# This Week in Virology

*with Vincent Racaniello, Ph.D.*

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## Episode #261: Giants among viruses

**Hosts: Vincent Racaniello and James Van Etten**
**Guests: Chantal Abergel and Jean-Michel Claverie**

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Vincent: This Week in Virology - the podcast about viruses - the kind that make you sick. It's time for This Week in Virology, Episode number 261, recorded on November 19th, 2013. Hi everybody, I'm Vincent Racaniello and you are listening to TWiV, the podcast all about viruses. I have a special episode for you today. I'm in a town called Tegernsee, Germany. It's about an hour outside of Munich, and I'm in a castle. Although it doesn't look like a castle because we have the widescreen television here for those of you looking at the video, but this castle was converted to a conference center and there's a meeting here that I'm attending.

It's called the International Symposium on Giant Virus Biology and this has been organized by Matthias Fischer and Ilme Schlichting and I'm really lucky to be here because the virus I work on is really tiny. I'm here because we're doing a science podcast. There are about 40 investigators here who have been talking about their work on Giant Viruses, and it has been a great meeting. I've picked a couple of people to give everyone a flavor of Giant Viruses, and on my left, he's a professor at the University of Nebraska. He is also the co-director of the Nebraska Center for Virology, back for his second time on TWiV, Jim Van Etten. Welcome back.

Jim: Thank you.

Vincent: Thanks for coming. I should also say that we have a very enthusiastic audience here composed of people who spoke at the meeting, so thank you for coming. It's really nice of you to do that. I know you have better things to do. Actually, there's nothing to do out here, so that's why you're here.

Jim: Drinking beer.

Vincent: A number of us were drinking beer. I am not, but after this is over, I shall. Bless you. We have two guests today from the meeting. They are both from Aix-Marseille Universite. Is that right?

Jean-Michel: Absolutely.

Vincent: Thank you. On my right is Chantal Abergel.

Chantal: Yes, that's me.

Vincent: That's you. Welcome. Thank you for coming.

Chantal: Thank you.

Vincent: I feel like Johnny Carson. You know who Johnny Carson is?

Chantal: Of course.

Vincent: Well, he's not with us anymore.

Jim: He's from Nebraska.

Vincent: Oh, that's right. Now the guy who's doing it is Jay Leno, right? Okay, and also from Aix-Marseille Universite, Jean-Michel Claverie. Welcome to the show.

Jean-Michel: Thank you.

Vincent: After this commercial break, we'll start talking about- Actually, we don't have commercials. I would like to. I would like to have a band over here playing music, but it's very simple. I want to talk about some of the work you have done on really big viruses and let our listeners understand why they're so important. I always like to start out with our guests and ask them their training, where they're from. I presume both of you are born in France, is that right?

Chantal: Yes, that's right.

Vincent: Where abouts?

Chantal: In Marseille.

Vincent: Marseille, where does is that?

Jean-Michel: In Paris.

Vincent: Paris, okay.

Jean-Michel: The big city.

Vincent: The big city, like New York, right? You have a PhD, is that correct, Jean-Michel?

Jean-Michel: At least.

Vincent: At least? It wasn't a PhD? Where did you get that from?

Jean-Michel: From the University of Paris.

Vincent: In what subject?

Jean-Michel: Mathematical modelling of biological phenomenon.

Vincent: Okay. Do you do post-docs also like we do in the US?

Jean-Michel: Many post-docs, yes.

Vincent: Also in what area? Modelling mathematics?

Jean-Michel: No. One in somatic cell genetics, it was my worst experience. That was in Sherbrooke, Canada. Then I went back to France and I realized I was falling in love with Quebec, so I went back to Quebec and then I go to Southern California in San Diego at the Salk Institute, where I worked on theoretical immunology with Melvin Cohn, and my mentor there was Francis Crick. Then I went back to the Pasteur Institute in Paris, and I studied the first bioinformatics center at the Pasteur and then I turned to genomics. That was the beginning of that. Seven years after, I went back to the U.S. at the very famous NCBI NIH, Bethesda, Maryland. That was the beginning of the genomic revolution, so I was very involved in that kind of research from the bioinformatics side. At the time, [we were with 00:05:39] Chantal down there and then we went back to France, to Marseille, to create a new laboratory in Marseille where we have been since.

Vincent: That's quite a history.

Jean-Michel: Yes, you asked me for it.

Vincent: Yeah, I like it. At the Salk, Francis Crick was there, who was-

Jean-Michel: I have a very interesting story about this, if you want.

Vincent: Sure, we have plenty of time. There's nothing to do.

Jean-Michel: The only invitation I had- I was coming from France- I had one invitation to give a seminar to the only person that was doing the same thing that I was doing at that time on the planet. That was in Manhattan, Kansas. The guy invited me to give a seminar. I took the Greyhound buses and probably I landed in Boston or New York. I took the Greyhound bus and I went to Kansas. I gave my seminar and then I went back to Boston to have an interview at MIT with a very famous person- that I won't tell you the name- and I had a terrible interview with him.

Vincent: That's why you don't want to tell us, right?

Jean-Michel: Yes.

Vincent: Okay.

Jean-Michel: He was a very famous person and I didn't like MIT. I didn't like the ambiance there. I didn't like Boston because it was so much like Paris and I didn't like the guy. At one point, I wanted to do theoretical biology, which was very brand new. I'm talking about 1982, the [president's center 00:07:11]. It was a long time ago though. I was fighting with the guy, which is not the best interview you want to have. At one point, I said I wanted to do theoretical biology and he told me, "Well, the only person I know in the world that has been successful in doing theoretical biology is Francis Crick."

I said thank you very much and I took my suitcase and I took my Greyhound and I go through the United States to San Diego, to the Salk Institute. It was about 6:00 in the evening, it was pouring rain, November and there was nobody there anymore except a little bit of light and I was in the corridor and there was somebody sitting. He said, "Yes, what do you want?" I said, "I'm looking for Francis Crick." I was stupid enough to not even recognize Francis Crick when I saw him. He said, "Yes, what do you want?" I say, "This guy in Boston told me that you're the only successful theoretical biologist he knows about, and I like to do this kind of research, so I'd like to talk to you." He said, "Okay," and we talked for two hours. Nice story, right?

Vincent: Nice, and you just started working.

Jean-Michel: The next day, he said, "Well, you're too young. I'm not taking any post-docs anymore, but tomorrow come back and go to different lab at the Salk and say

Francis Crick is sending you in. That would be easier for you to find a job." That was a [inaudible 00:08:46].

Vincent: Didn't you work with him?

Jean-Michel: I was having lunch with him every Tuesday or Wednesday.

Vincent: Okay, that's a good story. Was Renato Dulbecco there at that time?

Jean-Michel: Yes, he was still there.

Vincent: My hero. He developed the plaque assay, right? It's one of my favorite assays. That's a great story. You were right. He has a lot of stories.

Jean-Michel: Excuse me, I was in Salk at that time and there was a fantastic history called Discovery of the Tyrosine Phosphate. [Crosstalk 00:09:18] I went to that very first seminar. It was so funny. It was like a small de facto seminar, but you knew that something very important was happening that day.

Vincent: Salk is a great place for all kinds of things. How about you, Chantal? What's your history?

Chantal: It would be much shorter.

Vincent: Much shorter, yeah?

Jean-Michel: He asked me.

Chantal: I did PhD in [inaudible 00:09:45] science and then I went to NIH for five years. I was in the [inaudible 00:09:51] lab doing the [inaudible 00:09:52]. As Jean-Michel said, we went back to France to start a laboratory, of course mixing experimental work with theoretical work.

Vincent: Do you consider yourself a structural biologist?

Chantal: I do that too.

Vincent: No?

Chantal: I've thought that it was a good way to address biology, so I started with [Christian Grotfield 00:10:16], but then I trying to accumulate as many techniques as possible, trying to address the precise questions.

Vincent: I guess, neither of you consider yourselves virologists, right?

Jim: Oh, we're not virologists at all.

Vincent: It's not a bad thing, you know.

Jim: I know, but you know …

Vincent: You don't consider and neither do you, Chantal?

Chantal: I do kind of rely on virology actually, because I got- It was really a passion to discover those viruses, it was something I didn't know at first and I really got a spirit by viruses, so I got infected.

Vincent: Yeah. A good part of the world who knows that your roles in discovery of really big viruses are- They think you're a virologist and that's not a bad thing. You thought it was a …

Chantal: I don't think so.

Vincent: Your papers reflect virology, so that's good. Jim, you … Can I call you the 'grandfather of giant viruses', would you be offended?

Jim: I certainly would not be offended at all. Again, I'm not a virologist, but frankly, I …

Vincent: Who wants to do virologist?

Jim: I actually got involved in the discovery of the first virus that infected algae that had a genome over 300 KB, about 330 KB and for a long time, this was the biggest genome among viruses until the viruses that the people- your two guests has discovered. In that sense, I maybe, but that means a real honor and at this meeting as … It's interesting now that the 25 speakers. I have an account and they'd got published with 13 of them at some point, so that's a nice honor.

Vincent: Yeah, you heard them clapping, it's okay. For you, this must be an amazing meeting, right?

Jim: I've enjoyed it immensely, it's probably one of the best meetings I've ever been to in terms of all the talks have been very interesting and things I'm interested in.

Vincent: I must say that on TWiV, we're fascinated with really big viruses. We talked about them a lot and sitting at this meeting, I heard a lot of papers- a lot of individuals who wrote papers that we talked about on TWiV and I have also written about on my blog, so I feel very honored to be here and kind of a honorary big virologist, because I think about them a lot. What I would like to do is since you have been instrumental in the development of this field of really big viruses, I would like to give our listeners the sense for the discovery and what it means and where we're going, okay? I wonder if we could start with the discovery of mimivirus, the first one. I know that you're involved with that and the world knows lots of stories, but can you tell us how it was actually discovered?

Jean-Michel: It was, I feel, a long story. I think that I was not involved in that story at the very, very beginning. At that time, our whole lab was- had been working with Didier Raoult's Lab in Marseilles, it is a still in the world's specialists on Rickettsia, especially on the bacteria that grows as parasite inside cells- many people don't know that some bacteria only lives inside cells as parasite and Rickettsia are this kind of bacteria, so it was specialist on those things. He actually received a post-doc from a laboratory in Leeds. I received a post-doc and the post-doc came with a couple of samples in which the bacteria that was named Bradford coccus had been isolated by the head of the lab 10 years before basically, hoping, I guess, by coming to this very famous lab for cracking the secret of positive bacteria, they we'll finally understand what was that bacteria. They started to use the classical techniques to try to put this in culture, to try to characterize it and it was to a certain point … I think the difficulty, they've got some- Didier Raoult, I think, send the paper out the paper was not taken, they wanted to have more information …

Chantal: May I enter?

Jean-Michel: Yes, please.

Chantal: I do know that actually, the big realization- that was the start of the story- in Didier Raoult's laboratory was the idea of a [Thelma sequela 00:15:05] to look at the cells which were infected by this Bradford coccus using the electron microscopy, that's what I remember, as Michel said earlier, that's would made … When people had gather around the images of the cells which are infected, nobody could believe- It looked like a virus, because they had [opening dimension 00:15:28] whereas dramatic compared to what we are used to, that nevertheless, was actually … You do remember, nobody could believe that it could be a virus, so it was just freezing. At that time, nobody could decide that it was a virus …

Vincent: This was material that had been cultured, right?

Jean-Michel: No, it was easy to propagate from one [inaudible 00:15:51] to the next, but then we knew it was bacteria propagating or if it was a virus. What was really took so long for somebody to decide to look another electron microscope, because on the regular microscope … By the way, this is the first viruses that you could actually see using the light microscope, okay. There were just little dots. They were looking at very small round bacteria, Coccus, so it's used the name Bradford coccus. Only looking at it under the electron microscope, you could see that they have those regular shapes which would evocate a virus.

At this point, to be able to publish the discovery in the best journal, they were asked to present some sequenced evidence of that was truly a virus and this is where we got more evenly involved in the field, because at that time, where everybody collaborated with Didier on those different projects for Rickettsia genomics and then very quickly we got those couple of genes. I think we got- It [warm 00:16:59], we thought that through the genomic size was about 600 Kilobase at that time. We got a couple of genes and that was enough to come in Science to publish it. The funny thing is that the largest known virus at that time was published in the smallest possible type of [inaudible 00:17:17]. It was a graveyard in a single page in Science that appears in that format. The year after, we come back with the whole genome.

Vincent: Okay, then you were convinced there was a virus at that point?

Jean-Michel: It was clearly a virus. We got two or three genes out of it and just a quick [photogene 00:17:38], making tree out of those sequences, pretty sure that they were part of the classical large DNA viruses.

Vincent: It was being propagated in amoeba, right?

Jean-Michel: Yes.

Vincent: Why was it decided to do that, why was it cultured in amoeba as opposed to anything else?

Jean-Michel: This is back to Bradford, back to Leeds, it was because of that time, and there was a pneumonia outbreak, Legionella disease outbreak. It was where the classical way is to look around in those cooling towers to see if there are amoebas and it was amoebas are infected by legionella because this was the source of that contaminations and this is just because they were looking for at

the possible proof that pneumonia, but they grab the amoeba and the hostel has started [inaudible 00:18:32]. We're lucky, right?

Chantal: Always.

Vincent: Picked the right host to grow with it, right?

Jean-Michel: Yes, absolutely.

Vincent: You remember hearing about this?

Jim: Yes, I had. Actually, I was one of the reviewers …

Vincent: He was reviewing half of my paper …

Jim: The original …

Vincent: I'm tired of it …

Jim: I said they should sequence the whole genome, which they did, because the first paper only had 2/3's roughly though as I remember. Just for the audience, they may not appreciate this, but in terms of size, see the HIV virus- which causes AIDS- which the audience is very familiar with, has about 10 or 12 genes and the last was we worked with infected algae had about 400 and now you're talking about the virus, the Mimivirus virus that our members discovered has over a thousand genes. Just to put in into perspective, this is a huge advance and totally a surprise to the virus community that viruses could be this large. There's another aspect to that paper, which is still somewhat every controversial and that the authors may want to comment on is that is that they suggested these viruses might be the fourth domain of life along with archaea, bacteria and eukaryotes and I would assume that Jean-Michel or Claudia would like to come on comment on that.

Jean-Michel: Maybe it is too early …

Jim: I feel like advancing that, if you really …

Jean-Michel: One of the biggest surprise to tell you, non-educated … I mean, none of us were in virology, because Didier didn't know anything in virology either, he was a specialist for Rickettsia. We looked at the genome and, "Okay, it was a large genome, there was a lot interesting things there," but it took some time for us to understand that we're in fact breaking certain number of dogma, including the

fact that viruses are absolute parasite and one thing they don't do, when you see never virus doing, is helping or making proteins themselves and for the first time, in this virus genome we found not one, not two, not three, but four aminoacyl tRNA synthetase and those are very important enzyme because- with the key enzyme for translation because …

By the way, they're the only component of the cells that knows about the [generating 00:21:06] code, because they are the one that's in charge of putting to right amino acid on the right [journey 00:21:12]. Without those guys, nothing happened. Exactly, when Chantal gets into the picture for the second paper on Mimivirus, because it was then very important, because probably of the reference of being able to say this is not just a gene that just happened to be there by chance, has nothing to do with the whole process, you have to prove that this is the real protein, that it will form, that will be active and would have basically the same shapes, so maybe you want to say a few things about the structure of that protein?

Chantal: Certainly, I can say, it was not a recommendation of the review there, it was a fascination, right … To look at the genome and to see aminoacyl tRNA synthetase, we wanted to [solve 00:22:00] the structure, at least one of them and so we try to express all of them in this one, I would say, the easiest to work with, but that's true that even I struggle for quite a long time, before being able to solve of the structure, it was a shock to find out that it was in the sense completely- It was in a sense resembling was we are expecting from an aminoacyl tRNA synthetase and we know that it was functioning as well. The surprise was to see that the loop which is supposed to recognize actually the three nucleotides for the anticodon, but was shorter than for all the known aminoacyl tRNA synthetase and it was actually recognizing the [two latter's good 00:22:47]. At that point, we didn't know, was it a rule meaning that we were coming back to the simplest genetic code or was it really evolution of that particular aminoacyl tRNA synthetase? In fact, the codon that corresponds to tyrosine is to forget about disturb the little [tide 00:23:14] it can be that two tyrosine of two stop codons, so there's no need for [inaudible 00:23:21]

Vincent: When you did the complete genome sequence then you could … How many proteins were encoded in the genome?

Jean-Michel: The first time we looked, it was …

Chantal: 900

Jean-Michel: 950 … 918 or something like that.

Vincent: Which is more than any other virus that has …

Jean-Michel: That was also the first time that the virus that had more protein than many bacteria, because at that time, the smallest bacteria that was known to as mycoplasma, and mycoplasma had only 500, basically 500 proteins and even some of the Rickettsia we were working with were near that range. Some Rickettsia could only have about 1000 genes. For the first time, second dogma in a way that the virus was in fact did a little more complex than the singular organism.

Vincent: When you started looking for- When you translated these open reading frames and then said, how do they compare to known proteins, you were surprised, right? A lot of them were unknown?

Chantal: Mm-hmm.

Jean-Michel: That was a different … Yes, about half … Exactly 40% …

Chantal: That supposed of more than 60% that were complete [over 00:24:26], 65 …

Jean-Michel: They don't look like anything that was already seen on the planet.

Vincent: That was also a mouth full. That hadn't happen before either, right?

Chantal: I wouldn't say that.

Jean-Michel: That I don't really know for a fact, because do you remember about your …

Jim: I think when we sequenced the first of our Chlorella viruses back in the mid-90's out of the 365 genes, the original- –gain, there weren't a lot of genes in the gene bank. I think we were in about 25% might- it might grow and predict, that number now is up around 45% or so. I don't think that was necessarily a surprise in that part.

Jean-Michel: I'm sorry that you're saying about your old, but at that time, the database for us was [pretty 00:25:14] much smaller than it is now.

Vincent: Yes, right. I heard your talks the other day and it seemed that at some point, you needed to find similar viruses to show that this wasn't an anomaly, that there are others like it and to start understanding the evolution. Is that when you started to look for related big viruses?

Chantal: That's true that if you get only one giant virus, you don't know if, as I said yesterday, if it was just a [freak 00:25:45] or if it's something which is a representative of the biodiversity of viruses. That was one of the reasons why we wanted to find them, if there was another one. Perhaps that time, that traditionally, the viruses were always thought to be small, which mean that the way we were trying to reason it then was to go to filtering, so which mean we're actually getting out on the ones that we're higher in size than the filter itself.

Vincent: The classical definition of virus was at the point …

Chantal: It too, so that …

Vincent: micron filter from the early 1900's right?

Jean-Michel: The definition of viruses enclosed that one.

Vincent: Yeah, so now, is it a 0.8 micron filter or is that-

Chantal: There is no reason why we should fit to them.

Vincent: Unless you want to get rid of or the other-

Chantal: Is there another way to get rid of the virus?

Vincent: Yeah, I guess it's a problem. You started going on trips to collect viruses.

Chantal: That was a good view, opportunity to travel.

Vincent: Where did you go first?

Chantal: The first trip I think was- We're in Chile.

Vincent: Really?

Chantal: Yeah.

Vincent: I know that you eventually got a virus from …

Chantal: Two.

Vincent: Two, from the coast of Chile. Why Chile? Do you like the country?

Chantal: That was one reason, but that was not the main reason. We knew that the bio-diversity in Chile is supposed to be- at least in the Pacific coast- is supposed to be very wide compared to some other places, so that was one of the reason, plus the fact that it was a European program that was giving access to scientists to [some of the station 00:27:18], so there we [had to understand far-strictly 00:27:20]. We have divers, we have the boat, and we have everything to be able to [cross with for 00:27:25].

Vincent: That reminds me, I forgot to ask you. Is the natural host of that first Mimivirus in amoeba? Do we know?

Chantal: We don't know.

Vincent: You don't know?

Chantal: We don't know, but yes, it's very likely, because as soon as you try to go away from the acanthamoeba specie, you don't see the amplification of the virus on the amoebas.

Jean-Michel: It is not all amoebas. Amoebas are as diverse as animals basically, so it's a very specific genus of Amoeba acanthamoeba and all those fishes that we've tried except a few are capable of replicating this virus, but as soon as you get into lesser more classical, Entamoeba for example. Entamoeba will not replicate the virus and many other.

Vincent: What was your strategy in Chile to find additional big viruses?

Chantal: Actually, we did benefit from … I know there are expedition which was a [Tyra 00:28:26] ocean expedition. It was actually led by- for the giant virus fraction, but the role of nuclear [getup 00:28:33] and we see today. We have been thinking at first that it would be a good way to isolate new viruses would be to filter them and keep the filters to try to get the viruses from there, but this filtering 100 liters of water or something like that. We have very little success via trying to resist the filters, so it was- We also observed that the all the mimivirus like this is able to sediment. Actually, if you leave it, you can shake a tube, put the tube on the desk and there you would see that there in about few minutes, the sample is clarifying and you can get to [pail it 00:29:16] without centrifugation.

It's not that maybe those giant viruses would be easier to find at the bottom. That's why we started to look for sediment and then another approach was to try to get some kind of host at the same time just trying to purify it in the

laboratory, the samples that we bring back, using specific medium to get bacteria to grow, they are feeding the cells that are here and that we could eventually propagate the virus and get to isolate them and then amplify into acanthamoeba.

Vincent: One of the results was Megavirus chilensis, is that correct?

Jean-Michel: Chilensis, yes.

Vincent: I don't know if you remember but I wrote a blog about that paper and you actually emailed me and said good job.

Jean-Michel: I forgot that I even said that. Actually, I think you forget a little bit of the story because again, Jim was involved in a way in that part of the story. The reason we turned to other [inaudible 00:30:26] because I was still at that time a bioinformatician. As soon as we got the sequence of Mimivirus, I tried to look for other relatives of this virus in all databases I could find. Because I just left NCBI not too long ago, I still had friends there and at that time, Craig Venter was starting his big project on the Sargasso Sea metagenomic [inaudible 00:30:55] invented metagenomics again and I got access to this database. We found that the closest relatives that were known of Mimivirus were in fact not in the classical database but that they were in the Sargasso Sea.

This was published in 2005. [Inaudible 00:31:17] that there should be other various viruses that would be likely [inaudible 00:31:24] in the sea. That's why I started to look at who's doing marine or aquatic biology and I managed to talk to a couple of people. At that time again, the leader of the aquatic biology was Jim, the Chlorovirus that lives in the water basically and he helped us very much to get connected to that new community that we didn't know anything about, which was the aquatic virus community that was actually a very nice and very welcoming community because immediately in the very first meeting, we were invited to present a talk and we presented Mimivirus and all those people listened to us very carefully and very nicely. We started to have nice collaborations and this is, I guess, how I get to know about the [assemble 00:32:24] program and those types of things. Again, Jim was very useful in helping us to get to know those people. [Crosstalk 00:32:38]

Vincent: They call you Yoda.

Jim: I guess so. [Inaudible 00:32:44].

Vincent: It's a good thing. Yoda was a good guy.

Jean-Michel: The first one we went was the one organized by Corina Brussaard in Amsterdam.

Jim: I remember the meeting.

Jean-Michel: Yes, absolutely.

Jim: We had a good time. Of course, everybody was blown out of the water when they heard about viruses that big. That was amazing.

Vincent: These were related sequences in a marine database, so probably not [an amoeba 00:33:10] host, right?

Jean-Michel: Not [an amoeba 00:33:11] host.

Vincent: Right, something else and then this connected you with the marine world of virology.

Jean-Michel: Absolutely.

Vincent: The chilensis came from the coast of Chile? Is this from the sediment?

Chantel: Yes. No, it was from water, but the [inaudible 00:33:25].

Vincent: What did we learn from that virus?

Chantal: Many things actually. The first thing is probably those kinds of viruses were all over the place, in water, freshwater, in sea water. We learned that Megavirus chilensis was very close to Mimivirus and that was a big surprise because we were not expecting that [inaudible 00:33:59] that this Mimivirus was not the only one, so finding another one which was about 50% identical to the Mimivirus was a surprise. Then, that was the first time we got something to study in detail by comparative database, so that was very useful also. Jean-Michel said about the cellular genes that we are presenting in the Mimivirus and the Megavirus was even more [inaudible 00:34:31] representing the genome, so that allowed to make some hypothesis about the origin of those Giant Viruses even if it was very- I mean, it was a hypothesis, but we started to build a thinking about the origin of those Giant Viruses.

Chantal: The Chilean virus was this culturable?

Chantal: Yeah, with acanthamoeba.

Vincent: In amoeba?

Chantal: Yeah.

Vincent: Do you think that was its real host in the ocean?

Chantal: If we say yes for the first one, we have to say yes for the second one because as soon as you go away from acanthamoeba, we're not able to grow it anymore.

Vincent: Okay. This was a larger genome than the first types, right, more cellular genes in it and also a lot of unknown genes.

Jean-Michel: The same amount basically. Even though the two viruses look very much the same, the morphology is very much the same; one has shorter hair, the other one has longer hair. There's no difference that you can see, but the two genomes are in fact only 50/50 equivalent. That is basically 50% of the genes are shared and there are 50% identical at the sequence level, so they are extremely close relatives but they are in fact very distant relatives in way though. There's not all that difference in a virus. What was nice is that there was always a doubt that the time in our field I'm afraid in the bringing of many people that those four aminoacyl tRNA synthetase had been acquired just by chance from thin air or from [inaudible 00:36:14] even though we could not find the origin of those genes. In this one, we added four for the first one, the Mimivirus, and we added three more, so now we have seven.

That was more difficult for people to involve the fact that by chance, capturing four times the genome of the same class would be quite unlikely, but now seven was even more unlikely. When people started to turn around and say, "Yeah that might be possible." In fact, what we're looking at is not gene acquisition. This is still a big debate in the field. Those viruses are not derived from smaller viruses that are gaining genes, but maybe it is also possible now that the amount of transcription machinery or translation machinery was bigger before and what we are looking at are things that are in fact shrinking and so this guy, he was less shrunk than the other guys, so we still have seven aminoacyl tRNA synthetase and then we will lose of those. One thing that was very instrumental also in the direction was the discovery of an even more remote relative of Mimivirus, this time not infecting acanthamoeba, but affecting a very difficult pronounceable species called Cafeteria … [Crosstalk 00:37:42] Can you pronounce it correctly please?

Male: Roenbergensis.

Jean-Michel: You see, I would never be able to … I could not work on this virus. This virus was yet smaller than Mega. It was about 600 to 700 kilobases, 700,000 bases, six [inaudible 00:38:09] genes, but it had at least one- I mean [inaudible 00:38:14] so it was the first bonafide- This is a marine organism, this was the first giant bonafide marine viruses and this one also had a lot of genes that were equivalent to the Mimi and the Mega being which were on the [inaudible 00:38:28] genes including those aminoacyl tRNA synthetase that was of a different kind of the one that we had already see, so now that was eight different aminoacyl tRNA synthetase seen in those big viruses, which is definitely, to me, nailing the coffin, but for many other who are still not nailing the coffin.

Vincent: Maybe we should pause and talk about this idea a little bit. What you're referring to are two theories for how virus has evolved, one is that they started as a cell and lost genes and another that they started small and gained genes, right? Were you always thinking about this or did this get stimulated by Mimivirus?

Jean-Michel: It got stimulated entirely by the discovery of Mimivirus.

Vincent: You agree?

Chantal: Yeah, I agree.

Vincent: What's wrong with starting small and getting bigger?

Jean-Michel: Do you want me to answer that?

Chantal: There are many reasons. It's difficult to imagine that you are acquiring genes that do not resemble anything. I don't want to talk yet about Pandoravirus, but there are so many often genes in the viral genomes and it's not only true of the Giant Viruses, it's true to all viruses. It's difficult to imagine that you will acquire genes that do not resemble anything. It has to go from somewhere at some point. If the [inaudible 00:40:04] doesn't exist or has not been discovered then that's one point, but the point is you have to do something that would be useful for something … So 50% of the genome which is made of genes that do not resemble anything, it's difficult to imagine that it was just created like that.

Jean-Michel: If I can complement her answer, the misconceptions coming from the phage, the bacteriophage situation when you have viruses, that goes for the DNA viruses, it is absolutely in clear in bacteria that those viruses are capturing genes from the bacteria that they infect absolutely all the time, which is a very, very common-

It's very difficult to distinguish in the bacteriophage world the genes that are actually coming from the bacteria from the genes that are actually truly viral genes in a way. People had a generalized conception that some viruses, including eukaryotic viruses, are capturing genes and are capturing their genes from where, from their host. The very first test was if you are capturing genes all the time, the first source of genes is your host and then it was very easy to see that none of the genes that were supplemental or none of genes were resembling the host. You just go on a blast search and you'll see that definitely.

The second part is that, okay, if it's not from the host, it's more difficult to explain, but still it must be from somewhere else. If the database searches don't give you anything, then you have to go into a third explanation, yes, they are getting genes all the time and because they mutate very fast, you don't see the resemblance with those genes. On the other side, there is 50% of the other genes that you can still recognize perfectly well, so they don't mutate so fast because you can still recognize very easily those other 50% genes. The [inaudible 00:42:05] of the bacteria are more and more [inaudible 00:42:08]. The other side is I think much easier because I think it's almost a universal rule in biology, which is when you are a parasite, when you become to be a parasite, you never return back. You never go back to free life. It's just a one way situation. Why, because as soon as you become the parasite, especially an obligate parasite, you may lose functions. It's not that much of a problem because the host is going to provide that function for you if you lose it, so there is no real incentive to keep things that you can lose and this is what we see all the time. Parasite becomes more reducing, more reducing, more reduced.

I knew that because before that, I was working a lot with Rickettsia and we already observed that phenomena, documented that phenomena and all the techniques were documented, so I was very much more in favor of the other direction, you start big and because you become a parasite, there is no reason to become bigger. The only one way is just going back. Of course, from time to time, because we are not silly, we are open people, you can gain genes. Pox viruses do that all the time to grab a few rules to try to combat the immune system or whatever, but there are very few genes, let's say a handful of genes doing that, but the rest is just shrinking, shrinking, losing, losing, expecting the host to provide the function for you. This is why I do prefer this kind of hypothesis rather than the gain, which is [inaudible 00:43:46] hypothesis.

Vincent: You view these very big viruses as very early on in this loss scenario, so they'll be giving us a picture of something that probably happened a long time ago. We should say these viruses encode their own transcription apparatus, right?

Chantal: Of course.

Vincent: They have their own DNA replication, so they do everything in the nucleus?

Jean-Michel: No.

Vincent: I'm sorry, the cytoplasm. I'm thinking ahead. It's a very early- So they've lost the translational apparatus, right?

Jean-Michel: Most of it.

Vincent: And energy making too, right? They can't make energy?

Jean-Michel: Yes.

Chantal: Some people here can tell you that-

Vincent: Some people think they make energy, okay.

Jean-Michel: No, not ours. [Crosstalk 00:44:30]

Vincent: Certainly they've lost the translation … Would you view losing the translational apparatus as the first step in becoming a parasite?

Chantal: I'm sorry?

Vincent: The first thing you lose-

Chantal: Obviously, it's a rule for the viruses. For viruses, it seems like you first lose the translation and then for cells like bacteria and eukaryotes, obviously, it's the other way around. It's one of the last things that you lose.

Vincent: What would be next, transcription?

Jean-Michel: Yes, this is probably what happens. When you look at the big viruses, you can see many different intermediary steps, so it's very easy to lose translation because if you just lose one or two critical or ribosomal protein, you're dead. The host has no use for you, so what you see now are just remnants of things that have not yet disappeared. Translation is gone. When you are positive bacteria, you keep translation. You are on the path of genomic reduction of a certain kind, so you will become smaller and smaller and smaller bacteria. You will now be bacteria that only have about 150 genes.

Vincent: Yeah, right.

Jean-Michel: You can very much reduce but still remain like a bacteria. There's another carrier, if you want, pathway that if you lose translation very early on, then you are primitive to the carrier of the smaller and smaller viruses, this is the first simplistic hypothesis that we have basically.

Vincent: The adenovirus have lost transcriptional apparatus, but they still have the DNA telomerase, right? If you go further the polyomas have lost everything and they depend entirely on the host.

Jean-Michel: The coronavirus, for example, have lost transcription doubling, Immuno Epstein virus, another [inaudible 00:46:27] virus has kept a little bit of transcription. PVCD1 and one that we just sequenced was sent to Corrina Broussard and there are other virus. As maintained, the whole transcription apparatus. You can only see all those gradations in the viruses that we know at the moment.

Vincent: Would you say that out there, there should be the continuum from what you're seeing now, maybe there are even big viruses with more of the translational apparatus, right? They may be out there you think and you could find them?

Chantal: We sense that yes, we should be able to find some viruses with some more translation in there and to complete what you were saying there is even cases where you have obviously viruses that do have a transcription, but yet they don't put it into the particle, so which mean that they are dependent on the host at that very beginning of the infection, but then now are able to become a telomerase for their own transcription of the rest of the cycle, so we already see a little of those intermediary stages now, the viruses which are already in the database system.

Vincent: Are you saying that you could start as a cell and then be a very large virus and eventually get down to as P40 polyoma viruses? Is that the same lineage or it would have be a separate ….

Jean-Michel: No, no doubt there are examples now. They're not on the same linages, but there are examples now of viruses that don't have any genome anymore. Those put it any viruses that … wasps fighting, okay. Basically, they provided all their genes to their host, the virus genome is in the host and I think the end of the career for most viruses is to give a little more genes, their own genes to the host at the end and they disappear completely.

Vincent: I'm just wondering some of the vision, a really big capsid like you have in these giant viruses and then it's shedding genes. At what point does the capsid get smaller, what is this selection or is there one for the capsid to get smaller? At some point it has to, right, because the polyoma capsids are tiny, but what would be … I think you said that there's a lot of extra room in the Mimivirus capsids right? What point does it reduce the actual capsid? I can't envision how that happens.

Chantal: I would say that maybe there is some pressure … What you have been presenting are so about the compression of the genomes in the capsid and [inaudible 00:49:00] is very difficult to diffuse in the cytoplasm. Maybe at that point that maybe, you need to shrink your capsid at some point to be able to have the DNA compact enough to be able to deliver it properly to its true hypothesis.

Vincent: Yes. I think that's one of the areas that I have problems envisioning, how to make a big capsid is not easy. We've heard that at this meeting and to shrink it …

Jean-Michel: To make a bigger capsid is not easy.

Vincent: That's our …

Jean-Michel: Your sequence to start with is not easy.

Vincent: Shrinking.

Jean-Michel: As you know, I have an answer to everything.

Vincent: It's okay.

Jean-Michel: I have an answer to your question, why is that that we find more frequently very big viruses in phagocytic organisms? Amoebas, okay. It's probably because being big is also an incentive for those guys, because amoeba feeds on bacteria and to decide that your are food in front of you, size matters, because this is one part of the signal and that's been worked out by people a long time ago in the 40's using latex beads and all that in order to trigger phagocytosis for an amoeba, you need to have particles that are basically exactly the size that those viruses have. It might be the reason why they keep that big of a capsid even though they don't need the space anymore, because otherwise, if they shrink too much, then they would not be as good as food for the amoebas. If you have lesser than 0.5 micron diameter, you need two of them to trigger phagocytosis. If you are even smaller, you need three and if you are in the water, in the ocean and except

when there are blooms, there is one protist here, one virus here and they will never meet, so you want to absolutely optimize any single hit that you have and if a single is enough to get you in that's what you want and size may be very important. Also, we know that the hair that covers the virus probably taste like bacterial wall, we know that. We collaborate with …

Chantal: Meet to that …

Jean-Michel: People that works with sugar and glycosylation, those type of things and we know that those things are coded with sugar, so they probably to the amoeba, they look like food for their size and even the taste of it.

Vincent: Amoeba have a sweet tooth.

Jean-Michel: Probably, they have some receptors for those glycosylation, receptors.

Vincent: Let's talk about Pandoras now. How did you find those?

Chantal: We found them near in Chile, this time from the sediment.

Vincent: Sediment off the coast, so salt water, right?

Chantal: Actually, that was- We thought that maybe we would be able to find some amoeba at the mouth of the river in the Pacific ocean, so we decided to sample for sediments to determine to contain sometimes amoeba and at least … Those sediments were taken back to the lab and since in between, we had time to optimize the protocol to which we dispense the sediment. We do this protocol, and infected the acanthamoeba cells and the only thing that mattered to us was to adapt the cell to antibiotics to be sure that nothing would grow. Only the viruses would be used by the acanthamoeba and could eventually proliferate into the cells. We were just watching the acanthamoeba cell dying, they were dying, we suspected that it should be something that killed them so we went on to trying to characterize what was killing them.

We usually purify particle after amplifying them and look under a light microscope and those were really visible under the light microscope, but opposite to the classical, because they're [drawn viruses 00:53:00], the particle looked very heterogeneous an it was … We thought that first that it was a typical bacteria, yet we went further and to look at them by electron microscopy and there, what we are looking at was resembling nothing we have seen before and we could not … We didn't know what we are dealing with, so was that … What I said yesterday at first, we didn't even know how to name them, so seems to

have- you have name those things to talk about them. We named it amulefs, so a new life form, this lasted until we understood better what we were dealing with and when we suspected that we were working with a virus.

Vincent: You showed a picture of Jean-Michel in Australia right, also? At the same time, you were looking there?

Jean-Michel: That was a funny story. I was invited to give a talk at Lathrop University. They always give a bottle of one or two the speakers and during a break, I was visiting around, at most 20 meters from the site where I was giving the seminar. There was a little pond here and so I grabbed a little bit of mud from the pond and actually and I put it in my pocket and went back to the seminar room and – put that in my luggage, probably totally illegal and then I went back to the lab and did a sampling and there was the second.

Chantal: Yeah, just second … The point is that, in this room, you can ask all the people in this room and I'm sure that they always have a bottle of water and are sampling wherever they go …

Jean-Michel: No, you should …

Chantal: Before, I was still … I never do … Jim, might be doing at all … don't you?

Vincent: Do you do that too?

Jim: I have for a long time.

Vincent: I don't even put wine in my luggage [I would say 00:54:58]

Chantal: I tell you, you look for giant viruses.

Vincent: Yeah, afraid the bottle will break.

Jim: I don't worry about it, because we now know the viruses we work with are all over the world, they're in fresh water and we can find two in the same pond, they're more different than if we find one in the pond here and one in Argentina, so it's clear that birds or something have been spreading these things around all over, so I don't think that's an issue. The other thing that should come out is that with these meeting, lots of these other people now are finding many big viruses like the ones, not Pandoravirus, but certainly ones that are big or bigger than Mimivirus and that's one of the things that makes this meeting so exciting.

Vincent: Remind me of all the talks, are they mainly icosahedral that people are finding or they're also some with odd more follow …

Jim: The ones that Jean-Michel found, the shape is very different from the other ones, but they're still unique as far as I know to that property, yeah.

Vincent: Tell us a little about the properties of the genome of these Pandoravirus.

Chantal: They're huge.

Vincent: They're huge, bigger even than the Mimi's right?

Chantal: Oh yes. It's about 1/10$^{th}$ of a human genome.

Vincent: 1/10$^{th}$ of a human genome, okay.

Chantal: The number of genes.

Jean-Michel: In terms of genes.

Chantal: In terms of genes, yes.

Vincent: Right.

Chantal: Sorry. I just mixed it.

Vincent: 2 ½ million base pairs?

Chantal: Yes.

Vincent: How many genes would that be?

Chantal: 25-

Vincent: 2,500?

Chantal: Yeah.

Vincent: We would say this somewhere even older in the loss scenario, losing genes? No?

Chantal: When we started to analyze the genome and actually matches here, who did the job and what was very surprising to find that we didn't find any- Barely nothing was resembling things that representing the data. The one reason that the bigger

genome would help us understand the evolution of those giant viruses, wherein from the [something 00:57:06] that was going nothing, so it was kind of a shock.

Vincent: Were there any genes related to Mimi viruses in the start?

Chantal: Two of them yes …The [feel 00:57:15] that was sure …

Jean-Michel: That sure as … You don't …

Chantal: It was about 6% of their genes were resembling something in the [Mega there 00:57:23].

Vincent: What does this mean?

Jean-Michel: To go back first to the- Because in fact the discovery of those viruses is a failure, because we are not looking for large viruses. Just say we have the largest virus of all even though we like that. The theory behind that the bigger you are, the closer you should be from the ancestor and the whole idea was not by looking for bigger viruses, with bigger genome, we will finally understand where those genes, those stellar genes are coming from and get 10 aminoacyl tRNA synthetase there, having to see a little bit of fiber or protein or those types of things, you know, just to go back in time. That's the tool, the theory. When we found those gigantic viruses and when we saw that, there were 2.5, no, almost 2.5 times bigger than the Mimivirus, you know, that was it. We were finally going to understand the origin of those large viruses, except those viruses are from a totally different evolutionary path. They are not at all from the same lineage. To prove that theory of the loss gene theory, they've been totally unuseful, totally, because it's a new chapter.

Vincent: You don't recognize most of the genes, so you can't say they came-

Jean-Michel: Only, I should say 6% genes, if you remove all the totally uninformative would be or whatever only 6% which is [left and right 00:58:58] about 100 genes match anything known in the planet. Again, the question that those guys have been expanding by capturing genes from somewhere, at least you've been capturing genes, okay, I can accept that, but from where? Remember, you said you had no almost very few matches, okay, 10 years later with the Mimivirus, we still had 40% of the genes with no matches, but now we are almost 10 years after that, the database has grown tremendously probably multiplied by it seems that where this is going [by a factor of 00:59:37] two every year. I don't know, maybe 100 times bigger. Now, we still have 95-94% of the genome that doesn't look like anything. To imagine that those genes that have been captured from somebody

that we don't know of is very bizarre. We've been doing something about as well missing something about – that we're missing something, deeply missing something that those genes it have been captured, had been captured by something that we've never seen before.

Vincent: Is that possible?

Jean-Michel: I don't know, I ask you, because we- For this one, we do not have any theory. The whole theory for all those regular icosahedral viruses, frankly for the Pandoravirus at the moment, we don't have any theory.

Vincent: Well, isn't it possible-

Jean-Michel: I don't have any …

Vincent: We haven't catalogued all the life on Earth, have we?

Jean-Michel: We thought we have, except for viruses, of course, but for the sake of our world …

Vincent: Let's ask the audience, who thinks we've- Raise your hand if you think we've cataloged all of the life forms.

Jean-Michel: Not all the life forms.

Vincent: No, you haven't, see? Stewart gets …

Jean-Michel: Of course, not all, but when you sequence any kind of bacteria at random, you will find in almost amount of resemblance. You will know that this definitely a bacteria … For example, eukaryotes.

Vincent: So one possibility is there's some life out there we haven't found and that's related to Pandoravirus?

Chantal: That's possible

Vincent: What's the alternative?

Jean-Michel: That there is a way for viruses to create genes, de novo.

Vincent: De novo?

Jean-Michel: Nobody has ever presented any kind of possible mechanism for this.

Vincent: You sound skeptical of that possibility.

Jean-Michel: I am totally skeptical, but this is- I know they exist. I know they have been captured or they are descendent from something yes, but to have been out there or they have been created every day by some totally unknown mechanism.

Vincent: Isn't this related to what you said way at the beginning and you said it was too early, that there was a fourth domain of life which is now extinct and these are descended from that, is that possible?

Chantal: Yeah.

Vincent: Don't you guys believe this?

Chantal: Yes. We have many theories right now, but I think it's too early to- Everybody can hypothesize, [inaudible 01:02:00] and then it just depends on the amount of water you have been drinking, you [inaudible 01:02:08] going very far. The point is right now, we just have to sit down, wait for more sequences, make as many hypothesis as we want, but we need at some point to get some answers by accumulating data. For us, I think that we are at a point where we cannot build a theory on. There are many hypotheses that can be said, but we don't have any support for them.

Jim: These viruses aren't the only ones where there's a small percentage now, as a virus come, we talk in a separate night called white spot syndrome virus, which causes this rare disease on shrimp and when they first sequence this, it's a big DNA virus. A few years ago and it the genome of about 300 kb, sick and has 300 proteins or so, only 5% or 6% of those proteins are predicted proteins matched anything in the gene bank. I don't know what the number is now, but it's clear, there's a lot of presumably stuff out there that we just don't know what it is yet, so it's not solely just with the virus, the Pandora virus, it's probably true of several others.

Vincent: So the solution is to keep looking and finding new things and trying to fill in the gaps?

Chantal: Yes, certainly.

Jean-Michel: Yes and I expect-

Chantal: Data is giving us some information and many people in this room have been providing data about that. We think that there is eventually some problem with

the data that comes, except that if you are working with bloom and- At the moment when there is a huge population of those giant viruses, whether we get from DNA coming from those viruses inside the cell or around the cell, we think that, because metagenomic data that has been done in the [weather colon 01:04:05] may not be the best data to actually look for those giant viruses. We may get more of those DNA, of these DNA in the sediment or in the bottom part of the water.

Vincent: Is that what you're doing now?

Chantal: We are starting to do it, but then I think we are not the only one. Many people are doing- but metagenomic data can be a way to accumulate data, plus all of these [plus 01:04:31] the forms of people who are trying to get some more viruses and to try to understand better what they are.

Jim: There's actually another interesting aspect of this whole Pandoravirus story and that is that when the report, these particles can actually been reported on and in publications eight or 10 years before, but nobody knew what they were, it was just a structure that was seen in whatever organism. I supposed it was an amoeba and so, so fascinating that 10 years later to find out that something has been seen that actually is a virus.

Jean-Michel: It's been twice now.

Jim: That's part of the story.

Jean-Michel: The Mimivirus was spotted 10 years before and misinterpreted as a bacteria and the Pandoravirus was spotted 10 years before, exactly it was misinterpreted as an archeo - endosymbiont or something like that.

Chantal: Endosymbiont, yeah. People who are here so have talking about cases where they have been hearing about those giant viruses. We spoke about somebody to present maybe images of actually what were giant virus, but which we are not interesting anybody at that time – maybe it was yours Mathias wasn't it, I don't remember – anyway who has saying that at that time, people, it was not related to any disease, so people didn't pay any attention to those and they were letting them go now. You started only much later when people understood that it was something to get-

Vincent: That's a good point; a lot of virology has been driven by disease.

Jean-Michel: Absolutely. Most of virology is driven-

Vincent: I don't know, the phages were the early theoretical and those were good times, but-

Jim: Of course they were discovered, because they thought they could cure bacterial diseases when you go back to 1918 or so.

Vincent: I would also say that the technology wasn't ready for big viruses until recently, right? People seeing them on pictures 20-30 years ago, they weren't ready to do anything with them, so it's a confluence of things then, but now clearly, as you see from this meeting, there's a lot of activity in this. Did we miss anything that's important to convey to everyone about these viruses? Is there anything else important? I know that we haven't talked about replication and structure and so forth, but-

Jean-Michel: I have something that I believe is important to say every time I have the chance to talk to a large audience is that again, this is totally the unexpected discovery that is suddenly coming from totally basic questioning in basic science is showing that there are still very big discoveries to be made and if we know half, maybe let's say we know half of the biology on the planet, putting all the money, putting all the effort in purely innovative research and [do some actual medicine 01:07:26] and things that it's maybe too early and we should preserve funding and we should preserve resources for purely basic research that has many, many potential applications, even much bigger applications than just to trying to cure cancer for 50 years and not making that much progress maybe the cure for cancer is in those viruses that we don't know nothing about. This happened all the time.

Vincent: It sounds like you have the same problem in Europe as we do in the US.

Jean-Michel: I think it's everywhere, right guys?

Male: I think.

Male: Yeah.

Jean-Michel: You want to vote on this?

Vincent: No, I'm sure we're speaking to the camera over here. You should come to the US senate and talk to them. On second choice, don't waste your time. They're not going to listen anyway, but this is a big point that basic science is where all the advances come from. Time and time again in science you can say serendipity is what made this advance, the restriction enzyme, Taq polymerase.

Jean-Michel: Antibiotics.

Vincent: Antibiotics, on and on and on. I want to ask you one more question then we'll let you go unless you have anything else to do. We've talked about how DNA, Double stranded DNA viruses may have emerged from cells and you have some evidence for it. How did RNA viruses emerge, because those are the viruses I work on? I know where they came from, do you have any- do you think about that at all?

Jean-Michel: I have absolutely no idea.

Vincent: No idea?

Jean-Michel: Frankly. It's already enough to try to convince all of my openings – in all our openings about our little theory about the DNA viruses. I won't dare to touch the RNA viruses world, which is-

Vincent: You know the biggest RNA genome is 30 Kilobase.

Jean-Michel: Yes 35.

Vincent: The coronavirus. You think we'll ever find a bigger one?

Jean-Michel: That's those limitations of having an RNA genome, which is very error prone and the limitations, so I think that if you want to have a bigger genomics, smash the [reference 01:09:32] to switch to the DNA chemistry and staying with the RNA chemistry.

Chantal: Particular genome.

Jim: I think it's just reinforcing your statement, it's clear that DNA viruses and RNA viruses probably evolved by very separate means and it wouldn't be totally surprising to me that in DNA viruses, the big ones and the small ones maybe had a totally separate evolutionary ancestor. We're pursuing this idea of going only from big to small. I don't know is that would account for all DNA viruses. I think there could be separate origins or separate origins there too.

Vincent: It's never simple. It's always complicated answers. Alright, on that note, this episode of TWiV will be found at TWiV.tv and also on iTunes. If you like what we do, the best thing you can do to help us is to go over to iTunes, subscribe and leave a comment or give us some star ratings. That helps to keep us visible, so we can attract more subscribers. We always love to get your questions and

comments. You can send them to twiv@twiv.tv and I bet there'll be a lot of questions about this episode, so when I get them, I'll send them to you guys, so you can answer them. I want to thank my guest today, Jim Van Etton, thank you for joining me today.

Jim: Thank you.

Vincent: Jim's from the University of Nebraska and from Aix-Mars- Aix-Marseille, how the hell do you say it?

Chantal: X-

Vincent: Aix-Marseille Universite. I took French for eight years and I … X, Aix-Marseille Universite, Chantal Abergel and Jean-Michel Claverie, thank you very much.

Chantal: Thank you.

Jean-Michel: Thank you for the invitation.

Vincent: I also want to thank Mathias Fischer for inviting me to do this. Thank you Mathias.

Jean-Michel: For organizing a fantastic meeting.

Vincent: The meeting was fabulous and thank you for that. If you're doing it again, I'm available. That's that. My name is Vincent Racaniello. You can find me at virology.ws. You've been listening to This Week in Virology. Thanks for joining us. We'll be back next week. Another TWiV is viral.

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