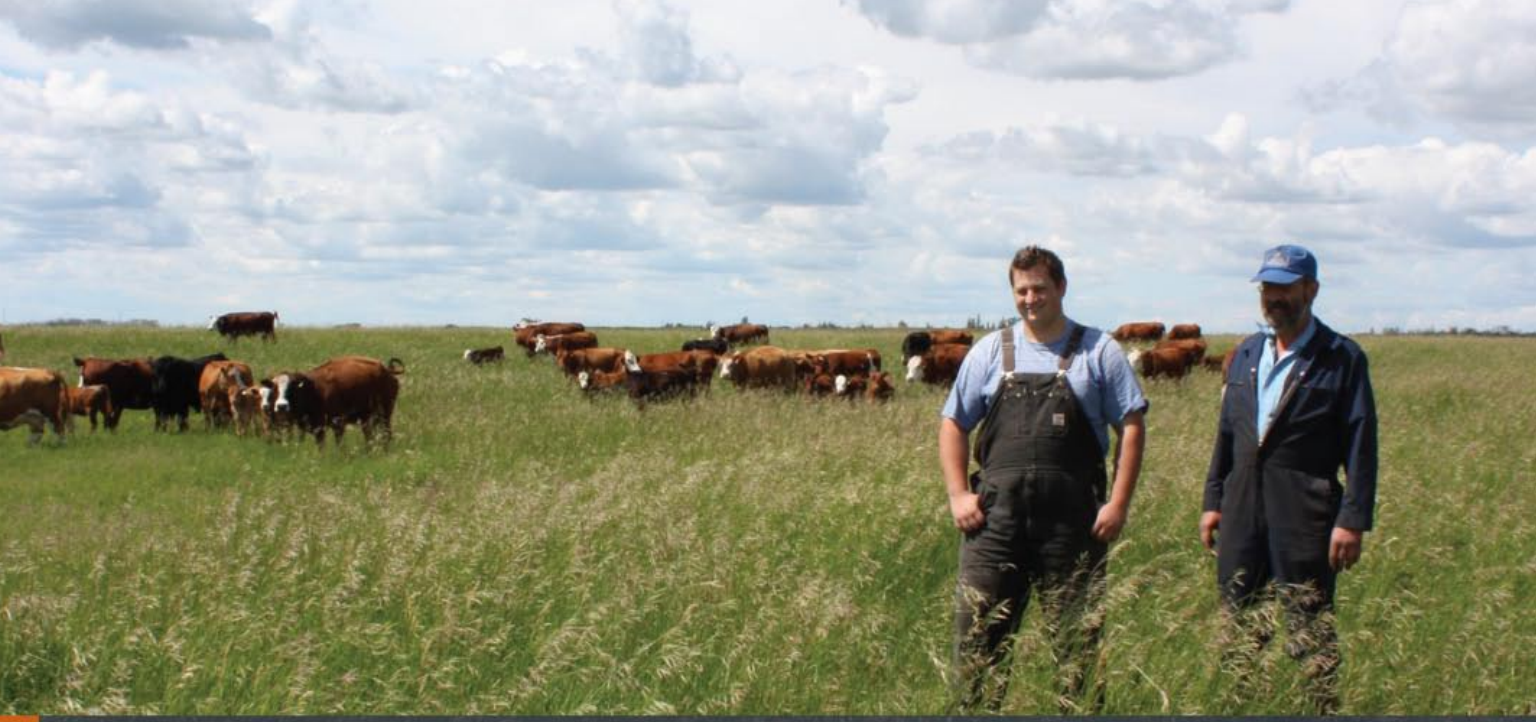
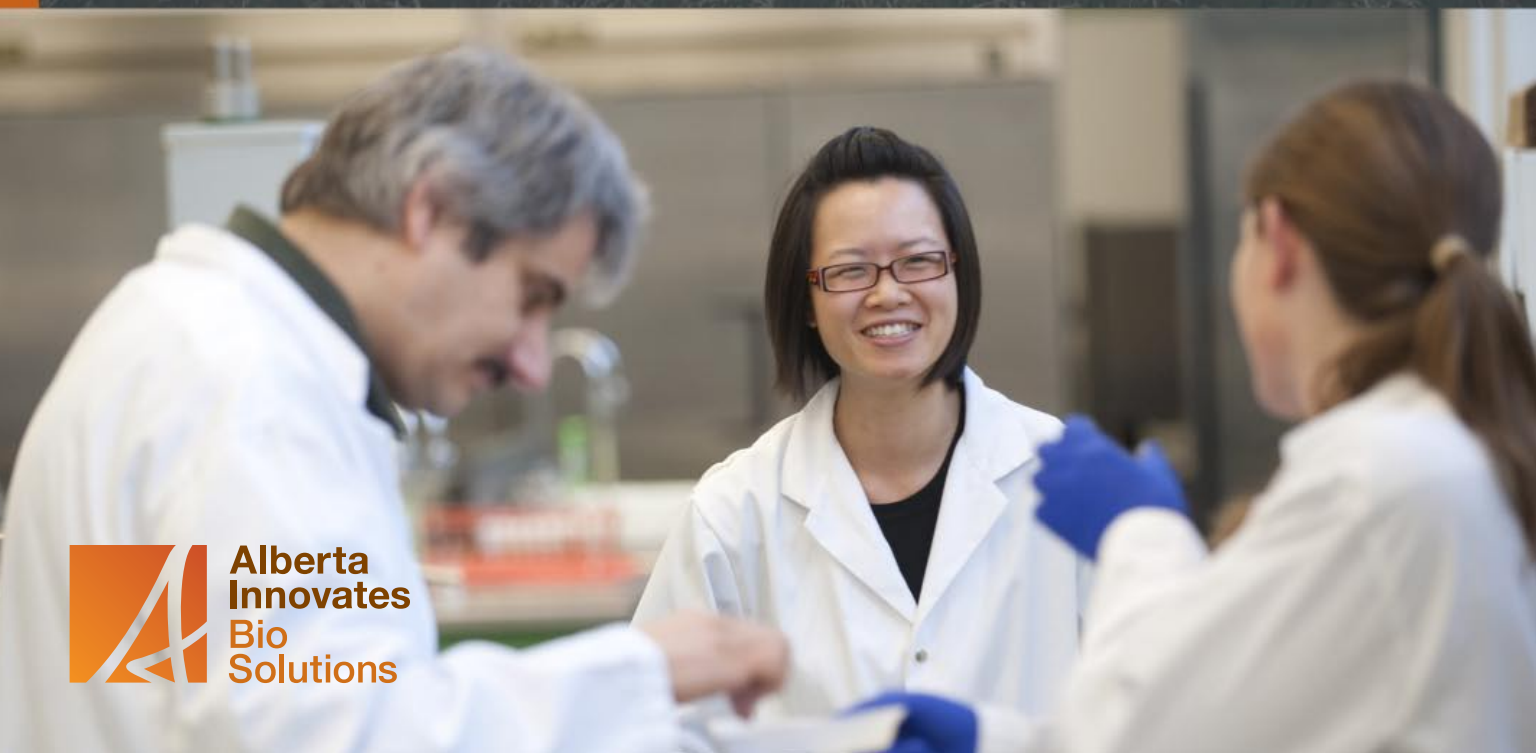


# Connecting Communities

Year 5 2009-2010 Annual Report

Alberta Prion Research Institute

prion



Alberta Innovates Bio Solutions

Year 5 2009-2010 Annual Report

# Connecting Communities

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Alberta Prion Research Institute

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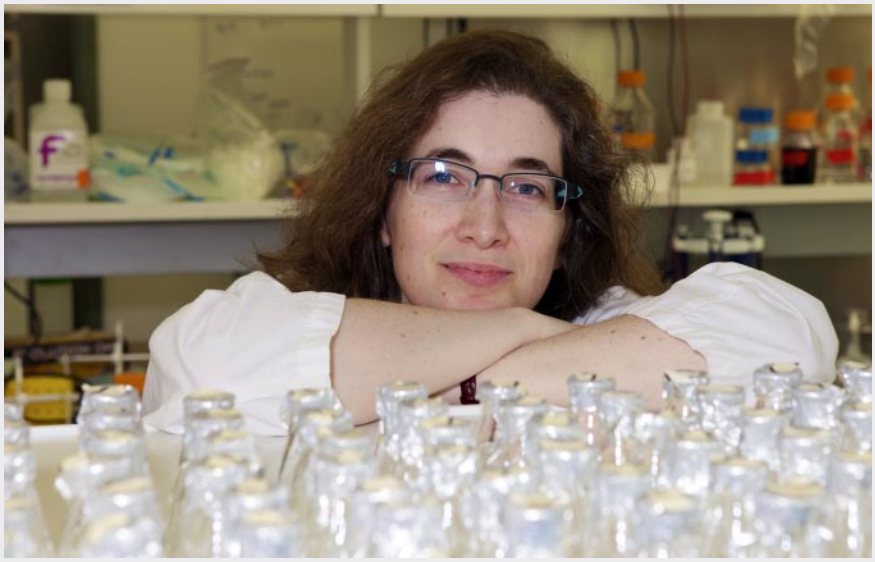
Alberta Innovates Bio Solutions

# PrionGirl, Neurologist and Musician Extraordinaire



Dr. Valerie Sim believes she helps people with her music as well as her science. She started her musical studies in Winnipeg when she was seven, and continued at the Mount Royal Conservatory when her family moved to Calgary the following year. She's a classically trained violinist, pianist, grand master fiddler, fiddling trickster, composer, conductor, musical director, chamber musician, orchestra member and CD producer. She now plays with TEMPO, The Edmonton Medical Professions Orchestra.

Dr. Valerie Sim has a passion for science. She also has a passion for music, but she's come to realize that science and music can indeed coexist. Making room for both passions helps her find fullness and balance, she says.

"Music is a huge part of my life," Dr. Sim explains. "But I think I've been a scientist from birth. I was always asking questions and being curious and wondering how things worked, or why."

For Dr. Sim, the best part of being a scientist is the excitement and challenge of discovery and the fact that you can never predict where your research will take you.

Dr. Sim has let her scientific curiosity lead her where it will. In junior high, she was a self-proclaimed geek who loved the concreteness of math and the physics of atoms and molecules. She got hooked on genetics in high school and, at university, enrolled in cellular, molecular and microbial biology.

It was in an undergraduate virology course that she got interested in infectious disease and first learned about prions. "They're not viruses and they're not bacteria. As far as we can tell, they're just protein. So how do they work? That really appealed to my sense of curiosity."

Her curiosity next drew her to medical school, where she hoped to learn about infectious disease from the human side, not just the virus side. And a nine-hour delay at the Toronto airport led her to neurology.

In her second year of med school, Dr. Sim was one of five Alberta finalists in the Grand Masters fiddling championship. Attending the competition in Ottawa meant missing some of her neurology course, but she took along three hefty textbooks so she wouldn't fall too far behind. When she found herself grounded in Toronto, textbooks were all she had to read. But she was soon hooked. >>

# Researcher Profile: Valerie Sim

"I found neurology really gripping," she recalls. "How the brain works is extremely complicated. It's also a bit of a black box, and I wanted to be the person who knew that stuff."

Dr. Sim didn't win the fiddling championship, but fell in love with Ottawa and opted to do her five-year neurology residency there. On a Christmas visit home, a chance conversation with a University of Calgary research neurologist rekindled her interest in prion disease. The mecca for prion research, she learned, was Montana's Rocky Mountain Laboratories—home to one of the oldest and most successful prion laboratories in the world. At this time, two months before the first case of BSE was discovered in Alberta, there were no prion researchers in the province.

Dr. Sim earned the nickname Mad CowgirI during her post-doctoral work in Montana, although she never actually worked with cows. Rather, her research focused on mice infected with scrapie—a sheep version of prion disease. Using electron microscopy and atomic force microscopy, she was able to study the shape, size and structure of prions and determine if there are differences between strains.

"I remember the first day I got an amazingly clear image," Dr. Sim recalls. "Nobody had ever published images of infectious prion fibrils using atomic force microscopy. So for that brief moment, I was the only person in the world who had ever seen this. I remember that feeling. It's such a rush. It's really rewarding."

To explore the underlying structure of prions when they stick together in long fibrils, Dr. Sim used an atomic force microscope, which she describes as being "like a record player on a lawn mower." Purified fibrils are spread on a grid and scanned with a "needle" that goes up and down to measure bumps and grooves as small as 10 nanometres. Moving the needle back and forth across the sample—as if you are mowing a lawn—provides a topography that shows the size and shape of the fibrils and indicates if they're twisted or folded.

Throughout her time at the Rocky Mountain Laboratories, Dr. Sim kept a close eye on prion developments in Alberta. When the prion centre opened at the University of the Alberta, she jumped at the chance to come to Edmonton and work with Dr. David Westaway, who could be a mentor to her. "Besides," she quips, "I was born in Winnipeg, so I'm immune to cold."

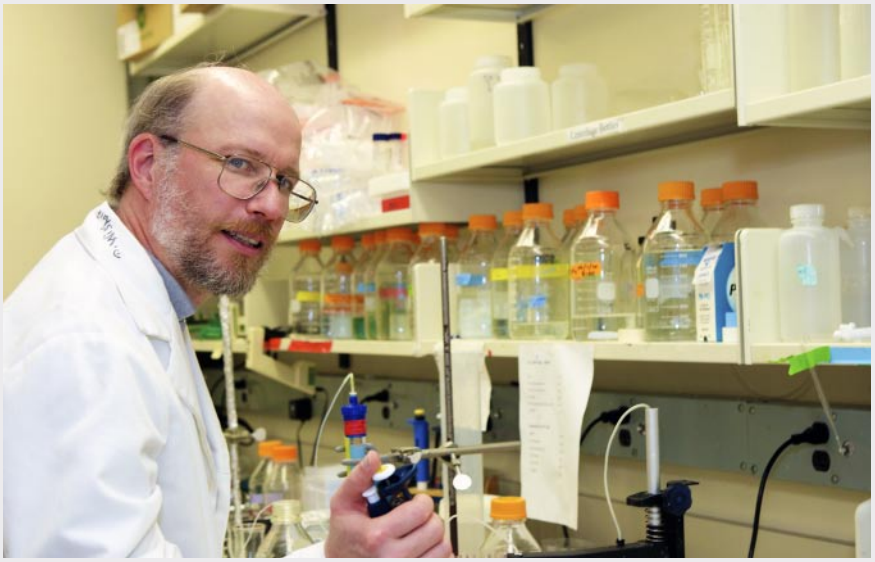
These days Dr. Sim's nickname is PrionGirl and her research centres on "prion disease in a dish." Her team is working with brain slice cultures that, when infected with prions, produce infectivity just as they would in the brain of a living mouse.

The goal is to understand why neurons die when abnormal protein accumulates in the brain.

"When we know how it all works," Dr. Sim explains, "we can stop the progress of prion disease and diseases like Alzheimer's, Parkinson's and Huntington's. These are all diseases where proteins misfold, aggregate and cause a degenerative disease where neurons die."

"At the end of the day, we'll be saving lives. And that's what it's all about." ■

# A Renaissance Man for the 21st Century



Dr. Wishart is a native Edmontonian who completed an undergraduate degree in physics at the University of Alberta. He earned his master's and PhD at Yale, where he specialized in molecular biophysics and biochemistry and completed a dissertation on the characteristics of unfolded protein. His post-doctoral work at the U of A was followed by joint appointments to the university's Faculty of Pharmacy and Faculty of Science, where he now teaches in the departments of Computing Science and Biological Sciences. Dr. Wishart is a senior research officer with the National Institute for Nanotechnology.

As a physicist, biochemist, molecular biologist, computer scientist, nanotechnologist and sometime soccer player, Dr. David Wishart is a Renaissance man whose radio dial is often tuned to stations playing the "sounds" of proteins.

Dr. Wishart has been tuned in to proteins since his days in graduate school at Yale, where he first used nuclear magnetic resonance (NMR) spectroscopy to characterize what denatured (unfolded) proteins actually look like.

NMR spectroscopy measures what's going on in the nucleus of an atom. That's why it's "nuclear": it's not a radioactive measurement.

How does it work?

Dr. Wishart explains, "Spectroscopy doesn't look for images of things. It simply measures signals. It's like moving a dial on a radio and tuning in to where the stations are. With NMR spectroscopy, the stations are atoms or molecules. We put our samples in a super-strong magnet, which makes them more prone to emitting radio signals. Then we tune the receiver of a giant-sized amped-up radio and dial it along to 'listen' to the atoms."

Each type of atom has a unique frequency that shows up as peaks on a spectrogram. By applying the tools of computer science and mathematics, scientists can read the peaks to figure out what atoms a sample contains, how close the atoms are to one another and whether they're moving or stationary. They can also tell if atoms are part of the same molecule and infer the actual structure of that molecule.

The computational models and experimental methods developed in Dr. Wishart's NMR spectroscopy lab have revolutionized the field of protein biology.

"Proteins have thousands of atoms all connected to each other," explains Dr. Wishart, "so it used to take months to measure distances and map how the atoms connect. Now we can measure the frequencies of atoms within seconds. That lets us study processes—like how proteins unfold and fold—in more detail."

Dr. Wishart has applied NMR and other spectrometry techniques to several prion-related projects. In APRI's first call for proposals, he partnered with colleagues in chemistry and computing science to look at prion folding and, in the second phase of the project, to study the structure of misfolded prions. In a related APRI funded project, he is looking at small molecules and proteins that might act as biomarkers to identify prion disease before infected animals show clinical symptoms. He is also collaborating with Dr. Burim Ametaj to determine if the prion misfolding induced by lipopolysaccharides results in infectious prions. (See p. 25 for details on this project.)

Among his many contributions to prion science is the development of techniques to clone prions for use in experiments.

When APRI was founded, Dr. Wishart recalls, scientists didn't have the raw material they needed to study prions. While prions could be cloned from animal genes, the process was challenging and time consuming, and it was difficult to produce prion proteins in quantities large enough to study.

Dr. Wishart came up with the idea of using synthetic genes to clone prions and developed techniques that produce very high yields. His lab produces 15 different variants of prion proteins specific to species that include hamsters, mice, cows and humans.

"We've now become the world's largest producer of prion proteins," Dr. Wishart notes. "We supply cloned prions to a dozen labs in Canada and the United States."

Dr. Wishart's interdisciplinary career is proof positive that the various disciplines of science are closely interconnected. "Science is moving away from doing things in silos," Wishart says, "and the walls are tumbling down. But it's often when people are at the interface of new areas that really interesting things happen. It's like when you mix two things when you're cooking. If you try sweet and sour together, you get an interesting taste, or if you mix pineapple and ham, you get an interesting pizza. That kind of mix, when it happens in science, is good fodder for discovery."

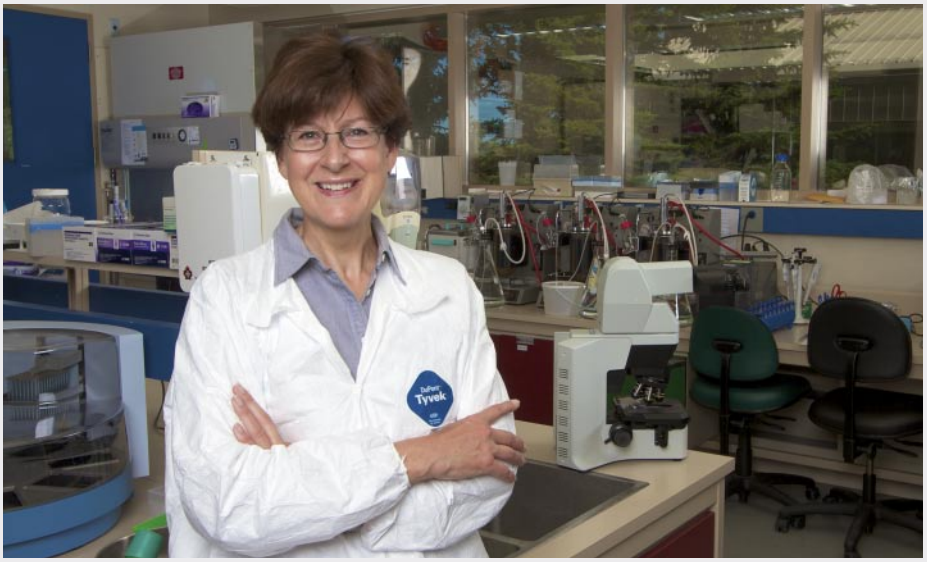
Dr. Wishart says it's not likely he would have turned his protein research in the direction of prions had the Alberta Prion Research Institute not been established. "The prion problem is challenging and the characteristics of prions make them experimentally unfriendly. At the same time, if you're challenged with a difficult problem, it forces you to come up with better ideas and ask different questions."

Because scientists now have the capacity to generate prions, they've been able to address fundamental questions about prion structure. Now they can turn their attention to new questions and practical applications. For example, what does a prion protein really do? Why do we have it? How do we stop prion disease? How do we discover drugs to treat it? How can we prevent it?

What Dr. Wishart loves about science is the opportunity to teach and to learn, the sense of community and the excitement of discovering something no one has ever found before.

"My profession is science, but my hobby is also science," he says. "I think to be a successful scientist, you have to be very passionate about it. For me, it's a hobby that's become a job and a profession. And that makes it fun."

# Science is a Global Affair




Dr. Czub is an avid reader and a dedicated gardener who enjoys hiking and kayaking with her husband, Markus, an APRI researcher and professor of virology at the University of Calgary's Faculty of Medicine and Faculty of Veterinary Medicine. Her favourite way to unwind is walking her three Chesapeake Bay retrievers in the coulees of the Oldman River.

Dr. Stefanie Czub is a veterinarian and neuropathologist who has studied prion diseases since her days in graduate school at the Free University of Berlin. In 2001, after post-doctoral work at the prestigious Rocky Mountain Laboratories and 10 years as a senior researcher at the University of Wuerzburg, Dr. Czub was appointed head of pathology at the Canadian Food Inspection Agency (CFIA) in Winnipeg. Over the next two years, she set up Canada's reference laboratory for BSE.

"BSE was just this tiny little attachment to my portfolio," she notes. But that soon changed.

In 2001, although the risk of BSE occurrence was believed to be small, Canada introduced a surveillance program to test cattle for BSE. It was the surveillance program that brought Canada's first case of BSE to Dr. Czub for confirmation. This happened in May 2003, just days after her reference lab was up and running.

For the next three days, staff worked around the clock to confirm that the specimens they had received, from an Alberta cow, were really BSE.

"It was quite an exciting process," Dr. Czub recalls. "I was sitting behind my microscope at midnight on the May long weekend. When I saw what I saw and realized that it was BSE, I knew what the impact of this case would be. Sure enough, 15 minutes after the first press conference, 35 of Canada's trading partners shut down their borders."

BSE is not the only prion disease under Dr. Czub's microscope. She coordinates a five-year, $5 million CWD research study that is APRI's largest project to date.

"Our concern is that chronic wasting disease, like BSE, can pass from animals to humans," explains Dr. Czub. "We want to find out if eating or dealing with hunted game poses a danger to the human population. Can hunters get infected through contact with infected tissues or through the minor cuts they might get when field dressing animals? What happens if a human who is infected with CWD donates blood that is then transfused into another person?"

To answer these questions, Dr. Czub assembled a team of two dozen researchers from her own laboratory, the University of Calgary and four leading institutions in Germany—the Robert Koch Institute in Berlin, the Technical University in Munich, the University of Goettingen and Goettingen's German Primate Research Center, where the team is working with rhesus monkeys as a model for humans.

The Goettingen centre is one of a handful of facilities in the world that conducts primate research and also has the biosafety certification needed to work with prions. Dr. Czub got to know the researchers there through her earlier work on simian immunodeficiency virus as a model for HIV, the human immunodeficiency virus that causes AIDS.

As a research scientist and APRI Scholar, Dr. Czub wears many hats. As head of a national and international BSE reference laboratory, she does a lot of research and diagnostic work. As a member of APRI's advisory committees, she helps to set priorities for prion research. As the manager of CFIA's pathology, TSE and virology sections, she heads a staff of 25 who help keep Canada's food supply safe.

But her "absolute favourite" part of her job is the hours she spends sitting behind her microscope.

All cases of BSE in Canada are confirmed at Dr. Czub's reference lab, which is now located on the Canadian Food Inspection Agency's 1,400-hectare facility near Lethbridge. In 2006, the World Organisation for Animal Health, which is known as the OIE, designated Dr. Czub as an OIE expert on BSE. (The initialism OIE comes from the agency's pre-2003 name, the Office international des épizooties.) The OIE has BSE reference labs in Canada, the United Kingdom, Switzerland and Japan. Each lab is headed by an internationally recognized expert who coordinates research and provides the agency and its member countries with expert advice on BSE surveillance and control.

Dr. Czub credits her curiosity and fascination with science to her paternal grandfather, a country doctor with a lifelong passion for medical puzzles.

"I thought I would be a veterinary practitioner," she recalls. "But in the end it was the laboratory that drew me. I very much enjoy it. Laboratory work and being a pathologist satisfy my innate curiosity."

Working with animals was a natural career choice for the daughter of two practising veterinarians who often took their children to work. Dr. Czub recalls tagging along on one of her mother's meat inspections in Marburg, Germany, and seeing an omentum maior for the first time. "It's the great net that keeps an animal's guts in place, and it's fantastic and beautiful to look at. I was four years old and I was totally fascinated."

When she was about the same age, she watched her father perform surgery on a cow that had eaten a collapsible umbrella. When the cow's stomach was exposed to the cold fall air, a magical cloud of condensation emerged.

Her career was decided in that instant. "It had to be the vet school," Dr. Czub says. "For me, there was no other option." ■

# Dealing with the Complexity of Our Time

A California native, Dr. Debra Davidson completed a bachelor's degree in environmental science at Berkeley and a master's in conservation biology and sustainable development at the University of Wisconsin–Madison, where she earned her PhD in rural sociology. Post-doctoral work brought her to the U of A, in 1999, for what she thought would be a short-term stay. She's since succumbed to Edmonton's charms as a livable, family-friendly city with wonderful river valley parks where she loves to run. She can play ultimate frisbee here. "And it's close the mountains," she notes. Bonus!

The 21st century is an era of complexity in terms of the technology, organizational systems and social structures that govern our lives.

Climate change, nuclear power accidents, food safety and all sorts of complex issues confront us with greater frequency and magnitude than at any other time in human history. Social scientists speculate about society's ability to deal with these issues. Are we capable of managing uncertainty? Do we learn from crises so we can reduce the chances of them happening in the future?

Dr. Debra Davidson, a sociologist and award-winning professor of Rural Economy and Renewable Resources at the University of Alberta, is looking for answers to these questions. Using the issue of food safety as a case study, her APRI-funded project will explore if and how large bureaucratic institutions deal with unexpected crises.

"The food production system is complex," Dr. Davidson explains, "so there will always be uncertainties around the corner. The very nature of a complex system is that everything is interconnected, so even a little mishap can blow up into something huge. BSE is a perfect example of that. We had a single case of mad cow disease and the industry turned upside down."

As Canadians learned with the BSE outbreak of 2003, threats to the safety of the food supply can have dire economic consequences and, if they are not addressed, negative effects on community structures and on human health.

The challenge for society is to create organizations that can deal with complexity and protect public health and safety.

Dr. Davidson and a five-person research team from the University of Alberta and the University of Guelph have launched a two-year study that will look at institutional and public responses to BSE in Alberta and Ontario, two of Canada's largest beef producers. >>

# Researcher Profile: Debra Davidson

"We want to find out how people are defining BSE," Dr. Davidson explains. "Is it defined as a crisis? Is it defined as a pesky political issue? As an economic issue? If it turns out that everyone is treating BSE as an economic issue, and our policy responses have all been about managing the economics, what does this tell us about our preparedness for future food safety outbreaks?"

In the first phase of the study, federal and provincial regulators, former elected officials, industry representatives, consumer advocates and community based producers will be asked to tell their stories about what BSE meant to their organizations, how they defined the problem and how their institutions' operating practices changed in the aftermath of the crisis. The interviews will be transcribed and analyzed to define key themes and implications for policy outcomes. The final phase of the study will survey members of the public to determine their level of concern about food safety and their level of trust that regulatory organizations can keep our food safe.

At the end of the study, Dr. Davidson and her team hope to have the answers to several key questions. Was the BSE scare treated as an opportunity for learning? Has the experience changed the way we do things organizationally? If lessons were learned, how can we apply these in other contexts? If learning has not occurred, what were the roadblocks? What ideas can we offer to improve our responses to crises in the future?

Dr. Davidson first explored the issue of BSE as a co investigator for Dr. Ellen Goddard's APRI-funded study on the socio economic impact of prion diseases in Alberta. The findings showed that perceptions about food safety affect consumers' responses to real or perceived crisis. It was clear that the BSE outbreak affected public confidence in regulatory institutions, and that industry and government have a role in providing timely, accurate information when issues of food safety arise.

The solution, Dr. Davidson believes, will require an interdisciplinary approach. "That's where we need to go in terms of addressing various social and environmental problems."

In her teaching and research and as the director of the Environmental Research and Studies Centre at the U of A, Dr. Davidson applies the tools of social science to environmental issues such as land use, water scarcity, forestry and energy. Her next projects will explore climate change vulnerability in forest-based communities in Alberta and Colombia.

Dr. Davidson is passionate about teaching and translating environmental and social research for a broader audience. One of the ways she does this is through a "very cool" virtual classroom project sponsored by the U of A, Edmonton Public Schools and Taking IT Global. High school students from around the globe complete two week modules on topical issues. They engage with one another and with graduate student mentors through videoconferencing and online, through blogs and discussion boards.

The technology is sophisticated and the issues are complex. It's a sign of the times. ■

# Canada Research Chair in Prion Disease

Dr. Westaway's doctoral work on beta-thalassemia—an inherited blood disease that causes anemia—discovered one of the first splicing mutations found in human molecular genetics. His pioneering work with transgenic mice discovered two new prion proteins, shadoo and doppel. In 2007, Dr. Westaway was named Canada Research Chair in Prion Disease; his Tier 1 designation marks his peers' acknowledgement of his outstanding contributions to his field.

London-born Dr. David Westaway decided to become a biochemist when he was 17.

It was a book that hooked him—Steven Rose's The Chemistry of Life—and a description of the speed with which ribosomes in cells slide down messenger RNA to make protein. "I couldn't figure out how on earth you could measure velocity on some sort of sub-cellular railroad track. That got me interested."

Dr. Westaway enrolled in biochemistry at the University of Sussex, where he first encountered what would come to be known as prions in a copy of Nature magazine. "I was sitting in the biology library, reading about this unusual agent that replicated without a nucleic acid," he recalls. "I remember thinking that was pretty weird. But no one knew about prions then. So it just lodged in my mind as a bit of a biochemical curiosity."

Dr. Westaway completed his PhD in biochemistry and molecular genetics at St. Mary's Hospital, University of London. "This was at the dawn of the era of molecular genetics," he recalls, "when people were just learning to clone DNA. I found that absolutely fascinating and decided I needed to learn how to do it."

He learned the technique and then spent two months at "scientific boot camp" in the Zurich lab of Charles Weissmann—a pioneer of reversed genetics—with whom he would later collaborate on prion research.

He also got interested in cancer biology, which led to a post-doctoral position at the University of California, San Francisco (UCSF). There he worked in the lab of Harold Varmus, whose discovery of cancer-causing genes subsequently earned him a Nobel prize.

He was finishing up his post-doctoral duties just as another UCSF researcher, Stanley Prusiner, was looking to hire a molecular biologist. Dr. Westaway took the job.

Prusiner's work on scrapie had identified prions, but although he had published his findings in 1982—and would win a Nobel prize for his discovery in 1997—there was lengthy resistance from scientists who believed that scrapie was caused by an unconventional "slow virus." >>

# Researcher Profile: David Westaway

"In 1984, Stan Prusiner's ideas on prions were still looked at a little bit askance," Dr. Westaway recalls. "The ideas he was coming up with were the opposite of what mainstream virologists were comfortable with. They weren't really believers."

But molecular biologist Charles Weissmann was a believer, and in 1985 Weissmann's Zurich lab partnered with Prusiner's to push the science further. It was Bruno Oesch, in Weissman's lab, who first cloned a copy of the prion gene.

"Then we started work on the basic molecular biology of the disease," Dr. Westaway recalls. "We established that sheep and other animals make a normal prion protein. So I suggested that this normal, cellular prion protein be called $PrP^{C}$—using the biological naming system that had been established for cancer-causing viruses."

In 1994, Dr. Westaway joined the Toronto-based Centre for Research in Neurodegenerative Disease. There he expanded his research horizons to Alzheimer's disease, which was less understood than prion disease.

"An area that's a bit murky is a good area to play in when you're a researcher," Dr. Westaway explains. "But there weren't any animal models that could be studied."

Alzheimer's is a degenerative, terminal disease that affects half a million Canadians and their families and imposes an economic burden of $15 billion per year. One in 20 Canadians over 65 and one in four over 85 currently suffers from Alzheimer's disease. But it's not just older people who are affected: 50,000 Canadians under 60 have Alzheimer's disease. If a cure is not found, more than a million Canadians are expected to develop Alzheimer's within the next 30 years. The human cost is incalculable and the financial burden will exceed $150 billion per year.

This situation changed when a number of North American researchers—including Dr. Westaway, Peter St. George Hyslop, Paul Fraser and their colleagues at the University of Toronto—made transgenic mice that carry genes for early-onset Alzheimer's disease. Research labs and pharmaceutical companies across Canada and the United States now recreate and study Alzheimer's disease using the TgCRND8 mouse model developed at the U of T.

In 2006, Dr. Westaway was recruited to the University of Alberta to set up the Centre for Prions and Protein Folding Diseases, where he continues his research on Alzheimer's and prion diseases. The centre houses six state-of-the-art laboratories staffed with some of the world's best researchers in the field of prions and protein misfolding.

Funding from the Alberta Prion Research Institute helped get the centre rolling, says Dr. Westaway, who was named an APRI Scholar in 2006. APRI also supports several of the centre's research projects on prion diseases and other human neurological disorders.

The centre provides an economy of technology. "The technologies you use for prion disease can be used for Alzheimer's disease," Dr. Westaway explains. "And there are connections at the level of biochemistry, so if you discover something in one disease, it's often worthwhile to make an analogous experiment for the other disease."

Experiment by experiment, Dr. Westaway and his centre add to the body of knowledge about prions and protein misfolding diseases. In time this will lead to understanding and perhaps a cure. ■