On-farm study targets Q fever

BY MAURICE HARVEY

For a disease that can have a drastic and detrimental effect on animal production – and can also make humans ill – little is known about Q fever's prevalence in Ontario's small ruminant farms. The causative bacteria *Coxiella burnetii* can infect any species of animal, including mammals, birds and insects, but sheep, goats and cats appear to express disease most commonly, usually as abortion and stillbirth. Farm workers usually contract the disease when caring for animals during the birthing process. Signs of the disease in humans include fever, headaches and pneumonia. Although most infected people don't become ill or experience mild illness, some become severely ill and may require hospitalization.

Researchers at the Ontario Veterinary College are trying to find out more about this disease. Profs. Paula Menzies and Andria Jones, Population Medicine, are working with Dr. Jocelyn Jansen of the Ontario Ministry of Agriculture, Food and Rural Affairs and master's student Shannon Meadows to learn how many small ruminant operations in Ontario are infected with Q fever, the effects of that infection on animal health, and the risk factors that influence Q fever's spread to humans.

"This is the first time our research has directly involved human disease, and we're very excited about it," says Jones. "Once we have an understanding of how much risk is associated with Q fever in Ontario's sheep, goats and human farm workers, as well as the factors that put us at risk, we'll be able to take a proactive stance to keep our province healthy."

For her part, Menzies has seen first-hand how this disease can affect farm families and the animals they care for. "We believe that this research will give an excellent grounding on understanding the risks in order to make sound recommendations on the control of Q fever," she says.

The risks associated with Q fever are illustrated by the events in the Netherlands in 2009. There, a Q fever outbreak led to thousands of cases of the disease in humans – including several deaths – as well as the culling of more than 60,000 pregnant goats from infected dairy herds. In addition, lifetime breeding bans were levied against infected herds and vaccination against the disease became mandatory.

In Ontario, researchers will determine how many infected sheep and goats exist in the province's livestock and dairy farms by collecting and testing blood samples, looking for antibodies to *C. burnetii*. In total, 150 farms throughout southern Ontario have been randomly selected, with more than 5,000 animals included in the test.

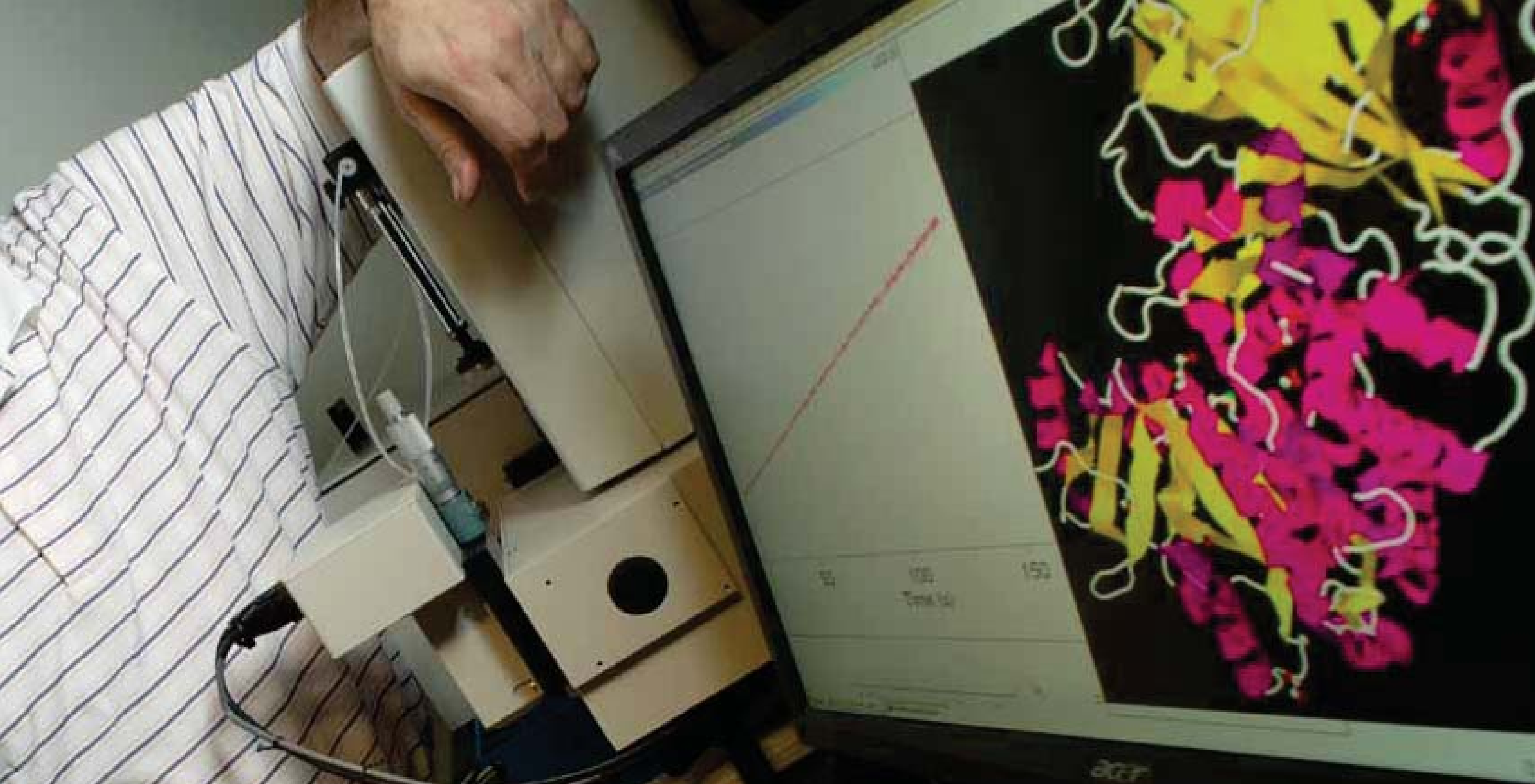
As well, each participating farm will have up to four workers randomly selected for blood testing and participation in a survey about factors that predispose people to contracting the disease, such as their overall health, lifestyle, and the amount of time they spend on a farm.

This research is funded by the University of Guelph's Animal Health Laboratory, the Ontario Sheep Marketing Agency, the Ontario Ministry of Health and Long-Term Care and the Ontario Agency for Health Protection and Promotion.

Cue the inhibitor

Biochemists fight antibiotic resistance through new approaches to understanding toxins

BY ROBERT FIELDHOUSE



X-ray crystallography allows Prof. Rod Merrill (right) and graduate student Robert Fieldhouse to examine the structure of the toxins produced in their lab.

Antibiotic resistance is on the rise, making harmful bacteria armed with protein toxins increasingly worrisome, says a University of Guelph professor who's trying to find new ways to identify these toxins, figure out how they work and disarm them.

Prof. Rod Merrill, Molecular and Cellular Biology, and his team want to unlock the structural and functional mysteries of several toxins that enter target cells, alter key proteins and cause cell death – leading to disastrous outcomes for the infected individual.

They know that many bacteria use the same attack strategy, including *Vibrio cholerae,* which causes cholera; *Bordetella pertussis*, which causes whooping cough; and *Corynebacterium diphtheria*, which causes diphtheria. Understanding toxin structure and function makes it possible to find small molecules that can bind to – and inactivate – them.

"Bacteria wreak havoc using an arsenal of virulence factors, including protein toxins," says Merrill. "We're trying to figure out toxin structures so we can find inhibitors that will make people less dependent on antibiotics, which are becoming less and less effective."

To do so, they produce a protein toxin in the lab, using safe bacterial strains, and then purify it. The pure toxin is then mixed with chemicals under specific conditions that allow the toxin to form crystals – similar to making rock candy from sugar crystals. But finding the right conditions for the mix is the challenge.

Enter Dr. Hee-Won Park, a collaborator at the University of Toronto's Structural Genomics Consortium. He's an expert at finding crystal conditions; he uses many toxin variants and various chemical environments to test for crystals in a high-throughput fashion.

Then the researchers shoot the crystals with X-rays. The crystals scatter the X-rays in a specific pattern that allows Merrill and Park to calculate a toxin's three-dimensional structure with the help of computers. These structures allow them to find complementary small molecules that bind the toxin and physically block it from binding specific cell components. These small molecule inhibitors may one day prevent the toxin from causing harm.

Merrill and his team test the toxins (and the inhibitors that block their activity) with yeast cells. The yeast normally die from the toxin. If they don't, the researchers know the inhibitor is working.

Already, Merrill has found several excellent inhibitors against *Pseudomonas aeruginosa* exotoxin A and cholix, a new toxin he and collaborators found in *Vibrio cholerae*.

Next, Merrill and his team hope to track the toxin's motions as it reacts with its target, using advanced X-ray technology that produces many images.

"We'd like to make a movie of the toxin in action," says Merrill. "Fully understanding the mechanism will lead to the best possible inhibitors and, ultimately, the best treatments."

The University of Guelph research team includes graduate students Danielle Visschedyk, Zachari Turgeon, Adin Shniffer and Rob Fieldhouse; post-doctoral fellows Amanda Rochon and Ravi Ravulapalli; technicians Dawn White, Caroline McGregor, Patrick Edwards and Gerry Prentice; and undergraduate students Rob Gale, Sarah Legree and Alissa Cait.

Collaborators include Drs. René Jørgensen of Carlsberg Laboratory in Denmark and Roland Pfoh of the University of Toronto; Profs. Dev Mangroo of the University of Guelph, and Emil Pai and Matthieu Schapira of the University of Toronto; Norman Oppenheimer of the University of California at San Francisco; and Carmay Lim of Academia Sinica in Taiwan.

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