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Special Topics : H1N1 Flu : Peter Palese Interview - Special Topic of H1N1 Flu

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H1N1 Flu - September 2009

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Peter Palese

From the Special Topic of **H1N1 Flu**

In our Special Topics analysis of H1N1 flu, the work of Dr. Peter Palese ranks at #9 by total cites, based on 71 papers cited 3,073 times. His record in Essential Science IndicatorsSM from Thomson Reuters includes 86 papers, the majority of which are classified under Microbiology, cited a total of 4,255 times between January 1, 1999 and June 30, 2009. He is also a Highly Cited Researcher in the field of Microbiology.

Dr. Palese is Professor and Chair of Microbiology, Professor of Medicine, Infectious Diseases, and head of his own laboratory at the Mount Sinai School of Medicine in New York. Below, he talks with ScienceWatch.com correspondent Gary Taubes about his highly cited influenza research.

SW: What was the line of research that led to your highly cited 1999 *Journal of Virology* paper, "Rescue of influenza A virus from recombinant DNA" (Fodor E, et al., 73[11]: 9679-82, November 1999)?

This is literally the result of more than 10 years of work. My lab was the first one to develop a system that allows changing the genome of an influenza virus. So why is that important? In order to study influenza virus or other viruses, you would like to change a particular amino acid and then look for whether that change, for example, makes the virus more or less virulent. This system allows you to say something about the function of this gene. It also allows you to change this gene to alter the properties of that virus.

If you want to make a vaccine, this technology is very important. We started trying to do that back around 1985; we only succeeded around 1990, and that was for one particular gene. The 1999 *Journal of Virology* paper was when we succeeded in doing that for all genes in the virus in one shot.

SW: What does it mean to "rescue" the virus?

Remember, the influenza virus is an RNA virus, meaning there is no DNA involved in the replication cycle. RNA infects the cell, and more RNA is made—there's never any viral DNA. Proteins are made from the RNA and so more viruses are made and the cells are eventually killed. In order to do this changing of a specific amino acid—say, the amino acid in position 55—you have to go into DNA and make plasmids. Usually the flow of genetic information in normal cells is DNA to RNA to protein.

In the case of this influenza virus, there's no DNA. So in order to make a change in that amino acid at position 55, you have to go first into DNA and then the DNA is transcribed into RNA. This is also called

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"reverse genetics" for this reason. So you rescue the virus from the recombinant DNA. Then the DNA is transcribed into RNA. At the time we had to use 12 different plasmids to do that. Now it can be done simpler and easier.

SW: Was there one particular obstacle or challenge that you had to overcome to pull this off?

Well, as I mentioned, we had to use the 12 different plasmids. At the time, it wasn't easy to clone all this genomic material. We also didn't know whether just by putting those plasmids into one cell we would achieve the right level of regulation—maybe one plasmid would express more than the others. That looked very difficult and we couldn't predict whether it would work or not. It took us a long time to do it.

"There's actually very little similarity between the 1918 virus and the present one."

SW: Was there any serendipity involved with getting it to work?

No, this was just slogging along. Serendipity is always a good for us in this business. But, in this case, it was a matter of trying all kinds of conditions and making incremental steps forward. We started with one gene, and then we went to two genes and so on. There was no "aha!" or "eureka!" moment.

SW: How many genes does an influenza virus have?

It has eight RNAs, but 11 genes. A few of these eight RNA segments, these mini-chromosomes, code for more than one gene.

SW: What have you've learned from this research about influenza viruses?

Well, even before the 1999 paper—back in 1980, in fact—my lab was the first to establish a genetic map of influenza viruses. Using a different technology, we were able to identify which of these RNA segments, which mini-chromosomes, code for which genes. We were able to establish a genetic map, comparable to a human genetic map, but obviously much, much smaller. So at that time we were able to say that mini-chromosome one has these two genes, etc. That was important to know. Then we can ask what we learned from this reverse genetics. So that 1999 paper really reported on the ability to make an influenza virus in the laboratory.

One thing we were able to do with that is make the extinct 1918 pandemic flu virus in the laboratory. In that case, the virus didn't exist anymore. All we had was the sequence taken from samples found in people who died in 1918. The virus was gone but there were enough RNA fragments left intact so that the sequence could be obtained by Jeff Taubenberger. We were then able to use this reverse genetics technique to reconstruct the extinct pandemic virus in collaboration with Terry Tumpey from the CDC. That really gave us lot of information. It told us that, indeed, this 1918 virus was really the most virulent, the most pathogenic, the mother of all influenza viruses. And we were able to identify which gene was most important for the 1918 virus; what was really different from other influenza viruses since that time.

SW: That virus really was the most virulent of all influenza viruses? It wasn't just that there was little immunity and that soldiers returning from the war managed to incubate it and spread it far and wide?

I have maybe 5,000 different influenza viruses in my freezers, and that 1918 virus is clearly the most virulent human influenza virus that we have. This was not only one out of a century, but one out of a millennium probably. There are examples of people living in Iowa, having enough to eat, being in uncrowded conditions, not in a boat, not in a military installation, and they died within 24 hours after getting sick. So yes, the troops moving in boats from Europe to the States and back again were incubators, and clearly living in the trenches or in barracks wasn't healthful, with 15 people living right on top of each other, but the virus also caused a lot of damage, a lot of morbidity and mortality in areas where these conditions were not found.

SW: Considering what's going on in the world today with the H1N1 pandemic, I have to ask how does this new pandemic virus compare or relate to the 1918 virus?

There's actually very little similarity between the 1918 virus and the present one. Certainly the present swine influenza virus is an H1N1 virus, meaning it has a hemagglutinin and a neuraminidase—that's what the 'H' and 'N' stand for—and both are subtype one. And 1918 also belongs to that group of subtype of H1N1. It has to, since the 1918 virus went into the pig population and has basically circulated there for the last 91 years. The new virus is a direct descendant from the 1918 virus; however, 91 years lie in between. But the new virus, the novel H1N1 2009 virus, is very mellow; it is much attenuated compared to 1918 virus. So there are very few parallels other than that it's an H1N1, and interestingly enough this virus also appears to infect more young people.

SW: Do we know why that is?

"...this 1918 virus was really the most virulent, the most pathogenic, the mother of all influenza viruses."

It just happens that older people have been more often exposed to H1N1 viruses. People over 50 have seen many more of these infections than younger people. So it is not so much that the virus targets specifically the young ones. It is a fairly mild virus and it happens that the older populations are better protected because they have experienced infections with this virus. Therefore, they are more immune and they are partially protected against H1N1 viruses. So this manifests itself as a shift of morbidity and mortality toward younger people. In contrast, regular seasonal influenza affects more older people.

However, the total number of fatalities per infected individuals is much, much lower than it was in 1918—probably lower by a factor of 1,000. And in 1918, the higher incidence in young people (as compared to the older segment of the population) was probably for the same reason. There had been an earlier virus in 1889, which partially protected the older population.

SW: What research are you pursuing now in your laboratory?

We are interested in understanding and studying in great detail what this novel H1N1 virus is doing. We have an interesting transmission model, in which we measure how well different influenza viruses transmit from one animal to another. We're using guinea pigs. It allows us to say which gene of a particular influenza virus is responsible for (good) transmission. We can identify and pinpoint what it is in the virus that makes it very well transmissible. This is important because, for example, the H5N1 virus, the avian influenza virus, does not transmit well and therefore hasn't been a pandemic strain.

SW: Are you involved in the effort to create a universal flu vaccine that will work for all strains?

This is certainly a very important research agenda and many groups want to do that; to develop a vaccine that may be protective for more than a couple of seasons. That's clearly a direction many of us are taking, my lab included.

SW: If the 1918 virus were to come back, would it be as deadly as it was 91 years ago?

No. And the reason is we all have experienced, some more than others, infections with H1N1 viruses. So there would be partial immunity in the entire population—what we call herd immunity. That's point number one. The second is that we have drugs like Tamiflu that are effective against influenza viruses. Thirdly, and more importantly, we have vaccines now that we can use. So we can make vaccines in a very brief period of time. There wouldn't be any technical challenges. It's an H1N1 virus and we know how to make H1N1 vaccines.

And fourth, we have antibiotics, so we can treat all the bacterial infections that tend to follow the initial influenza infection and exacerbate the patient's situation. If there's another secondary bacterial infection, we can take care of it with antibiotic treatment. So far all these reasons, if that 1918 virus were to reappear it would be much less of an issue than it was in 1918. It wouldn't even be comparable. ■

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Peter Palese's current most-cited paper in *Essential Science Indicators*, with 266 cites:

Garcia-Sastre A, *et al.*, "Influenza A virus lacking the NS1 gene replicates in interferon-deficient systems," *Virology* 252(2): 324-30, 20 December 1998. Source: *Essential Science Indicators* from Thomson Reuters.

Additional Information:

Peter Palese is featured in ISIHighlyCited.com.

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