

The University of Minnesota Animal Cancer Care and Research Program: Innovations and Progress in Comparative Oncology

Since its inception five years ago, the Animal Cancer Care and Research (ACCR) program has been breaking new ground in scientific discovery and implementation of new strategies to improve our ability to detect, treat, and ultimately prevent cancer in companion animals and people.

Our approach

Our mission is to advance knowledge and translate it to reduce the impact of cancer in human and animal patients. Our vision is a world where we no longer fear cancer. We will reach this vision through innovative research that is relevant and responsive to the needs of the people we serve, especially by focusing on the status of companion animals as family members. Our research program is the only one in the nation that fully integrates resources from our College of Veterinary Medicine and our National Cancer Institute-designated Comprehensive Cancer Center, emphasizing research on cancer prevention, causation, diagnosis, and treatment. Some examples of our research programs, which have been made possible in part through the generous support of the Golden Retriever Foundation, include:

Tumor-specific studies

Brain cancer

This program is one of the crown jewels of comparative oncology at the University of Minnesota. Drs. John Ohlfest and Liz Pluhar have developed advanced, comprehensive, and successful strategies to treat otherwise untreatable tumors. Many of the strategies that are being applied in clinical trials were conceived, refined, and validated in their laboratories before making their way into the clinic. More than 70 dogs with brain cancer have participated in clinical trials led by Drs. Pluhar and Ohlfest at the University of Minnesota Veterinary Medical Center,

about 25 just in the past two years. The promise of these treatments is palpable, so much so that the Food and Drug Administration (FDA) provided accelerated approval to use a type of brain cancer immunotherapy on human patients that was developed in dogs. The Comparative Brain Cancer Program was recently showcased on “CBS This Morning,”



and you can see more about Dr. Ohlfest's and Dr. Pluhar's exciting work at www.cbsnews.com/video/watch/?id=7390631n&tag=cbsnewsMainColumnArea.

Sarcomas

This program has similarly shined over the past two years. The Masonic Cancer Center is building one of the premier sarcoma programs in the nation, thanks in large part to collaborations between faculty from the College of Veterinary Medicine and the Medical School to combat these types of cancer. Sarcomas are rare in people, making up only about 1 percent of all human tumors. However, they are quite common in dogs. This not only underscores the need to develop specific treatments to help our companions, but also opens doors to improve our understanding of these tumors that occur infrequently in humans.

Perhaps our most significant advances have been in the area of bone cancer (osteosarcoma). About 600 to 1,000 new cases of osteosarcoma are diagnosed each year in humans in the United States—most of them in children and adolescents. By contrast, it is estimated that this disease affects tens of thousands of dogs each year. Recent work by Dr. David Largaespada uncovered a novel group of genes that contribute to this disease in laboratory animal models. A collaborative project led by Drs. Jaime Modiano, Aaron Sarver, and Subree Subramanian extended these findings and developed new methods to predict the natural history and clinical behavior of these tumors in both dogs and humans. In turn, these efforts have created opportunities to explore whether a class of drugs that is approved by FDA for other diseases might delay or prevent metastasis and improve survival for patients with osteosarcoma. More information on this study is available through our local Minneapolis CBS affiliate at <http://minnesota.cbslocal.com/2011/07/29/cancer-gene-found-in-dogs-could-help-humans/>.

Our work on sarcomas doesn't stop there. The ACCR team recently completed a study in collaboration with our colleagues at ApopLogic Pharmaceuticals and the Colorado State University Animal Cancer Center to test a new gene-based immunotherapy for bone cancer. The results, which were published in *Molecular Therapy* in July, showed that approximately half of dogs with bone cancer that received this new therapy outperformed the expectations for conventional treatment alone. The study also identified a marker that could be used to predict which patients are likely to respond favorably to this therapy, providing a guide for rapid and targeted translation into the clinic.

Partly in response to this experience, Drs. Emily Lipsitz and Vicki Wilke partnered to expand our immunological arsenal against bone cancer. Drs. Wilke and Lipsitz have taken a strategy developed by Dr. Dan Saltzman, who is also at the University of Minnesota, where Salmonella bacteria are genetically crippled so they cannot cause disease. They are then modified to produce proteins that stimulate the immune system and allowed to retain their affinity to infect bone tumors. These bacteria, which are taken in water or juice (or in a pill if you are a dog), traffic to the tumor, where they recruit cells of the immune system that learn to attack tumors elsewhere. This new study is ongoing, and promising results could help Dr. Lipsitz and her colleagues at University of

Minnesota Amplatz Children's Hospital accelerate translation of this therapy to pediatric cancer patients.

Sarcomas are rare in people, but few are more rare or deadly than tumors that arise from cells that form blood vessels. These tumors, called angiosarcomas in people and hemangiosarcomas in dogs, are very uncommon in humans, accounting for only 1 percent of all sarcomas and 0.01 percent of all tumors. The results of a recent study led in canine hemangiosarcoma by Dr. Jill Schappa as part of a Howard Hughes Medical Research Institute Fellowship, and done in collaboration with Dr. Dan Vallera, will increase hope for both canine and human patients with this disease. Dr. Schappa tested the efficacy of a new, targeted drug, developed by Dr. Vallera at the University of Minnesota, to kill the cells that spawn hemangiosarcoma. These so-called "hemangiosarcoma cancer stem cells," which Dr. Schappa identified with help from Dr. Erin Dickerson's group, are uniquely sensitive to the effects of this drug, even though they are very resistant to virtually every known type of chemotherapy that can be safely used in the clinic.

These results provided the impetus for a new partnership between the ACCR and Angiosarcoma Awareness, Inc., to develop a clinical trial for dogs with hemangiosarcoma. This study, led by Dr. Antonella Borgatti, will be conducted in the "minimal residual disease" setting with plans to begin enrollment in the fall of 2012. This means that dogs that had surgery to remove their primary tumor and have no gross evidence of metastasis will be eligible. The drug has been manufactured and is now in the final stages of testing and validation. The trial will use a highly innovative "continuous reassessment" design developed by our biostatistical consultant, Dr. Joe Koopmeiners, to define a safe and effective protocol to treat dogs with hemangiosarcoma and to use as a starting point to treat human angiosarcoma patients.

Lymphoma and leukemia

We have developed a robust comparative team, consisting of veterinarians (Drs. Ito, Modiano, and O'Brien) and physicians (Drs. Veronika Bachanova, Linda Burns, and Michael Linden) to study fundamental causes of lymphoma and leukemia in dogs and humans at the molecular level. These studies follow from our long-term collaboration with scientists at North Carolina State University and the Lineberger Comprehensive Cancer Center, and at the Broad Institute to identify traits that contribute to heritable risk for this disease. The goals are to identify factors that are essential for the development and the progression of these diseases in both species, based on the underlying concept that disease-associated traits that are highly conserved in two species must be important drivers of disease, and therefore are attractive targets for treatment. We also have recently partnered with Karyopharm Therapeutics Inc. to explore mechanisms used by lymphoma cells to acquire therapy resistance and moved their promising compounds to the clinic, where we are testing their safety and efficacy in collaboration with The Ohio State University and Texas A&M University.

Other tumors

We are expanding our programs to tackle other tumors that significantly affect the health and well-being of pets and people. Dr. Largaespada has created a wealth of models to

understand the genetic events that drive cancer in the brain, bone, gut, liver, bone marrow, and other organs. One specific tumor type that is an untreatable scourge for dogs and children alike is histiocytic sarcoma. Dr. Largaespada and graduate student Raha Allaei have made considerable progress in the genetics of this disease, and Dr. Michael Henson is leading a new trial in partnership with Trin Therapeutics, Inc. to test a new drug that has shown preliminary efficacy against this disease.

We have not forgotten our feline friends. Dr. Claire Cannon, the first oncology fellow in our program, is working with Dr. Khalil Ahmed and the Veteran's Administration system to test an innovative, targeted nanotechnology platform to deliver a gene therapy product that is lethal for head and neck tumors. These tumors are common in cats, but they also are of great significance to the health of military veterans and their dependents. We have thus called this program Vets Helping Vets Helping Vets (veterinarians helping veterans helping veterinarians), a win-win-win situation.

Interventions

Cancer stem cells

The concept that specific subsets of cells within a tumor are necessary for that tumor to persist and spread has changed the way we think about cancer therapy. Specifically, it is apparent that we must develop strategies to attack these cells. This has been the focus of recent work in various labs at the ACCR, including Drs. Dickerson, Kassie, Modiano, O'Brien, Ohlfest, and Subramanian, among others. Dr. Dickerson is developing approaches to improve the efficacy of both conventional drugs and new drugs by enhancing penetration deep into tumor tissues. Dr. Modiano and Dr. O'Brien co-mentored Aric Frantz, a DVM/PhD dual-degree student who defined shared properties of cancer stem cells in canine tumors. And Dr. Daisuke Ito's discovery of a subset of potential lymphoma-initiating cells (LICs) in canine lymphoma was the basis for a recently completed multi-institutional clinical trial called "LICKing Lymphoma" (from "Lymphoma-Initiating Cell-Killing").



Cancer immunotherapy

The University of Minnesota is a leader in cancer immunotherapy, and that tradition is alive and well at the ACCR program. In addition to the immunotherapy trials for brain cancer and sarcomas mentioned above, Drs. Mike Henson, Matt Mescher, and Jeff Miller recently published proof of concept for immunotherapy of lymphoma using tumor-derived antigen vaccines, and Drs. Ito and Modiano have started an active project using passive immunotherapy for lymphoma, where the treatment consists of antibodies that

attack the tumors or activate the immune system to attack the tumors. Dr. Ohlfest recently partnered with Dr. Chris Ober to apply thermal ablation (heat applied by microwaves) in combination with immunostimulants to a variety of solid tumors. These pilot studies are in progress, with good evidence of safety. As part of their post-graduate training, Drs. Michelle Goulart and Helen Michael were first to identify subsets of immune cells in dogs that may block or stimulate anti-tumor responses, and Dr. Jong Hyuk Kim is working on strategies to block inflammatory mediators that promote tumor progression.

Diagnostic development

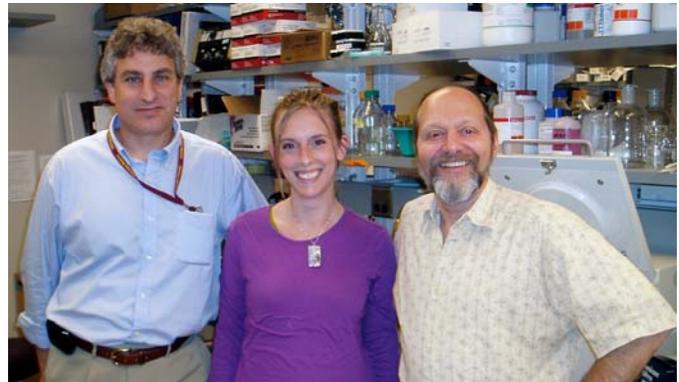
Understanding that early detection and refined diagnostics are essential first steps to improve outcome, Dr. Dan Feeney led a study using advanced medical imaging to assess the extent to which lymphoma affects major organ systems including the bone marrow. A large group led by Dr. Modiano devised a new test that can reliably distinguish subtypes of lymphoma with different clinical behavior. This test has been licensed to an industrial partner for further development.

Cancer prevention and control

We are proud to be one of few comparative oncology programs in the nation with an active emphasis on cancer prevention and control. Cancer prevention at the ACCR is led by Dr. Fekadu Kassie, who studies compounds that are found naturally in cruciferous vegetables and have potential to prevent the development or progression of tumors. Dr. Kassie's research is complemented by Dr. Anindya Bagchi's work on ageing, one of the major risk factors for cancer development. Dr. Kassie also has active collaborations with Dr. Rob Turesky from the New York State Department of Health, who recently partnered with Dr. Modiano to establish bioaccumulation of compounds created by processing food at high temperatures.

Training and education

Philanthropic support has been essential for us to develop training programs at every level, from veterinary summer scholars, where veterinary students can experience cutting-edge research as part of their education, to our residency program, where we train specialists in veterinary oncology, to our fellowship and post-doctoral programs, which are designed to train the next generation of leaders in veterinary cancer research and translational medicine.



Your role in the process

To learn more about our programs and how you can help, please contact Dr. Jaime Modiano at 612-625-7436 or by e-mail at modiano@umn.edu or Andrea Fahrenkrug at 612-626-6501 or by e-mail at fahre018@umn.edu. We are excited about the future as we continue to forge a path for a world without cancer.