscribed field. I can do it and I'm supposedly knowledgeable enough that it should be easy for me to do. It's just time in the end.

A: Exactly. I think really I wish more researchers would take that approach and the standard by which they should judge whether they're experts is if they got a paper on this subject from a peer review journal, would they be willing to review it.

V: Yea, that's a good point.

A: And if you would be, I mean, if you got a paper, a virology paper, you'd be willing to review it. So if you've got a reporter calling you about a story on virology and it's not your work, but it's a virology story, yea.

V: Yea, I find this very interesting, this science-journalism interface. As you know, we've had a couple of people on TWiV, Dave Tuller, Trine. I think we could do an episode or more on it, getting people to talk about this and how it works because I'm not sure scientists really understand it. I think most scientists feel that they're just rehashing press releases.

A: And sadly, there's a lot of it that goes on, particularly at some of the print newspapers that are in the process of going out of business, I'm sorry to report. They keep cutting costs and cutting costs and eventually you've got some sports writer who's now on the science desk, if they even have such a thing, and they do just rehash press releases. I get all the press releases and I see the same wording and the same quotes just smattered all over the place in all sorts of news outlets, so yea. There is a lot of that that goes on and it would be nice if we could get past that.

V: Then of course there's the headline writers who are totally different.

A: Frequently, yes. Most of the stuff that I do, I'm working for magazines, and in that environment, they'll often take the headlines that I suggest.

V: Right, but in a newspaper…

A: In a newspaper, the headline writer's somebody else. Headless body found in topless bar. Yea.

V: Yea, and they totally change the story sometimes or the conclusions of the story. I was reading a story this week, the panda gut microbiome sequence came out and looking for genes involved in cellulose

breakdown, right? So my son, I was explaining it to him and one headline we found was, this explains why pandas can eat bamboo. And, if you read the article, credit to the writer, they said, it doesn't prove anything. It just shows that the genes are there. Actually, you have to show that the proteins are expressed and that they degrade cellulose. But the headline writer didn't want to do that, so you have to be careful.

Ok, we have a pick of the week, Tony from Australia. "Here is my pick, I know Vince is interested in online education. This course from Stanford has over 130,000 students enrolled this semester. The two professors are both well-known in their field. The online students will be able to take quizzes, exams, and ask questions. The lecturer answers the week's most popular questions. I have enrolled partly because I'm interested in the topic and partly because I'd like to be part of this experiment. So, this is a class in Introduction to Artificial Intelligence.

A: Cool.

V: This looks cool, you might want to take this, Alan.

A: Yea.

V: I like this, I'm gonna check this out because I would love to do a virology course the same way, make it really public. I mean, I put my lectures up but it's not the same as this where he's actually interacting with the public so thanks for that, Tony, that looks pretty cool.

A: Neat.

V: Ok, so TWiV, of course, is found at twiv.tv, where we keep all our show notes and the letters that we read. You can send us email at twiv@twiv.tv. We love to get it. We're also at microbeworld.org and there you can find an app to stream TWiV to your iPhone or Android device. microbeworld.org/app. Well, Rich Condit is gone, he's still in his meeting, but he's of course at the University of Florida Gainsville. Thank you, Rich, for joining us.

[gruff voice] You're welcome, Vincent.

Oh, that was more like Chewbacca or something. Alan Dove is at alandove.com. Thank you, Alan.

A: Always a pleasure.

V: And I'm Vincent Racaniello at virology.ws. Next week, we will do a TWiV in Brazil! I'm heading down there for the national virology meeting and I have a couple of Brazilian virologists lined up to talk, so the next time you hear TWiV after this, it will be from near Buenos Aires, no Sao Paolo, so that should be a lot of fun.

A: Cool.

V: You've been listening to This Week in Virology. Thanks for joining us. We'll be back next week. Another TWiV is viral…

Transcribed by Janet Lei