Welcome!

We are glad to share our revived Purdue Comparative Oncology (PCOP) Newsletter with you. The newsletter was a popular feature of our program a few years ago. After a break in production, and after many request for it, we are reviving the PCOP Newsletter to share our work and its impact with you. There is so much to share! Although our program has been doing high impact comparative oncology research since 1979, some of our most important contributions have come from work in recent years and work that is ongoing now! The best description of our program is: “Cancer Research to Benefit Pet Animals and People”. We conduct studies in pet dogs with cancer to learn important information that will improve the outlook for pet animals and for humans facing cancer. Our work is possible because certain types of naturally-occurring cancer in pet dogs are very similar to those same cancers in humans, and provide good “models” for human cancer. Plus, the competency of the immune system and the complexity of the cancer in dogs are much more relevant to the human condition than that in experimental models. It is a “win-win-win” program. Each dog benefits, and new information is gained to help thousands of other dogs and humans.

We also want to take this opportunity to say THANK YOU! Our program is fortunate to work with incredibly dedicated pet owners and other individuals who are essential to our advances in helping improve the outlook for dogs and humans facing cancer. It is impossible to fully express our depth of gratitude to the people who make the commitment for their dog to participate in one of our clinical trials. Some drive great distances, e.g. 10 hours round trip! Others fly in from many states away. Many use personal vacation time or paid time off. One family skipped an anniversary cruise so they would not disrupt their dog’s treatment! Others make critical financial contributions to allow the studies to happen. We see you. We appreciate you. And we want you to know that the work we are doing that is improving the lives of dogs and people is directly because of YOU. We are amazed by your dedication and thank you for joining in this incredible work!

Dr. Debbie Knapp, Program Director
Hardly a week goes by without a pet owner asking us if their dog can receive the “Jimmy Carter drug”. In December 2015, former President Jimmy Carter announced that he was free of cancer after being treated for metastatic melanoma in his brain and liver. This was striking news, to say the least, because the outcome of most patients with metastatic melanoma had been grim. Yet, Carter has remained cancer free and celebrated his 95th birthday on October 1 of this year! He received the drug, Keytruda, a new type of immunotherapy called an “immune checkpoint inhibitor (ICI)”. The ICIs are the most promising new cancer drugs in decades. Unlike most of the earlier immunotherapies aimed at “stimulating” various parts of the immune system, the ICIs “take the breaks off” the natural regulators of the immune system. Please let us explain. The immune system has natural checks and balances. It is obvious that the immune system has to go into “attack mode” to clear infections and “foreign invaders” in our bodies. There are times, however, when the immune system needs to “back off” such as when an infection has been cleared and an immune attack is no longer needed. Or, when the immune system is set to attack normal cells or organs by mistake (autoimmune disease). The “brakes” which make the immune system “back off” are the immune checkpoints. While these checkpoints are essential for normal health, cancer exploits these same checkpoints to keep the immune system from attacking the cancer. This concept is illustrated in Figure 1.

Figure 1. This figure illustrates how cancer cells can send “messages” to immune cells (T lymphocytes in this figure) to tell the immune cells to attack (or to not to attack) the cancer. In Panel A, the T lymphocyte has attached to the cancer cell through the T-cell receptor on the T lymphocyte binding to the antigen (“foreign protein”) on the cancer cell. This connection should send a strong signal to the T lymphocyte to attack and kill the cancer. But, with a second connection in place consisting of PD-1 on the T lymphocyte binding to PD-L1 on the cancer cell (an immune checkpoint), the cancer cell tells the T lymphocyte NOT to attack the cancer. Immune checkpoint inhibitors (ICIs) are new drugs that disrupt this checkpoint connection. In Panel B an ICI (PD-1 inhibiting antibody, PD-L1 inhibiting antibody, or both) stop PD-1 from binding to PD-L1. This “takes the brakes off” the T lymphocyte so it can attack the cancer.
Some of the notable checkpoints include PD-1, PD-L1, and CTLA-4. Keytruda and other ICIs block PD-1 thereby “taking the brakes off” the immune system allowing it to attack the cancer. The ICIs have taken the oncology community by storm. Patients with advanced highly metastatic cancers that have failed to respond to several other cancer drugs are having dramatic remissions with the ICIs, and remissions that can last for years. The success has been unparalleled. In fact two of the lead scientists in this field, James Allison and Tasuku Honjo, won the Nobel Prize in Physiology and Medicine in 2018. But…. there is a major challenge yet to be met with ICIs. Only 20% of patients have the dramatic benefit that Jimmy Carter has enjoyed. This low remission rate is not surprising. The immune system can fail in the cancer attack in many ways, and the ICIs “correct” one of the sites of failure. More global strategies to improve ICI therapies are crucial.

Our program is conducting studies in dogs to improve immunotherapy across species. We are currently working on two broad fronts: (1) learning how to identify which individuals will respond well to ICIs and which individuals will not, and therefore better served with other treatments, and (2) studying how other drugs (that are not “immunotherapies”) can actually enhance the immune response and make immunotherapies work better, or in other words “fix” multiple sites of immune failure. Outstanding progress is being made on both fronts.

On the first front, one of the strategies our group is pursuing to identify individuals likely to respond to ICIs, is to characterize cancer at the molecular level. It is fascinating that tumors of the same “type” that look the same through the microscope, can be entirely different at the molecular level. As an example, in invasive urinary bladder cancer, two dominant molecular subtypes (“basal” and “luminal”) have been identified by analyzing the expression (presence) of hundreds to thousands of genes in a tumor mass. We have recently found that naturally-occurring bladder cancer in dogs also has these same specific two subtypes as in human bladder cancer (Dhawan et al., PLoS Genet. 2018). The reason this is important is the cancer in one subtype is expected to be much more aggressive than the cancer in the other subtype, and to respond to different drugs. Evidence is mounting that the response to immunotherapy is also driven by the molecular subtype. Please see Figure 2. We are ideally positioned to use pet dog studies (which are far more relevant to human cancer than lab animal studies) to determine subtype effects to optimize treatment outcomes. In the not-too-distant future, an individual patient’s cancer subtype is expected to become an important factor in selecting the best treatment for that particular individual. After all, cancer and cancer therapy is certainly not a “one size fits all” scenario.

On the second front, we are testing different drugs (drugs other than “immunotherapies”) for their effects in making tumors become more immune “hot”, as this should lead to better outcomes with immunotherapy. Please see Figure 2 again.

These and other studies will position us well for definitive studies when ICIs are available for use in dogs. Currently, ICIs are not available for dogs, and the human forms of these drugs can actually be harmful if given to dogs. Multiple groups are working on developing ICIs for dogs, so please stay tuned!

Figure 2. Immunotherapy is expected to be more effective in tumors that have certain immune cells (CD8+ T lymphocytes) infiltrating into the tumor mass. In the photomicrograph of canine bladder cancer in Panel A, there are not any immune cells infiltrating the tumor. This tumor is “immune non-infiltrated” or “immune cold”, and would be unlikely to respond to immunotherapy. The tumor in Panel B is heavily infiltrated by immune cells and would be classified as “immune hot”. Please note the small dark cells (immune cells, i.e. lymphocytes) between the larger tumor cells. This tumor would be expected to respond to immunotherapy. Recently, a more comprehensive technique is being used to classify tumors as immune “cold” or “hot”. In Panel C, the genes (more specifically RNA) in the tumor have been sequenced. A panel of genes known to affect the immune response was selected for the analysis. In the “heatmap” each column of little boxes represents one tumor, and each row represents one gene. If the box is red, that gene is overexpressed (present in larger “amounts”, more active), and in this heatmap, the red color means immune “hot”. If the box is green, the tumor is more likely to be immune “cold”. One of the key findings is that the tumors in the “luminal” subtype (yellow column heading) are mostly immune “cold”, and tumors in the “basal” subtype (green column heading) are mostly immune “hot”. We are testing strategies to convert tumors from “cold” to “hot”. In Panel D, the immune state has been measured in pairs of tumor tissue collected before and during therapy. Pairs are lined up under purple, yellow, and brown column heading. In the second and third pairs, the immune state becomes more “hot” (boxes go from green to red) with treatment. This is expected to lead to a much better response to immunotherapy.
The feature patient for this issue of the newsletter is Dexter, one of the cutest and friendliest Scottish Terriers that we have met. It is important to point out that through their genetics, Scotties have a 20 times higher risk of bladder cancer than mixed breed dogs. While this is obviously a discouraging fact for pet owners, this presents a very important opportunity to understand how bladder cancer develops, how to prevent it, how to find it early, and how to manage it more effectively. Dexter participated in a bladder cancer screening study at Purdue that began in 2014. The goal was to find the cancer early (if it was destined to occur), to intervene (treat it) early with the hope that treatment would be more effective, and to determine which test would help find the cancer early. We asked Dexter’s family to describe his experiences in their own words in the story below.

When Dexter’s family provided their perspectives in the fall of 2019, Dexter was feeling well and enjoying life 3 years after he was diagnosed with bladder cancer. Sadly, Dexter had a sudden decline in health in December due to chronic, slowly progressing kidney disease that surpassed the point where he could live with it comfortably. We have still included his story in this online edition of our newsletter along with an epilogue written by his family. They, like us, are focusing on all the good that came from his life, rather than only seeing the sadness that comes when a life ends. We appreciate the chance to know Dexter and his truly wonderful family. We are grateful that Dexter helped us so much in learning new information to improve the outlook for future dogs and humans facing cancer!

And so it all started. Dexter is our third Scottish Terrier and we were armed with all of the knowledge we could possibly have about the high incidence of bladder cancer (Transitional Cell Carcinoma, TCC) in Scotties. We knew about the negative effects of lawn pesticides—so Dexter never stepped on a treated lawn. We built a special sink so we could wash his feet and face easily after every walk, just in case. He ate pristine food, had fresh water bowls throughout the house, went on buggy rides, and the list goes on and on. Our commitment to Dexter is 100% — plain and simple.

In 2014, we were invited to participate in the Scottie TCC Screening Study at Purdue, and of course we jumped at the chance. The six-month screenings were going beautifully with Dexter until November 2016, when Dr. Knapp noted a tiny change in Dexter’s bladder wall. Thank goodness for Dr. Knapp’s eagle eyes and phenomenal skill because it was there, and a biopsy confirmed it was TCC, but it was caught very early. Fast forward to today. Dexter has been treated with Deramaxx and a year of Chlorambucil, and there is no detectable growth of the cancer almost three years after diagnosis! And, the best news is he has had no side effects from this treatment.

But, along the way, Dexter’s story takes some very scary twists and turns. He was diagnosed with a major heart problem, specifically, mitral valve endocardiosis, after having several collapsing episodes. After echocardiograms, heart monitoring, chest radiographs, and a new protocol of medications from the Purdue cardiologists, Dexter returned to his typical feisty terrier self and has not had another episode again. So, we now have Superdog Dexter managing both bladder cancer and heart disease very well.
But, the story is not over. Along the way Dexter developed a very swollen mucus-filled gall bladder (mucocele) and was treated with medicine. Although the medicine may have helped for a time, the mucocele progressed causing great concern for Dr. Knapp and Dr. Shaevitz. The worry was that it could rupture, which could be a fatal incident. But, the surgery could be very risky, and maybe the mucocele was not going to rupture. Again, fast forward. Dexter got very sick one night in October, and we rushed him to Purdue having a strong suspicion it was his gall bladder, and it was. Dexter underwent surgery to remove his gallbladder, and the great news is he survived. He spent a week in ICU under the skillful and caring eye of Dr. Aghili, and now he is home recovering like a champ, eating like a horse, and wanting to run around and play and bark at those pesky squirrels and people who happen to invade his territory! Who would have ever thought it!

Dexter has taught us some big lessons so far about the power of the convergence of commitment, love, science, and research. The research and clinical practice of Comparative Oncology is so important as it provides us with better ways to treat humans and animals. But, commitment, love, and dedication are also a part of the equation. And just as important is the will and determination to live — which Dexter has certainly demonstrated throughout all of his ordeals. All of this has come together for Dexter to achieve a wonderful quality of life of 12 years, 8 months and counting.

An Epilogue: A Life Well Lived

Surrounded with overwhelming love and tears, Dexter’s medical story ends on December 25, 2019, with significant kidney disease and the inability to overcome the decline in order to live a quality of life. As we reflect on Dexter’s almost 13 years of life, we celebrate the amazing experiences we had together, our appreciation for the Scottie TCC Screening Study and the knowledge it continues to produce, the commitment and care of the Purdue doctors who took care of him, and the comfort knowing he would not have lived as long as he did with a full quality of life without the Purdue University Comparative Oncology Program.

Dexter enriched our lives on a daily basis with his unwavering love, loyalty, spirit, and determination. And we enhanced his life by keeping him at the center of our universe and allowing us to care and love him throughout his life’s twists and turns. Dexter was a gift to all of us not only when he was alive, but even now and as long as we live with all of his beautiful memories. We would be different people today without having had our beloved Dexter in our lives and that too is a gift because his loss makes life that much more precious.
Congratulations to Deepika Dhawan, PhD who was awarded the 2019 Outstanding Research Staff Award in the Purdue University College of Veterinary Medicine. Dean Willie Reed praised her for “excellence in laboratory work, commitment to clinical research, and contributions to discovery at Purdue Veterinary Medicine and beyond; as well as her valued contributions to teaching students of all skill levels.” Our program greatly benefits from having Dr. Dhawan direct the work in our lab in which important discoveries are moved to the clinics and important clinical findings are moved to the lab for further study!

Each July is a bittersweet time in our program. The senior residents complete their training program and move on to the next step in their careers, and one to two new residents join the program. We wish our departing residents, Drs. Breann Sommer and Blake Marcum, all the best! Both have been outstanding residents and great people to work with. They have won the hearts and appreciation of hundreds of pets and their owners. Dr. Sommer has moved to the VCA Veterinary Emergency Service & Veterinary Specialty Center in Madison, WI, and Dr. Marcum to the Veterinary Specialty Center in Buffalo Grove, IL. We also welcome two new residents Drs. Bushra Zaidi and Luis Lembcke.

Kudos to Dr. Marejka Shaevitz, third-year medical oncology resident at Purdue who received the Robert S. Brody Memorial Award for Outstanding Clinical Research at the 2019 Veterinary Cancer Society Annual Conference for her oral abstract, “Results of the POOF Trial: Piroxicam with Omeprazole or Famotidine in Dogs with Cancer.”

Dr. Knapp accepted an invitation to Chair the Steering Committee for the National Cancer Institute – Integrated Canine Data Commons (ICDC). The ICDC is a developing program that will receive, store, and integrate all types of information from dogs with cancer including: dog features (breed, age, gender, medical and exposure history), cancer features (cancer type, genetic sequencing, etc.), clinical outcome data (cancer progression/regression, response to specific drugs), imaging data, etc. The ICDC will be integrated with human cancer data commons, allowing researchers to use collective data to answer emerging questions in cancer biology and cancer management across species.

As I mentioned in the beginning, our gratitude begins with our dedicated pet dog owners. There is yet another group of people whom we owe our continued gratitude, our donors. The power of private contributions to our work is what allows us to push through barriers and truly fight cancer.

While we are extremely grateful for the grants we receive from resources like the National Cancer Institute, various foundations, the Purdue University Center for Cancer Research, and other industry partners, these only cover part of our work. With growing costs per study and limiting parameters of grant support, individual private support keeps us at the forefront of our research now more than ever. Depending on the study, as little as a few hundred dollars can provide the data we need in order to apply for foundational grant opportunities where the bulk of the research occurs. Then there are the studies that require more than $500,000 to get off the ground!

Your support, no matter the size, helps us to maximize our work and therefore continue the ongoing fight against cancer in pet dogs and humans! Please continue to learn about our program and how to be a part of it. Visit us today at: purdue.edu/vet/pcop.

To learn more about matching gift opportunities, major giving, or legacy contributions please contact the Advancement Office at pvmgiving@prf.org or call 765-494-6304.

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