



© 2009 Nature America, Inc. All rights reserved.

Matt Hansen

Straight talk with... Ian Lipkin

How do you sequence a virus that no one has identified before? With the right technology, it's not as difficult a task as it might seem, says Ian Lipkin, director of the Center for Infection and Immunity at Columbia University's Mailman School of Public Health. Lipkin has been working on the technology involved with viral discovery since the late 1980s, when he became the first researcher to identify a microbe using only molecular tools. He and the Center's team of about 50 researchers have identified close to 200 new viruses so far. Most recently, Lipkin and his colleague Thomas Briese identified a new hemorrhagic fever virus that killed several patients in southern Africa last year. Now, in addition to processing samples from around the world, Lipkin has been working to export his sequencing technology—and the expertise needed to use it—to the developing world. **Erica Westly** spoke with Lipkin about how the viral discovery techniques he uses could help prevent future viral disease outbreaks, from swine flu to the unknown.

You've worked on a wide range of projects, from Colony Collapse Disorder in honeybees to SARS and West Nile. How do you find these cases?

Well, there are two types of scenarios. Sometimes people contact us because they have a disease that they have been studying for many years, and they have reached a belief that there's an infectious basis. Those may be a long shot: for example, a chronic disorder like multiple sclerosis. In the other scenario, the evidence that there's an infectious basis is already clear. And there, it's just a question of whether we have the time and the resources to pursue it.

What is a typical day like for you at the center?

Today we began with a conference call with the New York City Department of Health and Mental Hygiene, and with them we've been looking at influenza viruses, including swine flu. We've been following examples from the peak of the outbreak to the time that it waned. We've found that there's a lot more swine flu at the peak of the outbreak, but, as it wanes, we begin to see rhinoviruses and other forms of flu. As you do this kind of work it becomes clear that clinical syndromes are often not specific, and the laboratory has a very important role to play. One of the advantages of the multiplex PCR systems that we use is that we can consider a wide

variety of hypotheses. We don't step in with any bias, and, as a result, we're constantly surprised at the versions of these microorganisms and the fact that so many of them present in a similar way clinically.

Then, we had a meeting with the Gates Foundation to talk about infectious diseases in children in Gambia and South Africa, and that study is to help make decisions about what vaccines should be developed next. At noon, I had a meeting with some chemical engineers about ways we can make sequencing instruments that are smaller, more sensitive and more robust. Then, later in the afternoon, I have meetings to go over recent data in a number of different viral discovery projects. There's a reovirus that's affecting farmed salmon, a picornavirus that's affecting turkeys and then a whole host of human syndromes—basically they are too numerous to count. And that's kind of a typical day.

Last year, you published two papers on the LuJo virus, a new arenavirus that caused several fatal cases of hemorrhagic fever in Zambia and South Africa. How did that project come about?

At any given point, there are signals around the world about disease, and the WHO [World Health Organization] is asked to go and investigate what's wrong. What we elected to do with the LuJo virus, because we had been told that efforts to identify the agent had been unsuccessful, was to simply get the material and place it into high-throughput sequencing and identify the gene products. What's remarkable about this is that when we began using this approach a couple of years ago, the time required was several weeks. But, in this instance, we only needed 72 hours. We were able to identify so many different genetic fragments, and, with those footholds in place, we rapidly filled in the remainder of the genome.

And the faster turnaround stems from improvements in the sequencing technology?

Yes. If you think back to the 2003 SARS case as an example, the real success in that instance was that researchers could grow the virus in cells. But even then, to get the full sequence of the virus, it took an army of people over a week. So, in contrast, we did not grow the LuJo virus in culture. We took the material directly from a clinical specimen, and, essentially, after a little bit of amplification, we placed the sample into the sequencer, and we were able to identify this new virus with a fraction of the cost, a fraction of the effort and a fraction of the time. So it really was a paradigm shift in terms of what you can do. I think the other lesson here is that anyone can do this. If we can export this technology to the developing world and develop the expertise that's required to use it, I think we're going to be able to make diagnoses at the source.

What steps are being taken to get this technology to developing nations?

There are a number of sequencing technologies on the horizon, and they're going to get smaller, and they're going to get cheaper. I think you're going to find more and more people are going to have the capacity to use them, so it's going to be a great time for pathogen discovery around the world. We have a mandate as a WHO collaborative center to train people in the use of these sequencing technologies. So, what we do—and it's our privilege to do it—we bring people in for a period, sometimes it's just a few days, other times it's as much as several months, and they learn how to work with these tools. At this point, we've trained over 50 people from over 20 countries. More and more people are becoming conversant with this approach, so I'm very optimistic that this is going to make an enormous difference in terms of global health.

The recent swine flu outbreak seemed to catch many in the public health community off guard. Are there any lessons there in terms of predicting what viruses will pose a threat in the future?

The flu is a great example of 'expect the unexpected'. Since 1997, when we first had H5N1 [avian flu] in Hong Kong, people have been concerned about the emergence of a new flu strain that's going to wreak havoc. We've actually been talking about it since 1918, but 1997 was the event where people really became aware of how large the risk was. Then, when SARS emerged in 2003, everyone thought that was going to be a novel strain of flu. When SARS later submerged, we became concerned about H5N1 again, and while we were focused there, lo and behold, out comes a new strain of H1N1.

Is H1N1 the only risk we have to fear in terms of influenza virus? Absolutely not. There are many other candidates to consider, and they might all emerge. We have no way of knowing which ones they will be.

What kind of work has your group been doing on swine flu?

This year, because there is so much emphasis on flu, we are processing hundreds of samples a week for swine flu and other forms of flu. We're still working with samples from New York City, and we've also received samples recently from Argentina and New Zealand.

The samples from Argentina and New Zealand—we know they're swine flu. So there, what we're trying to do is follow the evolution of the virus and looking to see if it might be morphing in some way to become more or less virulent.

With the New York City samples, we're doing something different. We're looking at all samples that come in that meet certain characteristics of influenza-like illness, and we're trying to sort out to what extent we're talking about swine flu and to what extent we're talking about other types of flu.

How could viral discovery technology help prevent future pandemics?

The lessons from swine flu are really several. First, we need to be able to monitor very closely the appearance of respiratory pathogens around the world, and some of these viral discovery methods we've been talking about can recognize not only that there's a flu but that there's something novel about it.

Another lesson is that these agents may emerge in people, but, more classically, they emerge in wildlife or domestic animals. So animal surveillance is critical, not only domestically but internationally. We need to have satellite programs to collect materials from wildlife as well as from humans, and any time the animals get sick, we need to jump on it and figure out why they're sick.

We also need to remember that viruses can persist in reservoir species without much disease. If you presume that every vertebrate animal has some 20 endemic viruses, then, given the fact that there are over 50,000 vertebrate species, you have as many as a million viruses that may get discovered. Obviously, we can't find them all, but what we can do is look at those animals that we come into contact with most. We need to start characterizing these animals and get some idea of what viruses they harbor. We have projects [monitoring] bats, [for example, which] harbor a wide range of important pathogens including rabies virus, Hendra virus, Nipah virus, Marburg virus, Ebola virus and SARS coronavirus. There are very few viruses that are restricted to humans, and, as long as we have animal reservoirs, I don't see how many vaccine strategies are going to succeed. ■

Is H1N1 the only risk we have to fear in terms of influenza virus? Absolutely not. There are many other candidates to consider, and they might all emerge.
