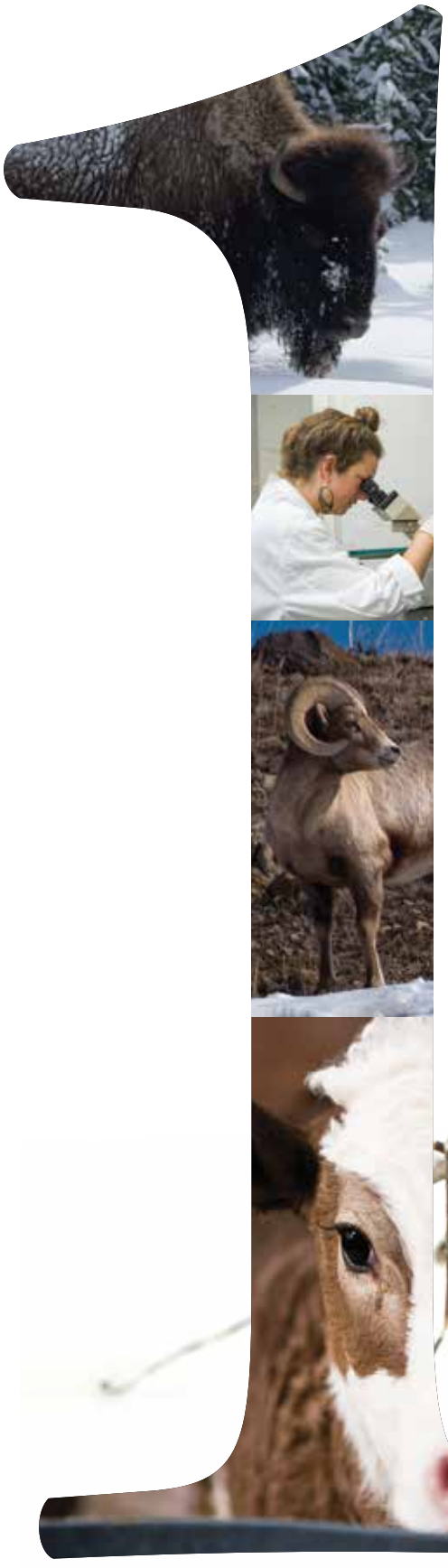

BISON, WOMAN WITH MICROSCOPE, SHEEP KELLY GORHAM
COW, MOSQUITO, BAT THINKSTOCK

meo

MSU scientists lead efforts to study diseases that cross from animals to humans

by Denise Hoepfner

We're in a unique position here at MSU because we have people who study animal health and human health, so we can tap into those resources on each side and make some progress using the knowledge we have of human health and applying it to animals and vice versa.

—Jovanka Voyich-Kane

dicine

In May 2011, a Montana child tested positive for *Coxiella burnetii*, the bacteria that causes Q fever. The source of infection was traced back to goats the family bought from a Washington farm seven months earlier. The Centers for Disease Control and Prevention found goats from the same farm were sold to 21 other farms in Washington, Montana and Oregon, with 16 of 17 goat herds testing positive for *Coxiella burnetii* infection. In animals like goats, cattle and sheep, the bacteria can cause aborted fetuses, stillbirths or births of weak calves, according to the CDC. Some people in contact with infected animals will contract chronic Q fever, which can show up weeks after an acute infection or years later. While most people with acute Q fever recover, some may experience pneumonia, central nervous system complications or inflammation of the lungs or heart tissue.

In 2003 and 2007, more than 200 human cases of West Nile virus in Montana were reported to the CDC. Of those reported cases, 75 in 2003 and 37 in 2007 were neuroinvasive, meaning the virus either reached the brain or the spinal cord, resulting in viral encephalitis or meningitis. Four people died in each of those years from complications of the disease. A virus spread by mosquitoes that contract it from infected birds, West Nile also affects horses. Thirty-two cases of West Nile in equines were reported in Montana in 2013, the third highest total in the nation for that year, according to the Montana Livestock Department.

Every year, outbreaks of infectious diseases originating in the animal kingdom occur in humans around the world. Scientists cite deforestation, changing weather patterns and the ease of air travel as reasons for these sometimes

BIGHORN SHEEP, LAB KELLY GORHAM

Samples in the Jutila lab are placed in a centrifuge in preparation for microscopic study. The Jutila group studies the RNA of bone marrow cells to better understand their immune response to an infection.

new and sometimes recurring threats. Whether these diseases target people or animals or both, the consequences can be devastating, leading to loss of life or, as among agricultural communities in Montana, loss of livelihood.

At Montana State University, researchers in the Department of Microbiology and Immunology, a department shared by the Colleges of Agriculture and Letters and Science, are working across the disciplines of human and veterinary medicine on infectious disease projects that focus on animal and human health.

Mark Jutila, head of the Department of Microbiology and Immunology, said that emerging and reemerging infectious disease agents are an ongoing problem in both animal and human health.

"The estimate is 60 to 70 percent of infectious diseases in humans come from animals; that is what we focus on," Jutila said.

A world-renowned immunologist, Jutila is an instructor in both the WWAMI (Washington, Wyoming, Alaska, Montana and Idaho) cooperative medical program and the WIMU (Washington, Idaho, Montana and Utah) cooperative veterinary medicine program, making him one of a number of faculty members with expertise in both animal and human health.

An indication of the success of this cross-over work is a recent $1.5 million grant from the state of Montana's new large-scale research initiative that has paved the way for a number of projects to reduce the impacts of infectious and inflammatory diseases on human and animal health, all under the umbrella of MSU's "One Medicine" grant.

One medicine

Rudolf Virchow, known as the father of cellular pathology, is credited as saying, "Between animal and human medicine there are no dividing lines, nor should there be."

More than a century after Virchow's death, there is a growing worldwide shift in medicine to consider the correlation between human and animal health by adopting a "one medicine" approach to research. By employing faculty with expertise in either the WWAMI or WIMU programs, and by conducting research in both animal and human medicine, MSU is doing just that.

"We're in a unique position here at MSU because we have people who study animal health and human health, so we can tap into those resources on each side and make some progress using the knowledge we have of human health and applying it to animals and vice versa," said Jovanka Voyich-Kane, associate professor in the Department of Microbiology and Immunology. "In some respects, we are so much more advanced with our animal research…. We can learn from our successes in the animal world and apply them to human medicine."

Jutila noted that some program research focuses on infectious agents that can be transmitted from animals to humans, such as *Coxiella burnetii*. The department also is starting a new project on brucellosis, a bacterial disease that affects cattle, bison and elk and which financially threatens Montana's livestock industry. And Voyich-Kane is working on ways to counter the antibiotic-resistant *Staphylococcus aureus* strains that can cause infections in both humans and animals.

Jutila also is working on a project that uses immune modulators called adjuvants to control bovine scours, a disease that is the major cause of death in newborn calves and results in significant financial losses for cattle producers. Jutila explained that adjuvants can be as simple as dietary or plant products or substances injected into humans or animals to make their immune systems work better.

Jutila's research has applications to Voyich-Kane's work in antimicrobial resistance in bacteria.

"Potentially, if you treat scours with adjuvants that promote an immune response that clears the infection, you could reduce the dependence on antibiotics and therefore decrease the pressure for bacteria to develop resistance," Voyich-Kane said. "It all links together."

Raina Plowright, an assistant professor in the Department of Microbiology and Immunology, said her research of how a pathogen crosses from one species to another puts "one medicine" at the heart of her work.

"One medicine is necessary while you have pathogens crossing species barriers," Plowright said. "Wildlife or domestic animals into humans—it's important we understand the pathogen and host relationship at all its various interfaces, and the environment."

While research is often thought of as a solitary pursuit, Plowright says it is becoming more important to connect the experts in different disciplines and areas of research and pull their findings together.

"To understand pathogen spillover from animals to humans, you have to be

able to understand what is happening in the animal reservoir hosts, how the pathogen is surviving in the environment, how human behavior facilitates exposure to the pathogens, and how pathogens overcome a series of barriers within humans, such as the immune system," she said. "That requires animal ecologists, disease ecologists, epidemiologists, psychologists, social scientists and a diverse group of disease biologists from microbiologists to immunologists. You can study all these processes in isolation, but if you don't bring them together, then it's very difficult to make the appropriate public health intervention. The one medicine approach is trying to bring in all those various perspectives to understand the big picture and make sensible interventions."

Here are a few MSU researchers and the work they are doing to learn more about one medicine.

Pathogen spillover

While scientists know that the majority of emerging diseases are zoonotic, meaning they can be passed to humans through an animal reservoir, not much is known about the way a pathogen crosses from one species to another.

Through her work on Hendra virus, one of several fatal zoonotic viruses spread from bats to humans in other parts of the world, Plowright studies the phenomenon known as spillover. While the bat-borne Hendra virus is not a large threat in the United States, Plowright's research could lead to an understanding of spillover, something crucial to all human and animal health.

"Although we have huge public health challenges from zoonoses such as Ebola, H1N1 influenza, or SARS (severe acute respiratory syndrome), there are also ongoing challenges from endemic zoonoses, like salmonella, *E. coli 0157* and leptospirosis," Plowright said. "These pathogens affect people and livelihoods on a day-to-day basis in many parts of the world. Even though zoonotic pathogens are a big public health threat, we know very little about how pathogens filter through the ecological systems to infect humans."

Plowright says understanding the dynamic of these pathogens within the animal reservoir populations (such as bats for Hendra virus) is essential to attaining a better understanding of how they spill over to domestic animals and humans.

Some pathogens can even survive for a period of time in the environment, making it possible for humans and animals to become infected without direct contact from the original source. Understanding how these pathogens survive outside the host is especially important to controlling outbreaks.

Plowright mentions Q fever and leptospirosis, a disease that can survive in water up to a year and is spread by rats. Outbreaks of both have occurred when pathogens from a livestock source miles away were carried by wind.

Spillover threatens not only human health; the transmission of disease between species is also a profound issue for livestock and wildlife heath.

Plowright studies pathogens that spill over from domestic animals to wildlife, causing conservation and livestock management challenges. An example is her ongoing study of bighorn sheep pneumonia, a disease that jumps from domestic sheep into wild sheep and suppresses wild sheep populations in Montana and across the West.

"The phenomenon of spillover is really important to Montana and in understanding zoonotic diseases," Plowright said. "We have all sorts of zoonotic infections we need to be concerned about—many of them are studied in this department."

The one medicine approach is trying to bring in all those various perspectives to understand the big picture and make sensible interventions.

—Raina Plowright

West Nile virus

Why do some people who contract West Nile virus experience minor flu-like symptoms, while others suffer potentially deadly illnesses such as encephalitis and meningitis?

That's the question behind Matt Taylor's research of the virus, which is spread to humans through infected mosquitoes.

"What we're trying to do is understand one of the basic principles behind (the virus') ability to cause diseases," said Taylor, an assistant professor in the Department of Microbiology and Immunology. "West Nile oftentimes causes very benign illness in most healthy people, but in some individuals it can invade the brain."

The virus first crossed the Mississippi River in 2003 and was a strong epidemic throughout the Dakotas, also making its way into Montana. Although Montana hasn't had many cases, some of the cases were severe. Taylor said that while Montana has the potential to support an epidemic, it is unlikely that it will become endemic, which is when the virus is seen every year.

Taylor began researching West Nile after some surprising findings during his research on the Herpes Simplex 1 virus.

"We observed in our Herpes virus work that in one direction of spread, very few particles are transmitted between cells, so there's this bottleneck on the size of the population that's transmitted to the brain," Taylor said.

Taylor explained that the West Nile researchers are trying to make similar observations as they track the population of viruses that move between cells in the nervous system because, like herpes, West Nile has the potential to cause

PLOWRIGHT SHIRLEY PLOWRIGHT

Raina Plowright researches diseases carried by bats.

Jutila lab research associates Kelly Christensen, left, and Deann Snyder store cell lines in canisters cooled by liquid nitrogen.

PHOTOS KELLY GORHAM

severe infection of the brain in the central nervous system.

He said the scientists also are examining the basics of West Nile virus and how it activates the immune system and whether the immune system activation can be changed to alter the spread of infection.

A West Nile vaccine isn't currently an option for people, Taylor said, because the risk of a bad reaction from a vaccine is greater than the odds of contracting the virus.

More at risk of West Nile virus in Montana are horses, and a spike of equine deaths from the virus was reported in the state in 2014. However, a vaccine for horses is available and is recommended by the American Association of Equine Practitioners.

"If we can just understand in general how this virus transmits within neurons, we can understand the human disease and the equine disease," Taylor said.

He also points out that many of the viruses in the news today share a common denominator.

"A lot of these viruses—Zika, West Nile, Chickungunya, even herpes, for that matter—all have the same capability of infecting the nervous system and causing dramatic illness and disease," he said. "This is a very understudied aspect of their pathogenesis."

'Blinding' infections

Once thought to be a problem specific to hospitals and nursing homes, infections caused by drug-resistant *Staphylococcus aureus* are now being picked up in the day care, the locker room and other places that involve skin-to-skin contact or where people share equipment and supplies. These community-associated strains cause a variety of diseases ranging from mild skin and soft-tissue infections to invasive diseases such as sepsis and endocarditis, said Voyich-Kane.

"Twenty years ago, *S. aureus* was really a problem occurring in hospitalized patients," Voyich-Kane said. "Now, it is a common infection occurring in healthy individuals without any underlying health issues."

Voyich-Kane studies how *Staphylococcus aureus* initiates infection in an attempt to identify targets for vaccines and therapeutics. Her lab focuses on community-associated methicillin-resistant strains of *S. aureus*, commonly known as MRSA. MRSA causes more than 12 million skin and soft-tissue infections per year in the United States.

MRSA is also a predominant cause of mastitis in cows, the most costly disease of the dairy industry, and one that has been a problem in Montana. It also can be transmitted between animals and humans.

The observation that healthy individuals were contracting *S. aureus* infections prompted the research into how *S. aureus* gets past a healthy immune system to cause disease.

"If we fully understand how *S. aureus* initiates infection by identifying the vulnerabilities of our early immune response to the bacterium, we can exploit this information to develop therapeutics that give the immune system the advantage," Voyich-Kane said.

Voyich-Kane explained there is a form of reciprocal communication between organisms and *S. aureus* and how they respond to each other.

"For a long time we were mammalian-centric and thought the host was choosing how to respond to the bug, and in reality pathogens are just as attuned to us as we are to them," she said. "They sense us to a great level of specificity, and they respond with precision to the host challenge."

One area of Voyich-Kane's research investigates "blinding" *S. aureus* by removing a sensory system that it uses to sense a predominant innate cell called the neutrophil.

"Basically, you catch *S. aureus* off guard, with its defenses down, and when it can't sense this cell, the host has the advantage and can respond appropriately to clear the infection," she said.

Voyich-Kane said such research may help fight the problem of antibiotic resistance in *S. aureus*.

"If we don't have to use antibiotics as frequently—for humans or livestock—the pressure on the pathogen to develop resistance decreases." ▪

MSU scientists are studying brucellosis, an infectious disease caused by the *Brucella* bacteria, which can spread from animals to humans. The disease affects cattle, bison and elk.