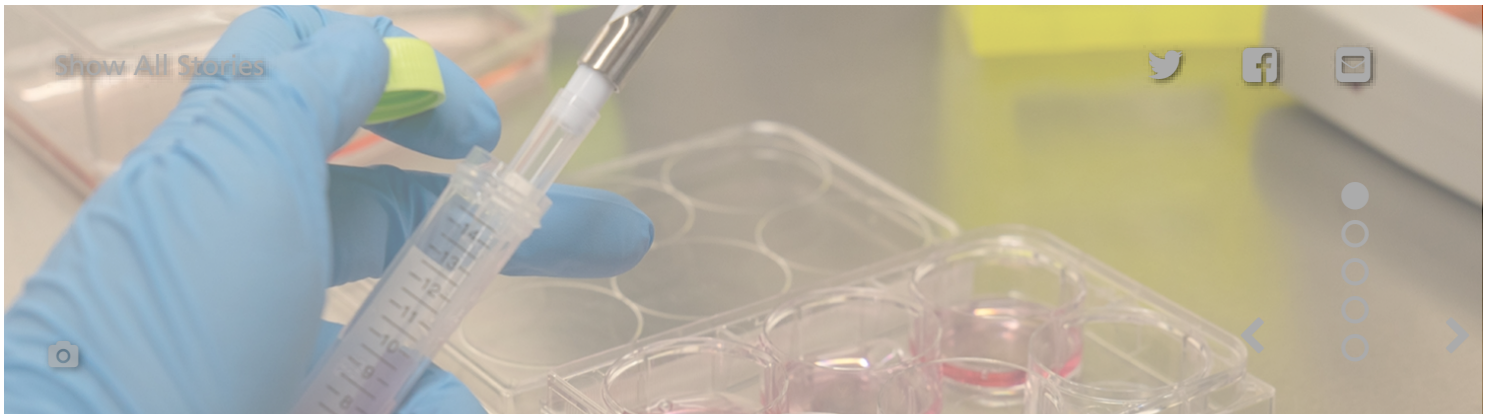

Viruses, Known and Unknown

Gary Whittaker tracks viruses that cause diseases in humans and cats—from the flu to the deadly FIPV feline disease.

Featured

Gary R. Whittaker
Microbiology and Immunology, College of Veterinary Medicine

by Jackie Swift

Year after year, new strains of influenza evolve. The past year's immunization becomes useless against the current year's virus, and scientists must create a new flu shot. Then, dangerous viral diseases like severe acute respiratory syndrome (SARS) and Ebola, seemingly appear from out of nowhere.

What's going on? How does the flu outpace our ability to contain it? How do previously unknown viruses emerge as pathogenic, able to cause disease in humans and animals?

"The way a virus changes and becomes pathogenic is often linked to how it enters a cell," says Gary R. Whittaker, Microbiology and Immunology, who studies influenza as well as emerging and virulent viruses, such as coronaviruses and Ebola. "The viruses I study all have membranes or envelopes. Cells have the same membranes, so for the virus to enter a cell, those two membranes have to fuse. Viruses have dedicated proteins, called spike proteins, to do this. I'm trying to link that mechanism of membrane fusion to changes in the viral genome that alter the spike proteins and allow the process of fusion to change."

Coronaviruses, Causing Diseases in Human and Cats

These days, Whittaker is especially focused on coronaviruses—a family of viruses that infect a wide range of animals, including humans. There are six known species of coronaviruses that cause human illnesses, such as SARS, which became a world epidemic in 2003, and the recently emergent Middle East Respiratory Syndrome (MERS). Whittaker is tracking mutations linked to spike protein activation in SARS and MERS, as well as in a deadly feline coronavirus called feline infectious peritonitis virus (FIPV).

"We're starting to make correlations between what happens in humans with SARS and MERS and what happens in cats with FIPV," he says. "The basic mechanisms of fusion are the same for all these viruses, but the nuances are different in different species. We're looking across species for common themes."

The Deadly Cat Virus, FIPV

FIPV arises from a mutation of a different cat-specific coronavirus, feline enteric coronavirus (FECV), which is benign. Cats become infected with FECV through contact with the feces of another infected cat, but the virus usually causes no symptoms. In five to ten percent of infected cats, FECV mutates into a fatal form of the virus, becoming macrophage tropic (using the cat's white blood cells to spread systemically through the body), ultimately causing the clinical symptoms of feline infectious peritonitis (FIP). There is no reliable test for FIP, no treatment, and no vaccine.

The Whittaker lab collaborates with Susan Daniel, Smith School of Chemical and Biomolecular Engineering, and Jack H. Freed, Chemistry and Chemical Biology, to study the structural chemistry of coronaviruses, including FIPV, and with Elizabeth A. Berliner, Population Medicine and Diagnostic Sciences and director of shelter medicine, to identify and secure samples from ill cats. Together with the Cornell Animal Health Diagnostic Lab, they are also working on a diagnostic test for the disease. "We're trying to track the key mutations that convert the benign virus into FIPV," Whittaker explains. "The conversion

seems straightforward, but I suspect it's like cancer. An accumulation of mutations, more than one, is what finally makes the virus deadly."

The way FIP develops, using the cat's own immune system to attack the body, is unlike other viruses. "Dogs have the same coronavirus, but it very rarely turns deadly," says Whittaker. "Humans, too, have coronaviruses that, if you look at basic structural biology and biochemistry, are almost no different from a cat coronavirus. But this doesn't happen in humans. Why not? There's clearly something different about the cat immune system. We'd love to know what that is so we can feed that information back into our study of human coronaviruses."

Influenza, SARS, and Ebola Viruses

Whittaker began his study of viruses with influenza in the early '90s. When SARS appeared in 2003, he took his expertise with influenza and used it as a stepping stone to SARS. "I asked, 'how is SARS similar to or different from influenza,'" Whittaker says. "I like to draw analogies across different viruses and compare function across virus families to see what we learn. That's been very productive. Now we're trying to do that with Ebola, as well. We're looking at the function of the Ebola virus, comparing the virus to coronaviruses and influenza, seeing how it changes over time, trying to gain some insights."

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To study viruses such as SARS and Ebola, Whittaker works with the Daniel Group to create pseudo particles, an engineered benign virus that looks like the target virus on the outside but with differences on the inside that prevent it from propagating. The pseudo particle virus can fuse with a cell, thus infecting it. "We've recreated the whole entry process in a controllable environment in the lab," says Whittaker. "Susan set up a platform recreating a cell on a surface, and we can add in and take out all the components of the virus and the cell independently. Like a car engine, we can dismantle it and put it back together again to see how it works."

Whittaker is interested in the basic biology of the viruses he studies. In particular, he focuses on the process of protein activation that results in the virus and the host cell membranes fusing, thus infecting a cell. Structurally, a virus has a number of proteins that protrude from its surface like spikes. Each spike protein is made up of a head and a stalk. The head binds with a receptor on the host cell, then an enzyme known as a protease exposes a

fusion peptide in the stalk, which is a key trigger for membrane fusion. When viruses mutate, the spike protein head changes. This is why last year's influenza vaccination won't work on this year's flu strain. "Our immune systems normally see the head," Whittaker explains, "and that's what's changing every year in the virus. What doesn't change is the stalk."

Creating Vaccines

Whittaker would like to create vaccines for the viruses he studies. "One trick is to design the vaccine to target the spike protein stalk instead of the head," he says, "But in the case of influenza, that is very difficult to do. Now that we know influenza's structure, we see that the head and the spike are intertwined. It's very hard to separate them out. With the coronavirus, though, the stalk is easier to target by itself. New data on the coronavirus structural biology has allowed the design of new vaccines that we're starting to test now. If you create a vaccine that works against the stalk, then even though new coronaviruses will emerge, you've already got a vaccine. In a way, you're vaccinating against viruses that don't even exist yet."

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