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Synchrotron sheds light on prostate cancer

University of Saskatchewan researchers are pioneering the use of synchrotron technology to study prostate cancer in humans and dogs.

The dog serves as a good model for the study of human prostate disease because it's the only animal known to spontaneously develop prostate cancer with advancing age.

Using the Canadian Light Source (CLS) synchrotron at the U of S, Trinita Barboza, a second-year U of S veterinary medicine student, is part of a multidisciplinary team investigating the best technique for imaging canine and human prostates.

"We hope to discover early indicators of prostate cancer by correlating what we see on synchrotron images with what we see using conventional imaging methods such as ultrasound, computed tomography (CT) and magnetic resonance imaging (MRI)," says Barboza.

"Earlier detection allows for more timely and effective treatment," stresses Dr. Elisabeth Snead, a professor with the Western College of Veterinary Medicine.

ABOVE: Trinita Barboza is part of a multidisciplinary team imaging canine and human prostate at the U of S synchrotron. *Photo: Christina Weese.*

Barboza's work is supervised by Snead and Murray Pettitt, a research associate at the U of S College of Agriculture and Bioresources.

The team is at the stage where they're trying to determine how to image details within the prostate gland. "That's never been done before, here or anywhere else with a synchrotron," says Pettitt.

The synchrotron is a source of brilliant light produced by using radio frequency waves and powerful magnets to accelerate electrons. This light can be used to study many physical, chemical and biological processes in plants, animals and humans.

The team uses the CLS's biomedical imaging and therapy beamline to create high energy X-rays that can image prostate tissue in immense detail.

"The synchrotron offers a unique way of seeing things," says Dean Chapman, scientific leader of the beamline and Canada Research Chair in X-ray Imaging. "It's unlike any other imaging tool. We're able to look at things at the micron level with very high resolution."

Barboza collects and prepares prostate tissue — both canine and human — for imaging, runs the imaging program at the synchrotron, performs computer-based reconstruction of these images, and helps with the CT and ultrasound imaging. She also organizes the team's shifts at the synchrotron.

She has participated in many back-to-back shifts at the synchrotron this summer that can add up to 16 hours at a time. While these days can be very long and grueling, the results are rewarding.

"It's very gratifying when I finish reconstructing an image and I send it out to the team members and everyone gets so excited," she says.

As synchrotron sciences are a new frontier in science, Barboza often needs to get creative to ensure effective imaging. "I'm creating little custom-made contraptions all the time," she says.

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SYNCHROTRON RESEARCH (CONT'D):

For example, the prostate tissue must be kept suspended and still in its container to properly image it.

Working with a multidisciplinary team has been another fascinating aspect of the research: "Everyone has their own specialty and they all want to teach each other and learn from one another," she says.

"One of the things the synchrotron is extraordinarily good at doing is bringing together people from different disciplines," adds Chapman. "You really need the engineers, physicists and medical experts to pull this stuff off."

Interested in pursuing a career in research, Barboza is glad to have had the opportunity to contribute to the advancement of both animal and human health using this state-of-the-art facility.

"It's amazing how much the synchrotron can do," she says. "Our project uses only a small portion of it. There are so many other researchers doing so many different things with this harnessed energy."

Funders for the project include the Saskatchewan Health Research Foundation and Motorcycle Ride for Dad, an organization that raises funds to support prostate cancer research.

Robyn Thrasher, a third-year veterinary student, was a summer student intern with the WCVM research communications and U of S research communications offices.

This article first ran as part of the 2012 Young Innovators series, an initiative of the U of S Research Communications office in partnership with the Saskatoon StarPhoenix.

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In Memoriam

Sylvia Fedoruk (1927-2012)



Sylvia Fedoruk, a renowned medical physicist at the University of Saskatchewan, an outstanding athlete and the province's first female lieutenant governor, passed away at her home in Saskatoon on September 26. She was 85.

Born in Canora, Sask., in 1927, Fedoruk received her BA from the University of Saskatchewan in 1949 and added high honours in physics to her degree in 1950. In 1951, she completed her master's degree in medical radiation physics and soon after, joined the Saskatoon Cancer Clinic and began lecturing at the U of S.

She was part of the U of S team that developed the world's first noncommercial cobalt-60 therapy unit for the treatment of cancer. In 1963 and 1964, Fedoruk was involved in the development of a scintillation camera for the detection of cancer cells. She retired in 1986 from a career that focused largely on diagnostic nuclear medicine.

During her career as a radiation physicist, Fedoruk was also a valuable friend to the Western College of Veterinary Medicine (WCVM). Medical imaging specialist Dr. John Pharr recalls the assistance that Fedoruk offered him when he first joined the WCVM in 1972.

"She helped me prepare an old X-ray teletherapy machine so I could do radiation therapy on some of our small animal patients," says Pharr. "Sylvia would also bring a Strontium-90 therapy wand over to the college so I could treat some superficial tumours and tumour-like diseases in places such as the eye in some of our patients."

Pharr adds that Fedoruk offered the now-historic Cobalt-60 radiation therapy "bomb" to the WCVM for free — an offer that the college had to turn down because of the multiple costs associated with housing and recharging the radiation unit.

The gesture was a classic reflection of Fedoruk's generosity. "Sylvia loved her dogs and was always willing to help us," recalls Pharr.



Study first step toward novel cancer therapy

Cancer — it's a diagnosis that no pet owner wants to hear and no veterinarian wants to make. What can be even tougher is coming up with a prognosis and an appropriate treatment plan for oncology patients.

Dr. Kirsty Elliot hopes she can help to improve the odds for pets with cancer. The oncology resident's research may help to pave the way to discovering novel methods of treating and predicting the outcome of certain cancers.

Under the direction of virologist Dr. Vikram Misra, Elliot has been collaborating with researchers to test the hypothesis that the unfolded protein response (UPR) is upregulated in spontaneous canine solid tumours, and that suppression of the UPR in these tumours will prevent their growth, spread and development of resistance to anti-cancer drugs.

Supervised by WCVM oncologist Dr. Valerie MacDonald, Elliot has begun to characterize the expression and activity of the UPR in various tumour cells in comparison to normal, healthy tissue — a vital first step.

"The UPR is a conserved cellular response to stress," explains Elliot. "Stressors to the cell, such as lack of oxygen or nutrients, results in the accumulation of unfolded or misfolded proteins within the cell. That turns on the UPR - a response that helps the cell survive in these adverse conditions."

This response benefits normal cells that need to survive transient changes in their microenvironment. But in cancer cells, research has shown that upregulation of the UPR in human cancers is associated in many cases with higher rates of metastasis and recurrence and resistance to chemotherapy.

This mechanism has been one of the more recently recognized pathways in tumour biology. Most solid tumours are characterized by regions of hypoxia (low oxygen) and lack of nutrients as they outgrow their blood supply. The WCVM team is the first to look at the UPR and its association with tumours in dogs.

Elliot's project, which began in 2010, involves collecting tumour samples from cancer patients at the WCVM's Veterinary Medical Centre. The study includes dogs with any type of solid tumour that are undergoing surgery.

Dr. Kirsty Elliot (WCVM '08)

Read her profile at www.cahf.usask.ca

After WCVM surgeon Dr. Kathleen Linn removes the tumours, Elliot takes tissue samples from within the tumour as well as from the surrounding normal tissue.

Each sample is divided into three pieces: one for histologic examination, one for cell culture and one for extraction of RNA (molecules that control gene expression and play a role in protein synthesis).

WCVM veterinary pathologist Dr. Elemir Simko performed histologic tissue analysis to confirm that the samples were taken from tumour or non-tumour sites. The cultured cells are used in an additional project in Misra's lab. These cells are exposed to Zhangfei — a unique protein that has been shown to suppress the UPR, preventing tumour growth.

Elliot runs polymerase chain reaction (PCR) tests on the RNA extracted from the samples. To detect upregulation of the UPR, she measures RNA levels of four different UPR genes in the tumour

samples and compares them to normal surrounding tissue as a control.

Since the sample size is small, the study's results aren't definitive. Elliot hopes to continue collecting more samples to provide support for their preliminary findings. However, there does appear to be a connection between the UPR and selected tumour types.

"It certainly looks like there may be some upregulation of a few of the different UPR genes in some of the tumour types examined," says Elliot. "The most exciting results we've had were from a metastatic hemangiosarcoma that had hugely elevated UPR genes compared to normal surrounding tissue."

Zhangfei was also used successfully in this sample to shut down tumour cell growth in culture while having no effect on the growth of normal cells

Hemangiosarcoma, a common and fatal canine cancer, is a highly malignant tumour of endothelial cells (cells found throughout the body lining the blood vessels). The research team has hypothesized that upregulation of the UPR is more drastic in metastatic, aggressive tumours as compared to primary or non-aggressive tumours.

This information may prove useful as a prognostic factor and may help guide treatment decisions, but Elliot points out that greater sample numbers are required to prove this association.

In human medicine, upregulation of the UPR seems to also increase resistance to chemotherapy. "It would be interesting to see if this holds true for dogs as well," says Elliot. "This could potentially explain why treatment fails at times."

Funded by the Companion Animal Health Fund and the Kaye Canine Research Foundation, Elliot hopes the results of her project will lead the way to alternative cancer treatments. "If we can learn more things about the UPR and how to manipulate it, we hope to improve cancer treatment not only in dogs, but in people as well." V

ABOVE: Dr. Kirsty Elliot (background) and animal health technologists Melissa Underhill (left) and Kim Foster (right) prepare Oliver for his chemotherapy.



"What we've seen recently at the VMC is that some of the sickest parvovirus-infected dogs also seem to be infected with EPEC, suggesting that there's something more going on than we usually consider."

Although EPEC can be found in the feces of healthy dogs, Rubin points out that what's normal for one animal isn't necessarily normal for another. "Many organisms that animals carry, including EPEC, have the potential to cause disease in the right situation."

As well, EPEC is known to be zoonotic, meaning infection can spread between animals and people.

"EPEC infections most commonly occur in infants," says Rubin. "Because small children don't understand the importance of hand washing and often

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explore their environment by putting things in their mouth, the zoonotic risks of EPEC may be underappreciated."

Oral contact with fecal material is the likely route of transmission for newly infected or colonized dogs, but it's unknown what tips the balance from healthy colonization to clinical disease. The study's research team predicts that infection with parvovirus may play a role.

The project, which began in June 2012, involves the collection of feces from 100 dogs less than two years of age that present to the VMC with signs of parvoviral infection. Dr. Casey Gaunt, another WCVM small animal internal medicine specialist, will identify suspected cases of parvovirus and co-ordinate the collection of samples.

Once the dogs are admitted to the VMC, clinicians will collect a fecal sample for bacterial culture and a parvovirus test. Due to inconsistent shedding of the virus, dogs that test negative for parvovirus will be retested when they're discharged from the medical centre.

To rule out other common causes of diarrhea, all dogs will be tested for $\it Giardia$ and $\it Cryptosporidium-protozoal$ parasites that infect the gastrointestinal tract.

Rubin will test any *E. coli* isolated from the fecal cultures for the eae gene using a polymerase chain reaction (PCR) test developed in collaboration with Dr. Janet Hill, a WCVM associate professor in veterinary microbiology. Hill's research associate, Dr. Bonnie Chaban, is also currently developing a diagnostic assay that will include EPEC.

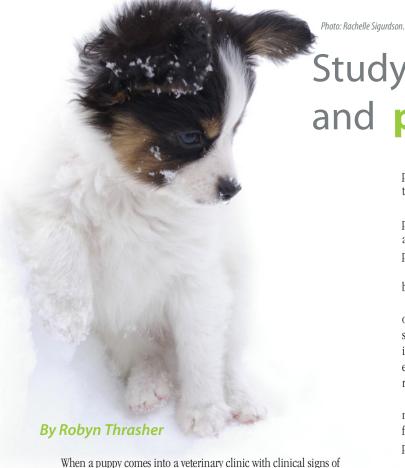
Medical records for patients with and without EPEC will be assessed for differences in survival, duration of hospitalization and cost of treatment.

Information regarding prevalence of EPEC in dogs, cats and people is very limited. Carr hopes to address that lack of knowledge with this project that's supported by the Companion Animal Health Fund.

"Identification of eae positive *E. coli* (EPEC) in patients diagnosed with parvoviral enteritis will allow the formulation of specific treatment protocols that may shorten hospital stays and reduce the cost of care," he says.

He adds that the correlation of EPEC infection with survival in affected dogs may serve as a prognostic indicator that will help veterinarians and pet owners make more informed decisions about patient care.

"The study will also raise awareness among veterinarians that any dog showing the classical signs of parvovirus may not necessarily be infected with parvovirus," says Carr. "You have to consider other possible causes." V



When a puppy comes into a veterinary clinic with clinical signs of vomiting and diarrhea, one of the top diagnoses on a veterinarian's mind is parvoviral enteritis — a viral infection affecting the gastrointestinal tract.

But what about other pathogens that may look like parvoviral enteritis? One such infectious agent is the bacteria, enteropathogenic *Escherichia coli* (EPEC), which appears to be clinically indistinguishable from parvovirus infection.

Recently, a couple of canine patients presented to the WCVM's Veterinary Medical Centre (VMC) with suspicions of parvovirus infection although no parvovirus was detected. What's interesting is that clinicians eventually discovered a large number of EPEC were seen on the dogs' fecal culture.

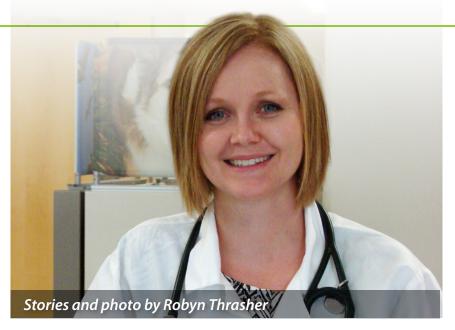
This incident triggered WCVM professor Dr. Anthony Carr to launch an investigation into EPEC and its role in gastrointestinal disease. The small animal internal medicine specialist is interested in the organism for two reasons.

"First, it has the capability of looking just like parvoviral enteritis. Secondly, we generally have very good success with treating parvovirus. Over 90 per cent recover with aggressive therapy, but at times, we have some very poor outcomes. We wonder if concurrent infection with EPEC might cause these poorer outcomes."

There are a number of different strains of *E. coli*, but EPEC can be differentiated from other *E. coli* by the presence of the eae gene.

"The eae gene encodes an attachment protein that allows these organisms to attach to the intestinal lining. That results in damage to the microvilli — the absorptive surface of the intestine," explains Dr. Joseph Rubin, a postdoctoral fellow in the WCVM's Department of Veterinary Microbiology and one of the study's lead investigators.

Interested in looking at "old diseases" in a new way, Rubin believes that some people may think there's nothing left to learn about parvoviral enteritis.



Small animal surgery clicked with **Plesman**

Dr. Rhea Plesman developed her keen interest in veterinary medicine while growing up on a feedlot operation in Coaldale, Alta.

"I really loved the farm and I wanted to have a career that was related to it," says the 2008 Western College of Veterinary Medicine (WCVM) graduate.

Given her background, Plesman initially intended to focus on bovine medicine. But during her undergraduate studies at the University of Lethbridge, she began working weekends at a mixed animal practice and was introduced to small animal medicine — including surgery.

"I loved going in to watch the vet perform surgery," she says. "It was the first time I really started to gain an interest in that field of veterinary medicine."

Still torn between bovine medicine and small animal surgery, Plesman spent the summer between her second and third year at the WCVM working in the college's Veterinary Medical Centre (VMC).

"That summer I was exposed to many referral-type surgeries in the small animal clinic. I remember seeing my first hemilaminectomy (spinal cord surgery) and thinking, 'This is so cool!" she says.

During Plesman's final year, her involvement in the WCVM's surgical rotations and a four-week externship at the Veterinary Emergency Clinic and Referral Centre (VEC) in Toronto, Ont., solidified her career choice of small animal surgeon.

After a one-year rotating internship at the VEC, Plesman returned to the WCVM in 2009 to begin a residency in small animal surgery and a Master of Veterinary Science (MVetSc) degree. During her program's final year in 2011-12, she was selected as the Companion Animal Health Fund's research fellow.

With a passion for orthopedic surgery, her research project involved identifying radiographic landmarks for evaluating knee instability in dogs following damage to their cranial cruciate ligaments

"I also enjoy soft tissue surgery and minimally invasive surgical procedures such as laparoscopy and arthroscopy," says Plesman. "I'd really like to continue working and developing my skills in these areas."

Plesman, who finished her residency on July 15 and joined the VEC clinical team in Toronto in late July, has found her years spent at the WCVM a valuable experience.

"The VMC has a good surgical case load so the opportunity to see a lot of different surgeries really prepares you for your career," she says.

"And one of the benefits of the VMC is that it's not just a referral centre: there's the private practice and emergency care aspects of it. You see a lot more in addition to the complicated referral cases which makes you a good, well-rounded clinician." V

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Thank you very much for your generosity and interest in the Companion Animal Health Fund (CAHF). This issue of *Vet Topics* highlights some of the most recent research projects and people that have received your support through the CAHF.

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Read more about Dr. Plesman's research at www.cahf.usask.ca



Pancreatitis is an increasingly important pancreatic disorder in cats, but what exactly is it? What happens when a cat becomes ill due to pancreatitis?

The pancreas is glandular organ has two main functions: to produce metabolic hormones that control blood sugar and to produce enzymes that aid in food digestion.

Normally, due to their destructive nature, the protein-digesting enzymes trypsin and chymotrypsin are stored in the pancreas in an inactive form. Once undigested food moves from the stomach to the intestine, the pancreas is stimulated to release these enzymes, which only become activated once they reach the intestinal tract.

When the enzymes are inappropriately activated within the pancreas, inflammation occurs causing a disorder known as pancreatitis.

Cats and pancreatitis

Feline pancreatitis is a fairly complex disease that is likely more prevalent than previously thought. According to a 2007 study published in *The Journal of Veterinary Pathology*, 67 per cent of cats had evidence of pancreatitis based on tissue analysis and almost half of these cats were considered clinically healthy.

In cats, the cause of pancreatitis is often unknown and reaching a definitive diagnosis is difficult.

"In dogs, pancreatitis is often thought to be secondary to a high fat meal or dietary indiscretion, whereas in cats this association doesn't exist," says Dr. Melissa Meachem, a graduate student in veterinary pathology at the Western College of Veterinary Medicine (WCVM). Typically, cats with pancreatitis have vague and non-specific symptoms such as anorexia and lethargy, which makes determining the cause of the illness challenging.

While vomiting and abdominal pain are classical signs of this disease in dogs, these symptoms are rarely seen in cats.

Affected cats may develop concurrent diseases such as hepatic lipidosis (also known as "fatty liver" — a type of liver disease that stems from inadequate food intake) that further complicate diagnosis and treatment.

Due to the anatomy of the pancreatic duct system, the cat is more susceptible to developing inflammation of the intestine and bile duct in addition to the pancreas..

"Dogs usually have two pancreatic ducts while cats only have one," explains Meachem. "This single pancreatic duct opens to the intestine in conjunction with the bile duct. If a cat has pancreatitis, there's a high likelihood that it also has inflammatory bowel disease (IBD) and cholangitis (inflammation of the liver and bile duct)."

Diagnosis

Along with physical examination, appropriate history and clinical signs, there are a number of blood tests that can be performed to aid in diagnosing feline pancreatitis.

One such test, the feline pancreas-specific lipase assay (Spec fPL), is fairly good at identifying moderate to severe cases. It does have limited ability to detect mild forms of the disease, which can result in these cases being overlooked. This test may also be positive in patients that have diseases other than pancreatitis, making it an imperfect tool in the diagnosis of pancreatitis.

Abdominal ultrasound is useful in recognizing pancreatitis. Specific changes in the appearance of the pancreas and the tissue surrounding the organ can

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signal inflammation and disease. Ultrasound-guided fine needle aspiration (FNA) can be done to collect a sample of cellular material from the pancreas for microscopic evaluation, but this isn't a commonly performed procedure in most cases.

"None of these tests are 100 per cent specific or sensitive," Meachem points out. "But they can help narrow down the list of potential diagnoses."

Treatment

The major treatment strategy for feline pancreatitis is to provide good supportive care.

"This centres on intravenous fluid therapy to maintain the patient's hydration status and adequate nutrition to maintain normal metabolism," says Dr. Casey Gaunt, a WCVM small animal internal medicine specialist.

Providing the required nutrients typically involves placement of a feeding tube until the cat is feeling well enough to resume eating on its

"As well, we often provide medication to control pain in those that demonstrate discomfort," adds Gaunt.

Prevention

No specific preventive measures exist for feline pancreatitis. With dogs, a common solution is to switch to lower fat diets to reduce the risk of recurrence of the disease. This approach doesn't work for cats: abrupt dietary changes can result in decreased food intake and severe liver disease in some cats.

"The best thing an owner can do is recognize when their cat stops eating and seek prompt veterinary care," says Gaunt. "This allows us to identify the problem and provide treatment early in the course of the disease before the cat becomes severely ill." V

Memorial tributes ease the grief

When Jim Dobie lost his golden retriever Angus to cancer in 1996, he was surprised and touched to learn that his veterinarian, Dr. Lloyd Abbey (WCVM '77) of Edmonton, Alta., had made a memorial donation to the Western College of Veterinary Medicine's Companion Animal Health Fund (CAHF) on his behalf.

"I certainly never expected that and didn't even know such a program existed," recalls Dobie. "And I decided that I would do the same for my friends and family when their animals passed away. I found that people were pleased with that kind of recognition."

Recently Dobie and his wife Terri Schindel decided to make a regular monthly donation to the veterinary college's pet health fund in addition to the memorial tributes. Their commitment was influenced by a strong relationship with their veterinarians as well as Schindel's personal connection with the University of Saskatchewan — she's an alumna of the College of Pharmacy and Nutrition.

"We depend on and value ongoing learning in our fields and have chosen to support the CAHF for all that it represents," explains Dobie. "We want to support the education of future veterinarians, the ongoing professional development and consultation services for veterinarians and also the research that leads to new developments in companion animal care."

The CAHF fills the bill for all of those goals by supporting specialized veterinary training, innovative research and the introduction of new technology. The not-for-profit organization helps to fund a wide range of companion animal health research studies at the WCVM as well as the purchase of vital equipment and new technologies at the WCVM's Veterinary Medical Centre.

While Dobie and Schindel have no particular area of research in which they are interested, they believe that there's a broad spinoff benefit from their investment in the fund.

"Whether it's a young veterinarian who makes a discovery or some little thing somewhere that just advances the cause of companion animal health, it's the idea of contributing to a research-based fund. It doesn't matter where the advances are made, be it orthopedics or cancer or diabetes. It all contributes."

That philosophy is shared by many veterinarians who particularly appreciate the idea of supporting a charitable organization dedicated to animal health. For many years Dr. Brian Gibbs (WCVM '70) of Saskatoon's Central Animal Hospital has been donating to the CAHF memorial program on behalf of his clients as a way of expressing sympathy with their bereavement.

"Their reactions are always positive. They appreciate that you're trying to do something of benefit to other pets on behalf of their pet. And I know it leads them to donate themselves."

Gibbs values the opportunity to help support studies directly related to the health of companion animals and has seen the significance of their findings in helping veterinarians treat a wide range of health issues including cancer, arthritis and hip dysplasia.

"The CAHF supports studies that are going to give value back to pets and benefit pets in the future. It's a very beneficial cause



ABOVE: Jim Dobie and Terri Schindel with their two dogs, Parker (left) and Banjo (centre). *Photo: Jeff Entwistle.*

that is not only going to be helpful to pets but could eventually have applications to people."

For veterinarians like Gibbs as well as for pet owners like Dobie and Schindel, memorial donations to the CAHF provide a unique opportunity to offer comfort while advancing the cause of animal health. And as Dobie points out, the payback is significant in the long run with benefits for anyone who has a special bond with an animal.

"As time has gone by, the scope of veterinary practice has broadened, and the types of veterinary care that are provided now are leaps and bounds ahead of where things were even 10 years ago, "says Dobie. "Without research, we would not be where we are today." V

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