When viruses cause disease and make local, national and international news, most of us react with some anxiety, take precautions to prevent or limit contact with the virus and adopt a heightened awareness of symptoms. When Professor John Morrey and his colleagues at Utah State University’s Institute for Antiviral Research hear and read stories of dangerous emerging or recurring diseases, it’s rarely “news” to them, but it brings a renewed urgency to their work.

“When people ask ‘How’s your work going?’ I tend to always look ahead and think of the challenges and needs instead of looking back and seeing our successes, and we’ve had some great successes,” Morrey, the institute’s director, said. “There is always more to do. We always need more data, more ideas, and there are always more grants to write, more papers to write, more things to understand.”

Morrey can be forgiven for focusing on the challenges. When your work is studying viruses, you may experience some exciting breakthroughs, but you are never really finished.

The institute’s team includes seven lead investigators who are Department of Animal, Dairy and Veterinary Sciences faculty members, six PhD-level senior research associates, and several full-time and student technicians. The viruses and diseases they study—think influenza, hanta, dengue, West Nile, chikungunya, SARS and Zika—could comprise an international “Most Not Wanted” list. The researchers don’t discover new drugs, they test possible treatments in cell culture and animal models, investigate basic mechanisms of how viruses function and cause disease and search for ways to disrupt a viruses’ particular ability to do damage.

Doing basic biological research is important, but not filled with daily, flashy “Eureka” moments. However, without basic research the development of drugs, vaccines and tests for diseases would never happen. For example, the researchers’ discovery of the ways in which viruses like West Nile infect the brain stem and cause respiratory problems is important because it gives drug developers better targets for treatments and vaccines.

The team reached a notable milestone in 2016, surpassing $100 million in grants and contracts since the institute was founded in 1977. But don’t go looking for them in a gleaming, high-profile research center. Most of their work goes on in secure laboratories with up-to-date equipment and protocols, but the modest surroundings belie the caliber of research that goes on there every day.

To Morrey, surpassing the $100 million mark in grant funding represents the group’s collective work and “the many pharmaceuticals in which we have played a part, and seeing them used by people around the world to fight viral disease and improve lives.”

Viruses in the Lab

Studying viruses in cell culture can tell scientists a great deal, but animal models play crucial roles in understanding viruses and testing possible treatments. Research Associate Professor Justin Julander explained that the complexity of the body, whether human, mouse or hamster, can’t be replicated in a petri dish or flask. Experiments in cell culture are
important for targeting and measuring some responses, but cultures don’t replicate nearly countless variables like neuron function, respiration and immune response.

“We do everything we can to limit our use of animal models,” said Research Professor Brian Gowen, who teaches virology in USU’s School of Veterinary Medicine. “But ultimately, if we just look at activity at the cellular level we cannot understand the complexity of, say, an antiviral treatment that stimulates a beneficial host immune response or that causes an excessive response and results in vascular leak.”

Studies in animal models are important steps on the path to treating humans and running complex and expensive clinical trials of vaccines and drugs in humans. However, mice and hamsters are not naturally susceptible to viruses that infect humans.

Associate Research Professor Bart Tarbet pointed out that a key reason the researchers can do their work is the institute’s colony of mice with specific genes “knocked out” to make them receptive to virus infection. Colleagues at USU also recently developed a first-of-its-kind, genetically engineered hamster that is proving valuable in the search for Zika virus treatments. Tarbet’s lab works with genetically engineered mice in the search for a new model for treatments of enterovirus D68 (EV-D68). The virus is one among a family that includes polio and more than a 100-non polio viruses, and has caused illness that the Centers for Disease Control and Prevention has tracked since 1987. But in 2014, there was a spike in the number and severity of EV-D68 cases. Most troubling though was that some people developed a polio-like neurological disease, not just the usual respiratory infection that causes problems primarily for the very young, the very old and people with asthma. With funding from National Institutes of Health (NIH), Tarbet’s lab is focused on developing a reliable testing model, and will follow that with 2 years of evaluating possible treatments.

It’s important to note that most drugs don’t make the cut from cell culture to tests in animal models and even fewer go to clinical trials.

“For example, three years ago the institute screened over 10,000 drugs to treat influenza in cell culture,” Tarbet said. “Of those, fewer than 2 percent showed activity against the virus and just those few were considered for testing in animal models.”

Julander said because it costs millions of dollars to develop a new drug and bring it to market, the institute’s team feels fortunate to be doing work at the university where they are not tied to a company’s bottom line. Morrey added that some people believe that any scientist who associates with the pharmaceutical industry has been bought off.

“The fact is, the data we generate is completely unbiased, and whether it’s good news or bad news for a particular treatment, they get whatever we learn,” Morrey said.

**Challenges: Past and Present**

Battling established and emerging virus diseases is a complicated task for many reasons, some due to the nature of the viruses themselves and some because of the actions of people and animals they affect.

“One of the things that makes viral infections so difficult to treat is that viruses rely on the host’s cells for growth,” Morrey said. “It is the biggest challenge in developing therapies. Viruses rely on the machinery of the cells they infect. That is not the case with bacterial infections because, with a couple of exceptions, bacteria live outside our cells. So some of the conceivable approaches to eliminating a virus also eliminates the host’s cell. Virologists like to do better than that and find very specific, unique viral processes that can be targeted so the cell is not harmed, but the virus is eliminated.”

Another vexing characteristic of viruses is their ability to mutate, adapting to new surroundings or drug challenges. This ability allows viruses to expand their ranges, cause infection in new ways and become less or more virulent. It also means that once researchers have characterized a virus and how it works, the virus may have already changed. When viruses change in ways that make them more virulent or easier to transmit, the results can be devastating.
Such was the case with Spanish flu in 1918-1919. That strain of influenza—a subtype of avian influenza H1N1—became more deadly and easier to spread, explained Research Professor Dale Barnard. As a result, 20-40 million people died in a worldwide pandemic, far more than the 17 million who were killed in combat in that final year of World War I.

“Sometimes research can be driven by fear and media attention,” Barnard said. “But the experience of Spanish flu is one reason we are so vigilant and put great effort into understanding newly emerging viruses. We want to be able to intervene before something like that happens again.”

Another public health challenge is that people are very mobile today and can transport viruses to new locales with greater speed. Barnard said that prior to the mid-20th century the geographic range of two viruses he studies, Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS), would have been quite limited. But today planes transport passengers and viruses between countries and regions of the world in a matter of hours.

Barnard and his team are at work screening antiviral drugs for effectiveness against MERS, coronavirus infections and respiratory syncytial virus (RSV) among other respiratory viruses. He observed that there are tools for drug development and testing that make the work faster than it was at the start of his career, but drug discovery hasn’t accelerated as rapidly as viruses’ abilities to spread.

Changing climate presents another challenge. Many virus-caused diseases are zoonotic, meaning they arise in animals and spread to humans. Mammals, birds and insects, like the now-famous, Zika-carrying *Aedes aegypti* mosquito, act as vectors for spreading viruses. Their ranges may expand or at least change as the climate and their habitats change.

Among other zoonotic diseases the team studies is hantavirus. Research Professor Brian Gowen studies several hemorrhagic fever viruses including hantavirus and others that are mostly exotic to the U.S. While he is usually focused on Arenaviruses, Gowen is also at work on Rift Valley fever, which is caused by a Bunya virus. Rift Valley fever has significant agricultural impact in sub-Saharan Africa where it can cause “abortion storms” in cattle, sheep and camels, affecting up to 90 percent of pregnant animals in a herd or flock. It also infects humans via bites from infected mosquitoes and can be fatal.

“We are studying a new technology that inactivates the virus with a new compound, but preserves the native conformation of the viral surface protein so it elicits a stronger immune response,” Gowen said. “And the fact that the virus is inactivated means you don’t have the risks associated with attenuated vaccines. We know the compound inactivates the virus, but the quality control is rigorous and making sure every particle is inactivated is more challenging than you might think.”

If proven effective, the technology his lab is testing could be used to create safer, more effective vaccines against a number of viruses.

**Zika Virus in the News**

By the time stories about Zika virus hit mainstream media in the U.S. this spring, the Institute for Antiviral Research had already been at work with the virus for several months with funding from the NIH. The team of researchers has since demonstrated in mice and hamsters that the virus does transfer from mother to fetus and cause growth restriction and other developmental anomalies at various times during fetal development. That gives the team good models for studies, including evaluation of a possible vaccine and use of therapeutic antibodies that may stimulate the immune system to attack the virus.

Julander, who leads the institute’s Zika virus research, said they have seen size differences and ocular deformities in mouse pups born to dams that were infected with Zika virus. It appears that infection during the first trimester of pregnancy is the most troubling.

“We previously found with West Nile virus that infection in the first trimester is the most critical time for abnormal fetal development and we see the same thing with Zika,” Julander said. “We need a vaccine to protect against Zika virus because more than 80 percent of people who get the virus have no symptoms or develop only a mild illness. The key to
fighting most viral infections is starting treatment when the viral load is small. No one is going to go to the doctor because they got a mosquito bite, so by the time someone feels symptoms the virus has become well established.”

Though both West Nile and Zika virus are spread by mosquitoes and can cause neurological disease, Morrey said there are key differences between two. Zika virus can be spread from one infected person to other people via mosquito bites. It can also be sexually transmitted. West Nile does not spread in those ways.

“Zika can mutate, and it does” Morrey said. “It’s very interesting because you can get a blood sample, but can’t culture it by some of the expected cell culture techniques because its genes have already changed in the time it took for viremia to occur (the virus to develop in the bloodstream). The viruses actually change when they go from mosquito to human and from human to mosquito, but Zika does this in a more obvious way.”

Earlier this year, members of institute’s staff and additional ADVS faculty members and technicians published the genome sequences of three primary Zika strains to further help researchers around the world in the search for a drug to combat the virus.

**What’s Next?**

The faculty members at the core of the institute’s research team have “self-selected” to focus on specific kinds of virus infections. But the relatively small size of the team means ideas easily cross-pollinate, and discussions in lab meetings or in the hallway may lead to new questions, answers and shared expertise. There is no shortage of known viruses on which to focus so the research leaders, technicians and students go on working, networked with the larger scientific community, and always watching for signs that a new virus may be emerging, or a well-known one resurging.

Morrey said one frustration is that the procedure for approving new drugs does not currently work well for fighting emerging diseases. Regulations require that clinical trials include large numbers of people. The problem is that cases of people infected with an emerging disease are often sporadic and geographically far apart, so it is extremely difficult or impossible to include enough people in a single treatment trial.

“It has prevented the development of some drugs that could be useful, but the FDA is bound by law,” Morrey said. “The law needs to be adapted for emerging diseases like Zika and West Nile virus. It will require political will to make those changes. It may require loosening some standards in order to accomplish the studies, and no one wants to be blamed for doing something that might not be safe.”