Futures in Biotech, 40: Virus Reborn

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Marc Pelletier
This is Futures in Biotech, Episode 40: A Virus Reborn.

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Welcome to Futures in Biotech. I am Marc Pelletier. Today's episode is on the influenza virus and to help me do the show I invited Vincent Racaniello and he is the host of a fantastic science podcast called This Week in Virology. He's also professor of – in the Department of Microbiology and Immunology at Columbia University. So I feel that I've been lucky and I brought out the big guns to help get a really clear understanding of influenza. So to our guest host, welcome.

Vincent Racaniello
Thanks, Marc, happy to be here.

Marc Pelletier
So could you tell us a little bit about Dr. Palese's work and why you thought that he would be the guest for this episode?

Vincent Racaniello
I've known Peter Palese for over 30 years. I actually did my Ph D. in his laboratory in the late 1970s on influenza virus. And interestingly I was his first graduate student and since then he's had a stream of very good students and post docs. He's done amazing work on influenza virus. He's covered almost every aspect of the field. He's done molecular biology, sequencing, he was the first to recover the virus from cloned copies – DNA copies of its genome. He's done pathogenesis, vaccinology, antivirals, he's done it all. So I thought, he has an incredible grasp on the whole field. He understands exactly what's going on. He's smart, he's a good speaker, he's engaging. So I thought it would be, perfect since people are really fascinated by flu as you know. It's in the news almost every day. And especially now that it's flu season, Vaccines, antivirals, avian influenza, I thought it would be great topic. And he's just the perfect person to do it and also since I know of my felt we can have a nice rapport as well.

Marc Pelletier
Absolutely. And this virus influenza, it really is a – it should not be underestimated, right?

Vincent Racaniello
Absolutely not.

Marc Pelletier
It kills in the tens of thousands per year in the U.S.

Vincent Racaniello
Right, it's quite a lethal virus and that's why we get a lot of attention. It's quite lethal, it causes a lot of diseases especially in older and very young people. It can be quite lethal. It's a global problem. And as we'll see every year it's a problem. It's seasonal. In temperate climates you have outbreaks every year. So it's a significant pathogen. Not on the order of HIV of course, but one of the runners up in terms of viruses for sure.

Marc Pelletier

We certainly shouldn't forget about it. It should be right up there, especially considering that every, either a hundred years or a thousand years, there can be a pandemic right, which can kill millions?

Vincent Racaniello
Well since 1890 we've had six pandemics. They used to be every 10 to 20 years. It was – say there was one in 1918, then 1957. 1968 was really the last pandemic. So, we're due for one now. And everyone is guessing whether – what strain it will be. That's always the problem, because the pandemic is a pandemic because you have a whole new strain or sub-type of influenza that appears. And some people think it might be these H5N1 avian strains that are very lethal in chickens and turkeys. But no one knows and that's part of the fascination with the virus.

Marc Pelletier
And one of the topics we're going to talk about is the 1918 strain. And Dr. Palese was involved in recreating that strain so that would be available in the laboratory.

Vincent Racaniello
Right. This is – that's an amazing story and as he will tell you it was recovered from just a sequence and where the sequence came from is even more amazing. But we'll let him tell us that.

Marc Pelletier
Absolutely, let's get right to it.

[5:42] How does a virus in the life sciences compare to a virus in the information technology world? Is it the same thing? Is it a question of information that's gone haywire?

Peter Palese
Viruses are basically no good. In contrast to bacteria, viruses appear to really take advantage of cells and of in our case obviously, most important of humans where they replicate and cause damage. And they really also need for replication the human cell and a live human being. So in that sense the virus which we're all afraid of in computers is very similar. These computer viruses would not be able to be replicated without the Internet, without the computer age and therefore as – and I think in most instances these viruses are no good. So I think there are some similarities but obviously, clearly, there are also big differences.

Vincent Racaniello
May I interject, Marc? One difference of course is computer viruses are made by people. And the biological kinds, well they evolved.

Marc Pelletier
Well, they evolved. But are they living? Are they – is a virus considered a living organism?

Vincent Racaniello
I would say absolutely not. I don't know if – I'm sure Peter would agree.

Peter Palese
Let me disagree with Professor Racaniello. It really depends how life is being defined, if one defines it as someone who can speak, laugh and interact. Whereas something which is replicating and then speaks, thinks and does all the things we are doing then obviously a virus is not life. But if we define it more stringently and have a sort of definition which would include copying of information, then I think one can assign "life" to a virus as well.

Marc Pelletier
I'd like to talk a little bit about the anatomy of a virus – or perhaps some of the anatomies, because there's many forms of viruses. What are the – how's a virus built? Is it just genetic material? Is there protein involved?

Peter Palese
The major component of a virus, in my opinion, is a genetic material. In other words, the information which tells a virus what to do and that can be either DNA or can be RNA. And that I think is the most important. Obviously, there are other components in viruses including proteins, including in many instances lipids, carbohydrates, so these are all different components. But I think the most important is the genetic information of the virus.

Vincent Racaniello
Yeah I guess you can view everything else as sort of a carrier for that genetic information. The proteins, carbohydrates, lipids, all they do is bring it from one host to another, right.

Peter Palese
Correct.

Marc Pelletier
What scale is a virus compared to a cell? These are very basic – I'm letting the audience in here…

Peter Palese
Sure. No, no, this is – I always try to sort of tell the students when we project a – an image, electron micrograph, or even if it's just a diagram of a virus on a screen. And then how big compared to that screen – virus – to that virus on the screen, how big would be a cell in comparison, blown up to the same scale. And people are always, and students are always surprised as to how small viruses really are as compared to the cell which gets infected. And one can have this image, if you blow up a virus, let's say, to the size of a fist, then the cell – and obviously it depends on the virus and depends on the cell – but the virus then may have – I am sorry, the virus which has the size of a fist may infect a cell which is half the Empire State Building. So, it's really a tremendous size difference between a virus and a cell.

And again depending on how big the virus is; some are smaller, some are bigger. But that sort of shows that within – one virus particle infecting half the Empire State Building, may within eight hours, basically change the entire machinery of the Empire State Building and basically kill it within eight hours and produce 100,000 or 1 million new virus particles in that very brief period of time of eight hours.

Marc Pelletier
That's amazing. That's absolutely amazing. I am astonished and I have seen viral particles in electron microscopy images and I never really put that scale together. And it's the amazing ability, to overtake to the life processes of a cell to destroy it in eight hours from such a small scale, is absolutely astounding.

Vincent Racaniello
Astounding for a non-living thing.

Marc Pelletier
Or living. All right, all right. Or a non-evolving thing? Or evolving? It's certainly evolving

Vincent Racaniello
Oh it's absolutely evolving. No question. Peter and I will agree that viruses do evolve.

Peter Palese
Yes.

Marc Pelletier
Does that grand ability to take over life processes fast – extremely fast, give the virus the world's fastest process of evolution?

Peter Palese
[12:12] A very good question. Clearly, viruses – and particularly if we talk about bacterial viruses – evolve at an unprecedented speed. So, I think, I mean if we talk about biology probably viral systems are the

fastest evolving ones. And some of us still believe in Darwinian evolution and I think it is sort of very clear that many viral systems really follow a very straightforward Darwinian evolutionary pathway, particularly, for example, influenza viruses are a sort of, almost a textbook example of how a Darwinian evolution works.

Marc Pelletier
So, maybe it would be a good time to talk a little bit about influenza. Everybody uses the term 'the flu', but it is so misunderstood. Some people confuse the flu with a cold and – or even a bacterial infection with a viral infection. Maybe the flu would be a really good way to sort of clean up that and I don't understand why, or it may be viruses are that elusive in our mindset. Perhaps you could describe a little bit what the flu is from maybe the viral anatomy and then how it creates pathology.

Peter Palese
So, particularly when we talk about respiratory infections, humans can be infected by bacteria and by viruses causing sometimes very similar symptoms. Clearly, bacteria are very different from viruses. Antibiotics only work on bacteria which are – and if you talk about live or not live, bacteria can certainly replicate on their own, on an agar plate, on cheese in some instances, on any sugar, fluid substrate. So, bacteria are really different from viruses but they can cause, if you talk about respiratory diseases, they can cause very similar symptoms and very similar disease. But they are really very different animals so to speak, very different organisms.

But then if we go to viruses, which are not able to replicate on their own, they always need a cell to take advantage of, to invade, to replicate in those living cells. But if you talk about viruses causing respiratory diseases, we can again think of different viruses. If we look at influenza viruses, which are the agents causing influenza, they are probably responsible for the – more of the severe respiratory infections. But there are also many other viruses which can cause respiratory illness or respiratory diseases and those are – you referred to them already, common cold viruses, those are rhinoviruses. But there are also other viruses such as adenoviruses which are also associated with those kinds of respiratory diseases.

So, influenza is sort of a famous virus to cause respiratory disease, severe respiratory disease in particularly the young ones, infants as well as the old ones and immune compromised population. But we should not forget that there are other agents, in addition to bacteria, other viral agents such as adenoviruses, rhinoviruses, common cold viruses which can, in addition to influenza, cause those kinds of symptoms.

Vincent Racaniello
So, why is it that influenza is the most notorious of all the viral respiratory infections?

Peter Palese
Because in general more hospitalizations are associated with influenza disease, also because the virus has a seasonality, meaning that particularly in the winter month, influenza is more prevalent. That means over a very short period of time, a lot of the epidemic disease, respiratory disease is caused by influenza viruses whereas some of the other viruses are year round and the frequency within a short period of time, December to February, March, is much more dramatic in terms of influenza virus infections.

Marc Pelletier
How many people are affected by influenza in the U.S. per year?

Peter Palese
It's probably maybe 5-10% of the people get influenza in the U.S. and this is associated with a large number of hospitalizations, more than 100,000. And the numbers of people who die as a result of infections by influenza viruses is very high. So, the estimates coming from the Center for Disease Control are that about 30,000 die per season per year of influenza virus infections, which are then in many instances are followed by bacterial infections. But the end result is death unfortunately.

Vincent Racaniello

Why is flu more severe than other respiratory infections?

Peter Palese
That's a $64,000 question. It probably has to do with the virus causing damage in the respiratory tract, inducing cytokines, which are associated with inflammation. Influenza viruses are really very locally in a sense. They are really only replicating in the respiratory tract. So one cannot find virus in blood; in serum. It doesn't replicate in my left toe. It really is associated with replication in the upper, and, unfortunately when it gets severe, in the lower respiratory tract.

So, one explanation is that where the virus replicates – that is influenza viruses – like to – severe influenza virus infections are associated with growth of the virus in the lung and that obviously can lead to emphysema and severe consequences.

Marc Pelletier
[19:40] I have two questions and they are completely unrelated. The first question is what was probably the best way to distinguish between an upper respiratory tract infection from a cold or from influenza? Is there a way to distinguish right away, within a day of…?

Peter Palese
In terms of symptoms, mild influenza can look exactly like a mild cold caused by rhinoviruses. So, clinically, it is not easy to distinguish, so, basically impossible many times. The seasonality helps the physician to diagnose influenza because if that's the 15th patient coming in having the same symptoms and the diagnosis was done by testing in the first case, so then it's likely that the remaining 14 also have come down with influenza virus infections. But just from the clinical picture it's not that easy to distinguish between common cold, or adenovirus infections, and influenza virus infections.

Marc Pelletier
Does influenza cause a fever, more of a fever? Is it more…?

Peter Palese
Fever is one of the manifestations of influenza virus infections, but again the whole spectrum can be seen basically sub-clinical, a-clinical, no fever and then to severe fever where people really are close to death that is unfortunately part of the picture of influenza virus infections. It's not only a question of the virus itself, but also the immune status of the patient. In other words, if a similar virus has been seen by that patient, then there is some immune protection and therefore the subsequent infection by influenza viruses will be milder. So, even, let's say what we call, a virulent pathogenic, a bad influenza virus may cause mild disease in one patient and a much more severe disease in another patient.

Marc Pelletier
So, you mentioned a person having seen a virus strain and then perhaps getting a less severe infection. Is this a good argument for vaccination? I mean even in the medical community, I know a lot of medical doctors, a lot of scientists, that would say, forego vaccination, whereas I tend to get the vaccine regardless. Because I feel that even in the slight chance that I get influenza, I don't have a week to take off, even though I know that I would be fairly confident that I could survive it…

I am wondering what's – maybe you could help us decide. Is it a good idea, or should we – is it necessary or does it help the community around us, the people around us, to get vaccinated?

Peter Palese
You have fortunately touched upon a very important issue that many healthcare workers, people working in the healthcare field are not convinced that influenza virus vaccination is a good thing. Unfortunately, that's very wrong and there is clearly no evidence that there are any adverse reactions, side effects caused by the current influenza, by the current FDA-licensed influenza virus vaccines. Unfortunately, not enough people are willing to take the vaccine. I always say if you want to get sick, then don't take the vaccine.

Clearly, influenza virus vaccination is very important for, in essence, all populations. Influenza virus vaccines are not 100% effective and we can talk about that, but they are certainly effective depending on the strain, on the year more than 60, 70% of the time. And it's clearly a medical measurement. We certainly take advantage of this armamentarium in terms of making us healthier, making us not come down necessarily with an influenza virus infection. So, clearly, vaccination is very important. There is no good reason why people should not take it.

Vincent Racaniello
Peter, what is the coverage in the U.S.? How many people get the vaccine? Do you know?

Peter Palese
I think the coverage has increased and it's about 50% now.

Vincent Racaniello
Do you think it would make a difference, this attitude – we have a generally anti-vaccine attitude unfortunately growing. Do you it would make a difference if you could get one flu shot and it would last your lifetime?

Peter Palese
That would make life certainly easier. However, I am not sure that in our lifetime, maybe Professor Racaniello may still see a universal influenza virus vaccine and Marc Pelletier, you may also be fortunate enough to see that, but I am not sure that this is around the corner. It would make life much easier obviously and it would really be a tremendous advantage to have. Let's not even aim for a lifetime, but for a vaccination which would last and give coverage for, let's say, 10 years. Even that would already be a major improvement. And there is some hope but I am not so sure it's – well, will be next year or the year after.

Marc Pelletier
Has, with the increase of vaccinations, the trend towards vaccinations, has that correlated – I mean this is an epidemiology question, has it correlated with the lower incidence? By having two people out of every family get vaccinated, does that prevent the spread of the virus to the rest of the community?

Peter Palese
Those numbers are not that easy to come by, but there have been studies in Texas where they have used similar school districts in terms of population density, ethnicity, et cetera and there it was very clear that when school children were vaccinated in one district and not in another that in that district there was much less influenza in the adult population in that particular year. So, I think I would like to answer your question with yes, there is protection there is protection not only for the individual who gets a vaccine, but also for people surrounding that individual, meaning family members, schools are more protected, et cetera. So clearly a more universal coverage would, in my opinion, really change the picture in terms of overall influenza virus infections.

Vincent Racaniello
So, Peter, you mentioned, or maybe you didn't, but I will ask it, the two sort of related questions, why do we need to get a vaccine every year and if that's the case how do people decide which vaccine we need to get?

Peter Palese
So, one of the hallmarks of influenza is that the virus changes from year to year. In other words the virus which is circulating in March of 2009 if different from the virus which will circulate a year from now or two years from now. So, we can not completely predict what the next year – what next year's strain will be. However, by knowing what will circulate during the summer months, August, in the Southern Hemisphere, we have a fairly good picture of the strains which will be probably around in March 2010. So, by pre-empting or by sort of hoping that those strains are similar to those which were six month earlier in the Southern Hemisphere, it is possible to predict what kind of strains will be prevalent and vaccines or the

vaccine formulations take into account those kinds of strains. And that means that every year or every other year, the components of the influenza virus vaccine are changed.

They are actually, it's complicated, there are two Influenza A viruses, and one Influenza B virus as part of the vaccine over the last, probably 30 years. And they have – but they have to be changed every year, every other year to take account of the ever-changing virus. And that is very different to for example polio virus or measles virus, where the virus does not change. And even though these polio virus, measles virus, influenza viruses are all RNA viruses, only influenza viruses really change that dramatically.

Vincent Racaniello
Why is that?

Peter Palese
[30:09] That's a very good question, and I don't think there is a good answer for it, you know. One of the possibilities is that the virus, the structure of the virus, the architecture doesn't permit variation. But this is sort of a lame argument. I think it's not really that clear why influenza virus changes more than other viruses. But that's what we have to live with.

Marc Pelletier
One quick question and this may be a stupid question, but do the people in the Southern Hemisphere look to the Northern Hemisphere to predict what kind of vaccine they should be making?

Peter Palese
Correct, the same thing, because they have, they have half a year sort of advanced notice from what happens to them, yes. Correct.

Marc Pelletier
Wow. Has aviation affected that?

Peter Palese
I'm sorry?

Marc Pelletier
Has aviation, you know, people travelling back and forth?

Peter Palese
Strangely enough, even though if there is a planeload of Australians coming in August, they are not shedding enough influenza virus so that it can take hold and that we have an epidemic. So that is only in very rare instances, for example on boats, on pleasure boats, these boats where 3, 4,000 people are in very close quarters, in those instances influenza outbreaks have also been demonstrated during the summer months. But in general it does not happen, there is seasonality.

Marc Pelletier
Wow.

Vincent Racaniello
So, the use of the Northern and Southern Hemisphere strains implies that there is trafficking of viruses north, south and south, north. So if it's not Australians on an airplane bringing – who is responsible or what is responsible for the mixing of the strains?

Peter Palese
It is travelling, I am sure. I mean if it's not on the plane then boats, et cetera, so there is clearly – I mean, one can prove that these viruses are very similar which are found in different hemispheres.

Vincent Racaniello
But, it has nothing to do with aquatic birds bringing the viruses back and forth?

Peter Palese
There is a component of aquatic birds in terms of mixing genes into different influenza viruses, but not for the seasonal ones.

Vincent Racaniello
I see.

Peter Palese
So, it is – you are absolutely correct, if you are talking about human influenza, we have to take into account that also animals carry influenza viruses and occasionally there is a mixing of animal influenza virus genes with those of human influenza virus genes and an exchange occurs. But that is very rare and that usually leads to a pandemic strain, to a strain which is a new one, which can cause a lot of damage like the 1918 pandemic, which was responsible for 50 million people death.

In the case of regular, seasonal influenza the animal reservoir is probably not of any significance. There it appears it's really a mixing among different human populations which results in the transfer and transmission of different influenza viruses from north to south or south to north.

Marc Pelletier
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Now, back to the interview.

What are the structural changes that would be dramatic that would allow the virus to evade the immune system? And maybe we could get a little picture here. Now we know that a virus is the size of a fist versus a half the Empire State Building. Now maybe if we could describe what that fist looks like.

Peter Palese
Yes. So, influenza virus particles, like many other viruses are round, are spherical particles. And in terms of what the immune system sees is really just the outside and there is one protein, which we refer to as hemagglutinin. It's a technical term because it agglutinates red blood cells, hemagglutinin. And that is the protein which is decorating the outside of this round virus particle and that is what is seen by our immune system. And if we get vaccinated with such a virus, than we make an immune response against this hemagglutinin.

Now, so that is good, if we can make a vaccine and if we get – and then we make an immune response which is protective against another, or a subsequent infection. On the other hand, if the virus changes, this hemagglutinin, then the virus is not recognized anymore by our protective immune system and the

virus can infect us and cause the disease. So, yes there's one – and it's really basically one protein, one structure on the surface of the virus, which is the important one in terms of immune response. If that changes, we have, we call this immune evasion and the virus particle cannot be protected. And in those very rare instances where a completely new outside hemagglutinin occurs and that is the result of this mixing of animal influenza virus strains with human influenza strains, then a completely different hemagglutinin is present on the surface of the virus and that leads to, or can lead to viruses which run rampant around the world and cause a global epidemic or we always refer to this as a pandemic, a global epidemic.

Marc Pelletier
[37:37] So influenza, or hemagglutinin, sorry, it has the ability to mutate to such an extent that it can avoid our cells' ability to detect it and destroy it, but still remain functional?

Peter Palese
Yes, that is one of the unique properties of sort of the virus. That despite being an influenza virus, despite doing all the things the influenza virus does, it can change enough so that the immune system doesn't recognize it anymore. So that's a very unique property of influenza viruses. Unfortunately, such a property is also shared by HIV and we all know that variation there is another big problem, in terms of making or developing an HIV effective vaccine.

Vincent Racaniello
So Peter, if the virus is a fist the hemagglutinins are sort of the size of the fingers would you say?

Peter Palese
Yeah. Yeah, probably, yes.

Vincent Racaniello
Okay.

Peter Palese
Short fingers. So pinky fingers.

Vincent Racaniello
Short fingers. So, how big is the change that would allow evasion of a strain from an immune response on that finger. How would you make the metaphor?

Peter Palese
It's...

Vincent Racaniello
A hair?

Peter Palese
Putting nail polish on, okay? So having – they are fairly small changes which can lead to a masking of the important sites which are recognized by the immune system. So it's really, I mean, yes, red color, green color, that all makes the immune system not recognize anymore the influenza virus.

Vincent Racaniello
So a little more, in a little more detail how many amino acid changes would that be?

Peter Palese
It could be three to four amino acid changes only.

Vincent Racaniello
That's amazing.

Marc Pelletier
How big is the protein in amino acids?

Peter Palese
It's about 700 amino acids so it's less than 1%.

Marc Pelletier
So, for the audience all… a protein is made up of a chain of amino acids that coil upon themselves and that three-dimensional coil gives it its function. So, you're saying that out of the 700 amino acids, three or four changes are significant enough that the virus can then run around our immune system, do circles around it?

Peter Palese
Yes, correct. And cause disease. That's the main problem, that it can – it is unencumbered by any protective immune response of our host immune system and replicates without any check and balance.

Vincent Racaniello
So, you mentioned this 1918 pandemic and you mentioned a number of 50 million deaths from that. Is that correct?

Peter Palese
Yes. So it's remarkable that within a very short period of time, namely December of 1918, to about February, March of 1919 in this very – two and half, three month period, basically 50 million people died worldwide. Most of the people even – today and also around 1918, 1919 lived in the Northern Hemisphere. So, that's why the number of 50 million is associated with a period of the winter time of 1918, 1919, December to February, March. And that virus within this very brief period of time as a combination of a very virulent virus and a new surface, a new hemagglutinin, against which no one at that time had any immune protection, resulted in this very devastating event. Namely the pandemic of 1918, 1919.

Vincent Racaniello
So, that virus is apparently much more virulent than any of the subsequent pandemic strains. Do we understand why that's so?

Peter Palese
It's probably one of a century or one of a millennium even, virus, which just had the right mixture of genes, the right amino acid sequences and it was really more virulent than other seasonal and other pandemic influenza virus strains, which we have been able to study in the laboratory.

Vincent Racaniello
So, when I was a student we didn't have that virus around. But since then it's been reconstructed in the laboratories and what do we learn from that?

Peter Palese
[42:41] The virus, the influenza viruses have been isolated for the last 70 years. So starting in the 1930s, influenza viruses have been obtained from the throat of infected patients and some of those are still available in refrigerators and freezers in different laboratories. But the 1918 influenza virus is extinct, was not – one didn't even know at the time whether this was, whether the disease was caused by bacteria or other agents because science was not at a stage which could distinguish and identify the etiological agent, the agent which was responsible for this disease.

So, the virus is gone. But by having pathology specimens, in particular the U.S. Army had material from soldiers who died in 1918 stored as pathology samples and they are actually preserved in a paraffin block. So, they took samples from lungs and other organs of patients, soldiers who died at that time and then stored them in archives of the Armed Forces Institute of Pathology at the Walter Reed Hospital in Washington. And using those specimens, Taubenberger who was working at the Armed Forces Institute

of Pathology, was able using modern technologies, to get the sequence of the RNA of the nucleic acid, of the genetic information of the 1918 virus.

And then techniques, which we have developed at Mount Sinai allowed us to reconstruct based on the sequence – so, we didn't use any component of the virus from 1918 other than the information, what the sequence was, what the amino acid sequence was, what the nucleotide sequence was and then made in the laboratory the virus. And this virus is infectious and we can study it now in very effective ways.

Vincent Racaniello
But which we presume is the same as the strain that circulated in 1918, so it's not synthetic in the sense that that didn't exist before.

Peter Palese
Yes, yes, it is really a reconstruction and we would say because it really is more virulent, more pathogenic than any other influenza virus which we have in the laboratory, we believe that this is really the same virus as 1918.

Vincent Racaniello
So, you must to have work with this virus under very contained conditions.

Peter Palese
So, the first – there are very strict rules and regulations under which we can work with the virus, even a gene from that virus. And these are high containment facilities which are designed to protect the people who are working in those facilities on one hand, but also obviously make sure that the virus does not escape, does not jump into an animal reservoir or even worse that people would get infected. However…

Vincent Racaniello
Yes, as you know – sorry, go ahead.

Peter Palese
However, I would like to say that even though the 1918 virus was devastating in 1918, we were able to show that the virus is one sensitive to FDA approved drugs, Tamiflu and other approved – and also vaccines. But also that old people have been exposed to similar viruses since that time. So, we are actually not – even if such virus would be infecting humans today, the consequences would not be as dire and as severe as they were in 1918, because we all have some partial protection against these H1 viruses, which the 1918 was a fierce one.

Vincent Racaniello
Certainly we don't want to let it out, right? And in fact many people have suggested that it wasn't a good idea to recover this strain because accidents do happen. So, how would you make them, besides telling us about the antivirals and vaccines, how would you make them feel better?

Peter Palese
I think the virus – to know what made this virus so bad I think is very, very important information. And then if we know what this virus was all about, it allows us, one, to really find drugs and medications against it on one hand, but also understand what we have to sort of do in terms of preventing the outbreak of another one of these very dangerous viruses. So, I think under the right circumstances, under the right restricting laboratory conditions, I think it is important to continue such studies, because the benefit of the knowledge, what we can learn from studying these viruses outweighs any kind of potential danger.

Vincent Racaniello
So in that vein then, would you say we should keep the remaining stocks of smallpox?

Peter Palese
I am one of the people who feels that the importance of knowing what this virus is outweighs the potential danger which – such as storing of the virus might bring along, I think it is more important to really to have

the right medications and the knowledge how we can prevent a smallpox disease, that we get better drugs, better vaccines in the future. That's more important than being afraid, particularly as there are other pox viruses in nature, which may jump into humans. And if we just stop research in this area, I think we will be – the damage will be much bigger than not studying such viruses.

Marc Pelletier
[50:00] The pool of viruses out there in the world is enormous, right? I think we did an episode, Episode 9 with an MIT professor who was describing the ecology of just bacteriophage in the oceans 100 miles north of Hawaii and he said that there was 10 times more phage or 10 to 100 times more phage per millilitre than bacteria and there were billions of bacterial cells in the – per mL.

Vincent Racaniello
10% of the mass of the ocean is bacteria and a million bacteriophages per millilitre of ocean water.

Marc Pelletier
Enormous numbers, well that's amazing. So, understanding this is going to be a – could save humanity, absolutely.

Peter Palese
Yeah, I think putting the head into the sand and ignoring these viruses and not working on them I think is more dangerous than doing it under the right conditions and working in the right facilities.

Vincent Racaniello
So, Marc can I ask one more?

Marc Pelletier
Well, sure. It's not up to me.

Vincent Racaniello
I don't want to – I know you…

Marc Pelletier
That's no problem. This is fantastic.

Vincent Racaniello
So, Peter, why is flu seasonal?

Peter Palese
So, the influenza virus is in the Northern Hemisphere limited to really a two or three months span, depending on the year, maybe starting in November and then going for two or three months and in the Southern Hemisphere in their winter time, which is July, August, September.

And so this has been observed for many, many decades since surveillance has become more scientific. And people have sort of always known about this but we did not have a real molecular explanation for that. And recently we have developed a system in the laboratory, which allows us to look at transmission. So, the question is, what are the molecular signatures, what are the precise conditions which determine whether a virus can be transmitted from one patient to the other, from one human being to the other? And such experiments cannot be done because of ethical considerations. We just can't take 20 medical students and put them in to a room and infect one and then check what determines how fast the virus can be transmitted. So, these experiments were possible may be 30, 40 years ago. But clearly we cannot do them anymore, because there is no benefit for the person in this trial.

So, what we can do, however, is to have animal models in which to study this and we developed an animal model which is a guinea pig and we put – we have two cages, which are separated by several feet and we put an animal infected in one cage and another animal – usually we take many more animals, but another cage with another animal, which is uninfected and then we ask the question, how easy is it to get

transmission from the infected animal to the uninfected? And it turns out that if we do this transmission under cold temperature, a temperature which is during the winter time and under low relative humidity, which is also imitating winter conditions and we leave animals there for 7 to 10 days, we observe that transmission of influenza viruses is much easier at cold temperatures, 5 degrees centigrade as compared to room temperature or even higher temperature. At 30 degrees, something like 80 something Fahrenheit there is no transmission whatsoever.

So, that I think is one of the I think explanation, maybe the explanations of why we do have seasonality with influenza virus transmission, which is important because one person infected doesn't start an epidemic, but transmission appears to be much more effective at low temperature and low relative humidity. And those are the conditions which prevail during the winter time and this I believe is one of the, is probably the most important factor which explains this seasonality.

Vincent Racaniello
So, does this mean we should keep our homes well humidified in the winter to stop transmission?

Peter Palese
If we could keep our rooms at 80 degrees and high humidity we would prevent influenza virus transmission, but we would probably buy a lot of other infections, bacterial, et cetera, et cetera, not to speak of the cost et cetera. So, this is not a practical solution. We can – simply we cannot for obvious reasons heat up all the rooms and also we cannot change the humidity. And clearly if we would go out on the street or in the elevator or in the subway, we couldn't keep those conditions up. So, this is not a practical consideration really. But I think it sort of gives us an explanation why we have more transmission during the winter time.

Vincent Racaniello
So, why does low humidity improve transmission?

Peter Palese
Yes, so the – it's both low temperature and low humidity.

One, the virus is probably more stable at low temperature and low humidity. There is some evidence that the virus does have a lipid membrane and that lipid membrane undergoes what they call a phase shift and that is that once it goes under 30 degrees centigrade, the virus becomes more rubbery and probably more, physically more stable against rupture and against spilling its guts, so to speak. So, it is a creation of the physical stability of the virus at low temperature, low humidity on one hand.

And probably also the host is changed on those different conditions that there is ciliary movement, which is probably slowed down than it is cold outside, meaning that the virus is not cleared as easily. The mucus is more viscous, which also leads to a longer carrying of the virus and therefore a higher probability of transmitting it from one patient to the other.

So it's both stability of the virus on the one hand and changed condition in the respiratory tract, which are inducible to a longer virus shedding.

Marc Pelletier
[57:47] I do have a question with respect to influenza versus adenovirus. If influenza has such an amazing ability to target to the upper respiratory tract, and as you mentioned not to the toes, is influenza a possible candidate for gene therapy? Will it be used to carry genes into the upper respiratory tract to one, maybe produce anti-apoptotic agents for cancer or for delivering the cystic fibrosis gene, the CFTR, the correct version to the patients with cystic fibrosis? Or is adenovirus really going to be the vector of choice? Is it too hard to engineer influenza to...?

Peter Palese
It is harder to engineer influenza viruses as compared to adenoviruses and – but I think even with adenoviruses there are limitations to how often we can deliver such a virus or how often we can give,

administer those genetically engineered viruses in order to deliver a particular gene. And it is I think still some time off before we can think about these viruses as good vehicles to express transgene. So, I think in essence influenza viruses would also be possible to be used for such transfer of genes as adenovirus is used. It might also be used in terms of oncolytic, as an oncolytic agent to possibly attack cancer. In all of these cases, however, the immune system is something, which is important as we talked about. That's why vaccines work and that's why we are protected. But the same kind of immune response may also make it less easy to use these viruses as vaccine, as vectors and as oncolytic agents.

Marc Pelletier
We fight them. So, we would be fighting the medicine.

Peter Palese
Exactly. Yes.

Marc Pelletier
I suppose one last thing that we should mention though. We talked a lot about vaccines and we didn't mention how they are made. And while they are safe and there is no literature out there that suggests that they are not safe to take; my son is allergic to eggs. He is deadly allergic to eggs. So, we always have him watched when he gets his vaccine. So, I guess I would, you know, tell people if they are concerned, just they should really only be concerned about their egg allergy. They are allergic to eggs, then they should talk to the doctor about vaccination.

Peter Palese
There is – the current manufacturing procedure for influenza virus vaccines involves growth in embryonated eggs and therefore people who are allergic against products, chicken poultry products' components are unfortunately in a position where it might not, or where they could have some side effects. It might be possible also to use a live virus vaccine which is given through the nose, where there might be less of an allergic reaction as compared to injecting the vaccine.

Marc Pelletier
Oh, wow.

Peter Palese
So, that might be a way for people who have allergies against chicken components. So there is some way of avoiding that. And also in the future influenza virus vaccines will be produced in tissue culture, human cells or higher primate cells and there would be no possibility that any chicken product would be in those vaccines.

Marc Pelletier
Oh, great.

Vincent Racaniello
Would that be in our lifetime, Peter?

Peter Palese
That one will be in our lifetime, yes.

Marc Pelletier
Is it in Vincent's lab? Does he have one? He was mentioning he was growing HeLa cells, so…

Peter Palese
Those are the kinds of cells which will be used, yes.

Marc Pelletier

Fantastic. Well, I think this is absolutely fantastic. It's a great service to everyone listening and to myself included, to clear up a little bit of the, some of the mystery behind influenza. And it's just a very mysterious virus and now I really feel that I can get a clear understanding here.

So, I would like to thank you both for being on the show. I really, really appreciate and I am honored that you accepted the invitation.

Peter Palese
Thank you. It was my pleasure and my honor for both. Thank you very much, Vincent. Thank you very much, Marc.

Vincent Racaniello
Nice to hear you again. Okay.

Peter Palese
Thank you very much.

Marc Pelletier
So, I would really like to thank Dr. Palese for his time today and I would also like to thank Dr. Vincent Racaniello, the host of the great science podcast called This Week in Virology. It's one that I listen to and the reason why I really wanted you on the show is to help us get a better overall understanding of viruses so that we don't fear them as much. Knowing that scientists like Dr. Palese and yourself are working on this, it gives me a lot more confidence to get out there and mingle, I suppose, during flu season. Can you tell us a little bit about your podcast, This Week in Virology?

Vincent Racaniello
This Week in Virology, I started back in September of 2008. I had for a long time been listening to the TWiT podcasts and I thought they were a fabulous way to convey enthusiasm about a topic. And I always wanted to do that with viruses and I was having lunch one day with my colleague, Dick Despommier and I told him and he said, well let's start it next week! I went to his office with a little recorder and two mikes and he knew a lot about West Nile virus.

So, that was our first episode and the key – the goal is simply to have a few people, very much like TWiT, who know something about viruses, to have a conversation every week and it depends on the weekly stories in virology, what's hot, what's going on in the news. We pick some interesting research papers and just talk about them and our audience is growing. We have – we do weekly picks just like the TWiT network does and Leo. We have a weekly podcast, a weekly blog and a weekly book, all science oriented. And it's our way of expanding the field of good podcast and good online media, so that everyone knows more about them.

Marc Pelletier
And you have been teaching at Columbia for a number of years?

Vincent Racaniello
I have been in Columbia since 1982, right. And I have a laboratory, we do research on viruses. I also teach and I have done a lot of teaching. And I am doing more and more and I am going to increase my teaching. I'm really, I really want to reach out and give back to people everything I have learned about viruses. I know an awful lot and the podcast and my blog also, virology.ws, is another way that I explain viruses to people. I have a lot to contribute and I think the internet is the best way to do this.

Marc Pelletier
So, you are extending your classroom…

Vincent Racaniello

You are absolutely right. You know Marc this is the neat thing; when I make a blog post or I put up a podcast, I get feedback, I get people asking questions. I have had more people ask me questions from those, the podcast and the blog than I ever had in all the courses I have ever taught in 30 years.

Marc Pelletier
You know, I think it's an amazing thing that people can get the equivalent of an Ivy League experience through podcasts.

Vincent Racaniello
Absolutely. You know many universities put their courses online now in iTunes. iTunes University.

Marc Pelletier
Though I have to admit there is some talent that comes out of those – the lectures. And This Week in Virology is more, definitely more along the lines of what we see on this WEEK in TECH in that it has incredible scientific integrity. You guys know what you are talking about, but also is far more interesting because it's the way you guys cover the materials. It's a lot more fun. So, I would recommend that people go to iTunes and go under the category Medicine and look at This Week in Virology. It's definitely a fun one because viruses are so, they are – how do you say it? They are pretty scary. I mean…

Vincent Racaniello
They are scary but they are also amazing, right? They're are just combing – they're both – well I'll tell you, I mean as Peter will say, or he said – this is a wrap-up. As Peter said, viruses are generally bad and that's true, but they do amazing things. And the more you learn about viruses, the more people learn about viruses, the more they are fascinated with them.

Marc Pelletier
So, there's always a story of good and evil.

Vincent Racaniello
You know there are some good viruses too. There are – some viruses do good things, yes. So for example, there are some very pretty tulips in Holland that wouldn't be as colorful if they didn't have a certain plant virus infecting them.

Marc Pelletier
Well, if you want to hear more as I said go to This Week in Virology. So thank you very much for coming on.

Vincent Racaniello
It was my pleasure and if you ever need a virologist at a future show, I am happy to come back.

Marc Pelletier
I think we are going to do a few more.

Vincent Racaniello
And Marc, I would like to have you on TWiV one day and you can ask innocent questions about viruses.

Marc Pelletier
That would be fun. I would definitely be there. Thank you very much.

Vincent Racaniello
You're welcome.

Marc Pelletier
Before we go, I would like to thank Phil Pelletier and Will Hall for the opening and closing themes.

I would also like to thank the team at Pods in Print, who have been producing the transcripts to the show, I think since episode 27. They have been doing a fantastic job, they can handle even the most technical material. So for those transcripts, you can get them at futuresinbiotech.com.

I would also like to thank Dane Golden and Leo Laporte for co-producing this show. And lastly if you have any comments or suggestions I can be reached at marc@twit.tv. For Futures in Biotech, I'm Marc Pelletier. Thanks for listening.