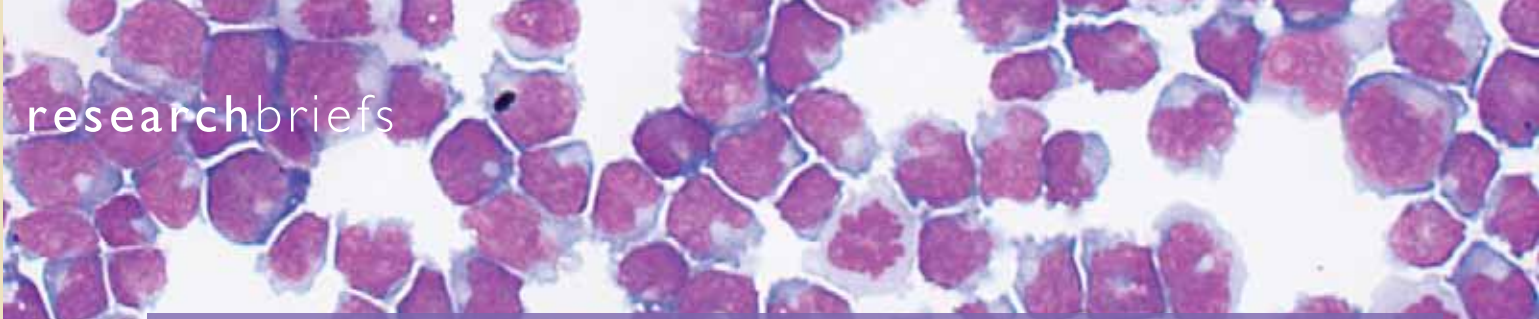


# Penn Vet Research

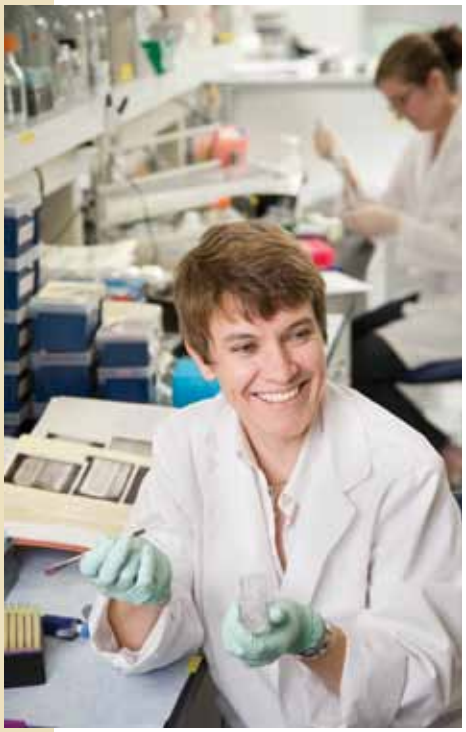
## *Drug Shrinks Dog Tumors, Could Benefit Humans*

BY EVAN LERNER

There are many kinds of cancers of the immune system, but one, Activated B-Cell Diffuse Large B-Cell Lymphoma, or ABC-DLBCL, is particularly common and pernicious. Researchers at Penn Vet have shown for the first time that dogs that develop this disease spontaneously share the same aberrant activation of a critical intracellular pathway with humans with ABC-DLBCL.

They also found that a drug designed to disrupt this pathway helps to kill tumor cells in the dogs' cancerous lymph nodes.

The research was conducted by Nicola Mason, PhD, assistant professor of medicine at Penn Vet, along with Michael J. May, PhD, associate professor of pharmacology; postdoctoral fellow Anita Gaurnier-Hausser, PhD; and veterinary clinical pathologist Reema Patel, DVM.



Dr. Nicola Mason working in her lab.

Their work was published in the May issue of the journal *Clinical Cancer Research*.

B-cells are the part of the immune system that produce antibodies and protect the body against invading microorganisms. In ABC-DLBCL, the normally tightly regulated intracellular signaling pathway involved in B-cell activation and proliferation is, as the name of the disease suggests, constantly activated.

"This signaling pathway, called NF-kappaB, is critical in immune function; following an encounter with antigen, lymphocytes need to be activated and proliferate so that there are sufficient numbers to deal with the invading organism," Dr. Mason said. "But in humans with ABC-DLBCL, and also in dogs with spontaneous DLBCL, this pathway is constitutively active and drives lymphocytes to proliferate continuously."

Moreover, these malignant B-cells are resistant to apoptosis, or cell death. Their unchecked growth is the basis of the lymph node tumors that are a hallmark of the disease.

For many years, researchers have been investigating ways of interrupting the malfunctioning pathway that forms the tumors and provides resistance to chemotherapy-induced cell death. In order to test whether a canine model for inhibitors would have relevance to cancer treatment in humans, the Penn team first showed that the same aberrant activation of the NF-kappaB pathway exists in dogs.

They then went on to demonstrate that inhibition of this pathway using a drug known as NEMO Binding Domain, or NBD, peptide led to increased cell death of malignant lymphocytes in a laboratory setting. The next step was to determine whether this peptide could similarly inhibit NF-kappaB activity when used in the dogs with the disease.

Treatment of DLBCL in dogs is similar to humans; in most cases, the cancer initially responds well to chemotherapy, but patients frequently relapse with drug-resistant disease. The five-year survival prognosis for humans with ABC-DLBCL is about 50 percent, but in dogs the survival rate is much worse, with more than 85 percent of dogs relapsing within the first year and the majority succumbing to their disease during the first or second round of rescue chemotherapy.

Having determined the presence of aberrant pathway activity in the dogs with spontaneous DLBCL and that inhibition of this pathway can lead to increased malignant cell death, the researchers performed a small pilot trial to determine the efficacy of the NBD peptide in dogs that had relapsed with drug resistant lymphoma.

The results were encouraging.

"We injected one malignant lymph node with the NBD peptide and followed up with chemotherapy. One week after a single dose of peptide, the lymph node we injected was a lot smaller than the other cancerous lymph nodes," Dr. Mason said. "This suggests that the peptide either acts alone or synergistically with rescue chemotherapy to kill the tumor cells."

Testing the peptide in a live animal model, rather than in tumor cells taken from cell lines in a Petri dish, accelerates the prospects of this research leading to clinical treatments for both dogs and humans.

"The identification of a comparable molecular pathogenesis of ABC-DLBCL between dogs and humans, coupled with our ability to investigate the therapeutic benefit of targeting this aberrant NF-kappaB pathway in a clinically relevant, large animal model is a great example of the 'bench to bedside' paradigm of translational medicine," Dr. Mason said. "It's been over 10 years since this pathway was recognized in ABC-DLBCL in humans; however, this is the first indication that specific inhibition of this pathway may have a beneficial effect in human and canine patients with this disease."

Dr. Mason and her colleagues are now testing whether the peptide is systemically effective when administered intravenously. Demonstration of safety and therapeutic success in this trial could not only pave the way to a novel approach to the treatment of this disease in pet dogs but also could lead to clinical trials in humans with this type of lymphoma.

The research was supported by the National Institutes of Health, American Cancer Society, Mari Lowe Center for Comparative Oncology and American Kennel Club's Canine Health Foundation.

## RESEARCH BRIEFS

Foundation Fighting Blindness has awarded Penn Vet Professor of Medical Genetics and Ophthalmology **Gustavo D. Aguirre, VMD, PhD** with a $230,000 grant to continue the Penn Large Animal Model Translational and Research Facility.

**David Artis, PhD**, associate professor, has received two National Institutes of Health grants (Regulation of protective immunity following enteric viral infection and Regulation and function of innate lymphoid cells).

The National Institutes of Health has granted **Peter J. Felsburg, VMD, PhD** a $626,059 grant to study gene therapy for canine X-lined SCID.

**Dr. Ronald N. Harty**, associate professor of microbiology, has been awarded a two-year (July 2011 - June 2013) Developmental Research Grant from the NIH Middle Atlantic Regional Center of Excellence (MARCE) for Biodefense and Emerging Infectious Disease Research. His application was entitled "Novel FLIM-Based Optical Measurements of Filovirus Budding Mechanisms" and was one of four selected for funding out of a total of 40 applications. Dr. Bruce Freedman, associate professor of pathobiology is a co-primary investigator.

**Christopher Hunter, PhD**, chairman of the Department of Pathobiology and Tajie Harris, PhD, postdoctoral fellow at Penn Vet, were awarded a National Institutes of Health grant to study the role of chemokines in the T cell response to ocular toxoplasmosis.

**Diane J. Gaertner, DVM**, professor in the Department of Pathobiology, has been awarded a five-year grant from the National Institutes of Health/National Center for Research Resources for "Translational Research and Laboratory Animal Medicine Education for Veterinarians."

The United Mitochondrial Disease Foundation (UMDF) has awarded Penn Vet Assistant **Professor Brett A. Kaufman** a $120,000 grant to study the role that mtDNA copy number control plays in the development of disease. Dr. Kaufman's grant was also selected for the UMDF Chairman's Award for the top grant this year.

**Dr. Charles Vite**, assistant professor, received $100,000 in funding from the National Niemann-Pick Disease Foundation.

## RECENT PUBLICATIONS

Lee Y-H. and Saint-Jeannet J-P. (2011). Cardiac neural crest is dispensable for outflow tract septation in Xenopus (2011) Development 138: 2025-2034. (Also featured in *Science Daily*, April 23, 2011.)

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Eroshin, V.E., Reiter, A.M., Rosenthal, K., Fordham, M., Latney, L., Brown, S., Lewis, J.R. Oral disease in a population of rescued ferrets: clinical examination findings. *J Vet Dent*, 2011, 28:8-15.

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Yuliang Liu, Sasha Stone, and Ronald N. Harty, (2011), "Characterization of Filovirus Protein-Protein Interactions in Mammalian Cells Using Bimolecular Complementation," *Journal of Infectious Diseases*, 204(6) (online August 16).