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The Buzz Behind the Bite

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THE BUZZ BEHIND THE BITE

How scientists tackle infectious diseases and the mosquitoes that spread them

By Jennifer Tidball
we need to prepare,” said Dana Vanlandingham, assistant professor of virology. “It’s eradicate — health threats such as malaria or Zika virus. They hope to make it easier to manage — and possibly someday No matter the virus and no matter the disease, scientists agree: Advanced research is the health of billions of people across the world.

What’s next? The possible list includes names like Japanese encephalitis virus, yellow fever viruses or Cache Valley virus aims to increase limited knowledge of the ... Research Institute — on an emerging type of Japanese

scientists are providing skills and expertise for further studies with Zika virus and Cache Valley virus ... University biologist Kristin Michel has a specific target in mind: the mosquito immune system.

Michel, associate professor of biology, and Bart Bryant, research assistant professor of biology, are studying Anopheles gambiae, the mosquito species that is the main transmitter of malaria in sub-Saharan Africa. Their goal is to identify ways to eliminate pathogens and parasites in the mosquito before it can transmit them to humans.

Michel and Bryant approach their work like a puzzle: Figure out what molecules are in the immune system, how they function and what immune responses they control. Then determine how these pieces fit together to contribute to the mosquitoes’ immunity as a whole and how they relate to the pathogens.

Their NIH- and USDA-funded research has determined the key role of parasites and their immune responses in controlling, and understanding, immune immunity as well as the role of hemocytes in cellular immunity.

Michel’s team recently showed that in the first 24 hours after a mosquito feeds, the immune cells — or blood cells — increase in a mosquito’s immune system as it prepares to fight any pathogens the blood contains. “Imagine if every single time you eat a meal, all your white blood cells were on an emergency response to be a massive infection or inflammatory response, and mosquitoes do that every time they take a blood meal,” Michel says. Bryant is using NIH funding to develop a gene therapy-type approach to turn off specific genes in specific tissues to Aspergillus gallop.
VIRULENCE OF VIRUSES

Researcher Scott Huang knows firsthand the effects of infectious diseases. Huang is from Taiwan, where Japanese encephalitis, yellow fever, and dengue viruses are endemic pathogens.

“Once these viruses are introduced, there is no way to get rid of them, because they can be present in mosquitoes or susceptible hosts,” said Huang, a university researcher who specializes in infectious diseases and pathology. “These viruses can infect humans and animals without showing symptoms, which makes them some of the hardest targets to control.”

That’s part of what motivates Huang to study mosquito-transmitted viruses. The Biosecurity Research Institute, a biosafety level 3 facility where scientists can safely study animal and human infectious diseases, helps Vanlandingham and Huang collaboratively are studying Zika virus, Japanese encephalitis virus, yellow fever virus and Cache Valley viruses with researchers from institutions in the U.S. and the U.K.

The university scientists were part of a multi-institutional team that recently developed a possible new Zika virus vaccine and published the results in Nature. The immunogenic vaccine potentially could protect against the virus once one dose and could become a tool to prevent future outbreaks, said Huang.

The Biosecurity Research Institute team played an important role during the Zika virus public health emergency in 2016. The institute has facilities needed to study mosquito-borne viruses and understand how they become infected with Zika virus.

Through a research project with Ross University, along with researchers at the National Institutes of Health, the scientists are providing skills and expertise for further studies with Zika virus and other mosquito-borne viruses.

But the university work extends to other emerging viruses as well.

Higgs, Vanlandingham and Huang are performing several studies supported by the National Bio and Agro-defense Facility Transition Fund and the Bone Health Information Center — an online boils database — part of the epizootics of Japanese encephalitis virus. Their studies are the first U.S. studies of Japanese encephalitis since the 1990s, and the researchers also are doing the first studies with the Cache Valley virus that is present in North America.

Japanese encephalitis virus is found primarily in pigs and birds in Asia, but it can transmit to humans and cause severe infections, or encephalitis, of the brain. The Japanese encephalitis virus research at the Biosecurity Research Institute is especially important. A new, emerging type killed 14 people in China in 2014. Other older strains of Japanese encephalitis virus currently are circulating in Asia and infect an estimated 67,800 people per year. Although many people in Asia are vaccinated, the virus is not very effective because it is made for the older strain, researchers said.

“As the virus continues to circulate, the threat still remains,” Huang said. “The new strain is just as bad as the old strain. If a strain is going to be introduced to the

THE NUMBERS ARE ENOUGH TO MAKE YOU FEEL ITchy.

Since 2015, more than 43,000 cases of Zika virus have been reported in U.S. states and territories.

Malaria caused an estimated 212 million clinical cases and 429,000 deaths worldwide in 2016.

West Nile virus has infected an estimated 2.5 million people in North America and caused more than 4,400 U.S. cases since it emerged in 1999.

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“We want to better understand what a gene is doing and what its role is in one tissue versus another,” Bryant said. “We’re trying to come up with a unique way to better regulate the expression of a gene.”

A better genetic understanding could help stop the spread of malaria, yellow fever and dengue fever. Scientists could redesign mosquito control strategies while minimizing side effects for the insect.

“Malaria is a global problem,” Michel said. “People agree that the current control methods need to be revised or eliminated for the insect.”

“It turns out that the gut and the surrounding structures — called the basal lamina — are a mosquito’s key defense against viruses. Through NIH funding, Clem and Paranavithana studied the basal lamina and its network of proteins to understand how it can act as a barrier against viruses and how that barrier is disrupted during a blood meal.

“When a mosquito bites a host, any viruses in the blood travel through the mosquito digestive system to the gut. Sometimes viruses are able to escape the gut, infect the salivary glands and shed in the saliva when the mosquito bites another host. Yet other times, viruses are not able to leave the gut and the mosquito does not spread the virus. The biologists want to know how the virus can escape the gut and travel into the main body.

“We previously identified enzymes that were necessary for midgut escape in an insect virus,” Paranavithana said. “We are now investigating whether mosquito-saaved viruses use the same enzymes to facilitate midgut escape.”

Specifically, the researchers are studying Sindbis virus, a mosquito-transmitted virus that can cause mild symptoms in humans, such as fever or a rash. The biologists use an artificial containment level-2 facility to safely study Aedes aegypti mosquitoes.

“By understanding detoxification mechanisms, we will be able to selectively use insects that may be able to control resistant insects, including Zika virus, dengue fever and yellow fever,” Bryant said.

“Many of these diseases are in other countries, but certainly are threatening to come into the U.S.,” Clem said. “With changing climates, some of these mosquito species are expanding their range farther and farther north. There is a lot of public awareness about the importance of these diseases and our research could help the millions of people affected by these viruses every year.”

INVESTIGATING INSECT CONTROL

Of course, a way to keep mosquito-borne disease under control is to control the insects that spread them.

That’s where Kun Yan Zhu, professor of entomology, fits in. His work starts with chitin, a major chemical component of a mosquito’s exoskeleton shield. When insects are not able to produce chitin, they can’t survive. But when insects produce a reduced amount of chitin, they may become more susceptible to insects.

“The exoskeleton is the first defense line for mosquitoes and other insects,” Zhu said. “Chitin biosynthesis is an important target for insect control. We are trying to understand chitin biosynthetic pathways and develop new techniques to prevent chitin production using chemical and genetic approaches.”

Zhu and his team recently patented a form of nanoparticle insect control that uses a genetic chain reaction to prevent mosquitoes and insects from producing chitin.

“Insect control that targets chitin biosynthesis is safer and less likely to affect humans because we do not produce chitin,” Zhu said. Zhu’s research also is addressing another major problem in mosquito control: insect resistance to insecticides. Over time, mosquitoes can become resistant to insecticides, which have to be replaced with newer versions.

Using USDA and other funding, his team is investigating a family of genes that are involved in chitin production. Researchers have found that when beetles, flies and mosquitoes and other insects lack the enzyme that produces chitin, the insects can’t survive. But when insects produce a reduced amount of chitin, they may become more susceptible to insects.

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“By understanding detoxification mechanisms, we will be able to selectively use insects that may be able to control resistant insects, including Zika virus,” Zhu said. “This is an important strategy to control one of the most devastating disease-spreading insects in the world.”
A CLOSER LOOK AT MOSQUITO-BORNE DISEASES

JAPANESE ENCEPHALITIS VIRUS
Japanese encephalitis virus is a rare leading cause of pediatric viral encephalitis, or severe inflammation of the brain. While most human cases are mild, about 1 in 4 unvaccinated young children and pregnant women infected only have mild symptoms, but the severe form that can be fatal if untreated.

CHIKUNGUNYA VIRUS
Chikungunya fever first appeared in the 1950s, but the first transmission in the Americas occurred in 2013 on Caribbean islands. Chikungunya fever is not often fatal, but it can cause fever, muscle pain, headaches and severe joint pain.

DENGUE VIRUS
Dengue fever is the main cause of illness and outbreaks in tropical and subtropical regions. Most infected people have only mild symptoms, but severe cases can cause liver disease and bleeding. Fatalities occur in 20 to 50 percent of severe cases. Severe dengue can cause high fevers, joint pain and mild bleeding. Dengue hemorrhagic fever is a severe form that can be fatal if untreated.

YELLOW FEVER VIRUS
Yellow fever is a rare, mosquito-transmitted virus that can cause mild symptoms in humans, such as fever or a rash. The biologists use an arthropod containment level-2 facility to safely study Aedes aegypti mosquitoes.

GOING WITH THE GUT
When a mosquito bites a host, any viruses in the blood travel through the mosquito digestive system to the gut. Sometimes viruses are able to escape the gut, enter the salivary glands and bud into the salivary glands to reproduce. The biologists want to understand how the mosquitoes become insecticide-resistant.

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Sources: Centers for Disease Control and Prevention, World Health Organization