Clinical trials with animal patients speed human translation

HOW OFTEN HAVE DOG OWNERS looked at their veterinarian’s prescription and noted that the drug is identical to one they are taking? Or that the type of cancer afflicting their cat also occurred in someone they know?

“People are often surprised that many of our medical challenges are shared by our pets,” said Erik Wisner, professor in the Department of Surgical and Radiological Sciences at the UC Davis School of Veterinary Medicine. “We have many biological similarities and live in the same environment, so it’s not too surprising that we develop many of the same medical disorders.”

Wisner explained that the pathogenesis, clinical manifestations, progression, and response to therapy of many diseases – including cancer, degenerative conditions, infectious diseases, metabolic disorders, and genetic defects – are often similar between humans and animals. And the UC Davis Veterinary Medical Teaching Hospital, which sees 55,000 furry, feathered, and scaly patients annually, provides an important opportunity for contributing to human medical knowledge.

“Joining forces across the UC Davis Schools of Medicine and Veterinary Medicine”

(Director’s Message)

Ted Wun, M.D.

WHEN I FIRST ARRIVED AT UC DAVIS (many years ago), one of the unique aspects I soon discovered was the attendance by Bruce Madewell, D.V.M., at our hematology oncology multidisciplinary patient care conference. It was in that forum that I was first educated about canine sarcoma and lymphoma, and cats that get kidney transplants could get a lymphoproliferative disorder very similar to that in humans. It was obvious how much human and veterinary doctors could learn from each other. Soon thereafter, I was in need of a platelet expert for a grant proposal and was lucky enough to be directed to Fern Tablin, D.V.M., Ph.D., who was also at the School of Veterinary Medicine. We were fortunate enough to get the grant. I not only enjoyed a fruitful collaboration, but had a great time learning comparative hematology from Fern and her graduate students during my trips across the causeway to her lab. Widely acknowledged as one of the best schools of veterinary medicine in the world, the UC Davis School of Veterinary Medicine (SVM) is a research powerhouse with a rich and diverse portfolio. School of Medicine and SVM faculty have had many productive collaborations – several of which are highlighted in this issue of the CTSC Connections Newsletter.

(Directors’ Message)
Clinical trials with animal patients speed human translation

Continued from page 1

Medicine just makes sense,” he added. “Instead of working in two separate spheres, we should be tackling problems together.”

Making collaboration a priority

To this end, Wisner, who directs the Veterinary Center for Clinical Trials (VCCT), is leading the efforts to promote animal-human medical collaborations at multiple levels. During the course of the current five-year grant award, the CTSC is allocating resources to advance clinical research collaborations informed by studying spontaneous diseases in companion animals. Examples of productive collaborations include:

➤ An educational video that highlights the breadth and depth of clinical expertise and resources in the School of Veterinary Medicine (https://tinyurl.com/TranslatingMed).

➤ A video that highlights clinical research opportunities for School of Medicine faculty interested in collaborating with School of Veterinary Medicine faculty in veterinary clinical trial (https://bit.ly/2KG0Am1).

➤ A workshop that will explore the administrative, regulatory, and clinical considerations in conducting veterinary clinical trials for faculty, fellows, and graduate students in the Schools of Medicine and Veterinary Medicine (late 2018 or early 2019).

➤ Future inclusion of veterinary clinical trials on the UC Davis Health clinical trial recruitment website (https://studypages.com/ucdavis/).

➤ Cooperative efforts between the Veterinary Center for Clinical Trials, School of Medicine, and the CTSC to accelerate the discovery and development of diagnostics and therapeutics to benefit humans and animals.

➤ Availability of animal biospecimens through School of Veterinary Medicine sources – valuable for early phase investigations – through the UC Davis Biorepositories Core Resource (See page four in CTSC Connections, Vol. 7, Issue 2).

➤ Appointment of a representative of the CTSC Clinical Trials Office to the Veterinary Center for Clinical Trials board.

➤ Integration of veterinary students with medical students in the CTSC T32 research training program.

(Continued on page 5)

DIRECTOR’S MESSAGE

Regenerative medicine, cancer, and ophthalmology researchers at both schools have enjoyed long-term collaborations, and we want to encourage many more. Naturally occurring diseases in companion animals share much in common with their counterparts in humans, and clinical trials in animal patients can inform the design of trials in human patients. The SVM has developed a robust clinical trials infrastructure housed at the Veterinary Center for Clinical Trials. Facilitating collaboration between SOM and SVM investigators is one of two “optional modules” within our grant. In collaboration with the CTSC, the SVM developed two informational videos about veterinary clinical trials, and a pathway for faculty to identify collaborators at both schools. For SOM faculty, I encourage you to visit the Veterinary Medicine Teaching Hospital and the rest of the SVM campus.

In the coming year, as part of the 50th anniversary of the School of Medicine, we will be highlighting SOM/SVM collaborations through a One Health symposium, a celebration of the 20th birthday of the Center of Comparative Medicine, and a special symposium featuring the whole-body PET Scanner (Explorer). I hope you will be able to attend some of these events, and eventually forge collaborations with our veterinary medicine colleagues. §
A CULTURE OF COLLABORATION

Partnering in animal-human eye research

WHEN TALKING WITH PHYSICIAN
Jennifer Li and veterinarian Sara Thomasy, the feeling of mutual admiration is palpable. Both researchers appreciate what the other brings to the table, and together they have joined forces on cutting-edge investigations that may change the way dogs – and people – with corneal eye disease are treated.

“Jennifer is the most gifted eye surgeon I know,” said Thomasy, speaking of Li, an assistant professor of clinical ophthalmology at the UC Davis School of Medicine. “I would definitely go to her if I needed an eye operation.”

“Sara is really amazing,” chimed in Li, referring to Thomasy, speaking of Li, an assistant professor of clinical ophthalmology at the UC Davis School of Medicine. “She is the driving force of our collaborations.”

Pets, patients, and models
According to Thomasy, Boston terriers’ trademark large doe-eyes come with a cost: they tend to develop corneal endothelial dystrophy, a degenerative disease that causes swelling of the cornea resulting in a cloudy-appearing eye, pain, and vision impairment. People develop a similar disease, known as Fuchs’ endothelial corneal dystrophy (FECD). Thomasy points out that canines are excellent models for better understanding FECD and exploring new therapies.

“Although laboratory rats can be genetically induced to develop corneal disease, their small eyes are difficult to operate on, and drug pharmacokinetics differ too much from humans because of the size difference,” she explained. “Spontaneous disease in dogs is much more applicable to human eye diseases.”

Thomasy and Li are using Boston terriers being seen for corneal disease in the UC Davis Veterinary Medical Teaching Hospital to collaborate on several projects. In a recent paper, they describe advanced ocular imaging characteristics of in vivo corneal endothelial dystrophy in dogs. (Thomasy SM, et al. Invest Ophthalmol Vis Sci 2016; 57:OCT495-503). Detailed investigations of Descemet’s membrane, which is attached to the corneal endothelium and is dysregulated in FECD, have also been published. (Ali M, et al. Exp Eye Res 2016; 152:57-70). Both studies support the use of canine eyes as a model for FECD.

Towards better treatment
Li explained that in developed countries, FECD is typically caught early, when people start to develop visual symptoms and eye discomfort and can generally be treated with a corneal transplant as the disease advances. Corneas from deceased donors are usually readily available from tissue banks.

Thomasy described a very different situation in dogs. They usually come to medical attention at a more advanced stage of the disease, when vision is less likely to be restored. And, she added, corneal transplant surgeries are rarely done due to the scarcity of tissue banks for dogs.

In the absence of corneal transplant, corneal swelling can be treated surgically to help with pain, although improved vision does not usually result. Another collaborative project developed and tested in dogs involved a surgical procedure known as a superficial keratectomy and conjunctival advancement hood flap. The results were encouraging; they found that corneal swelling was reduced, and that to their surprise, even vision improved (Cornea 2016; 35:1295-1304). In addition to the surgery’s applicability to canine patients, it could possibly be used for people with late-stage FECD with little potential for vision improvement, as well as for people in less-developed countries without access to corneal transplant surgery.

Longstanding collaborative culture
Thomasy and Li place credit for their fruitful partnership squarely in the lap of the longstanding culture of collaboration that exists between the ophthalmology departments in the UC Davis Schools of Medicine and...

(Continued on page 8)
COLLABORATION ACCELERATES TRANSLATION

From dogs to humans – novel cancer therapy clinical trial

**AN INNOVATIVE APPROACH** to treat advanced solid tumors and lymphomas is in a Phase I/II clinical study after a canine study found increased survival and good tolerability. The proof-of-concept trial in pet dogs, a collaboration of the UC Davis School of Veterinary Medicine and UC Davis Health, eased the way to the human trial now underway at the UC Davis Comprehensive Cancer Center.

“The publication of our dog trial was the first to report on this novel triple therapy,” said Michael Kent, professor and researcher in the School of Veterinary Medicine’s Department of Surgical and Radiological Sciences. Kent co-led the dog study (Clin Cancer Res 2016; 22:4328-4340) with Arta Monjazeb, associate professor in the UC Davis Comprehensive Cancer Center’s Department of Radiation Oncology. This work involved a great team of researchers from both human and veterinary medicine, including William Murphy, Robert Rebhun, Liz Sparger, Robert Canter, William Culp, and many others.

“The encouraging outcomes observed in dogs were much more powerful evidence of the potential benefits for people with cancer than had we only used laboratory animal models,” added Monjazeb, who is principal investigator of the current human clinical trial. “Testing a therapy by treating spontaneous disease in pets is not only humane, but also relevant.”

**Triple therapy – a promising recipe**

The novel strategy consists of radiation therapy, local injection of an immunostimulant into the tumor, and administration of a systemic agent to help reverse the effects of immunosuppression. Monjazeb explained that radiation therapy for cancer is effective not only in shrinking a solid tumor, but also in releasing tumor antigens that could act as a target of the host immune system. This allows the patient to destroy any remaining and newly growing cancer cells.

Previously, experimental therapy involved simultaneously injecting an immunostimulant into the tumor during radiotherapy. For unknown reasons, most patients failed to respond to this strategy and some suffered from immune-mediated toxicities. Monjazeb and Kent hypothesized that the poor outcomes may have been due to a naturally occurring immunosuppressive enzyme – indolamine-2,3-dioxygenase (IDO) – that a patient may produce in response to the double therapy. To combat that possibility, they proposed introducing a third compound to the cancer-fighting cocktail: a systemic IDO blocker, to allow a patient’s immune response to do a better job.

Results of the triple therapy used in five dogs with spontaneous metastatic melanoma or sarcoma were very encouraging: they survived, on average, for nearly 6 months, significantly longer than controls in other published cancer trials. In addition, tumors shrunk by 50 to 100 percent, and a systemic response – determined by behavior of metastases – was also evident. One dog had complete disappearance of metastases, two had a partial response, one had stabilization, and one had metastatic progression.

“The results of the dog trial demonstrated that our triple therapy combination can be safely administered, resulting in significant anti-tumor effects in metastatic disease,” Kent said. The success of this companion animal study led to the approval to begin the Phase I/II clinical trial in humans.

**Keys to rapid translation**

Kent and Monjazeb have previously contributed to a paper on the advantages of using dogs as a model for cancer immunotherapy studies (Immunother Cancer 2016; 4:97). They explained that the many similarities canines share with humans – in terms of environment, development of spontaneous tumors and effects of aging on the immune system – make results of studies much more applicable than murine (mouse) models. Disadvantages were also discussed, including the difficulty of controlling for confounding variables and the possible differences posed by the variety of dog breeds.

(Continued on page 5)
Novel cancer therapy  

Continued from page 4

“Overall, dogs make a pretty ideal animal model for human cancers,” Kent said. “Like people, dogs are experiencing an increase of cancer incidence, and their owners are highly motivated to seek novel treatments.”

Neither Kent, who was in the first class of the CTSCs Mentored Clinical Research Training Program, nor Monjazeb, who was in the CTSC KL2 program, can quite remember how their collaboration began, but they both recall that they deliberately sought out a partner across the causeway.

And the key to their success? “Mutual respect,” Kent said. “A human medicine investigator needs to fully understand that my patients aren’t laboratory animals.”

Monjazeb agreed. “We have an intellectual collaboration; we don’t merely share data,” he added. “We understand that both species have a lot to gain from successful work.”

Veterinary clinical trials – rigorously controlled

Wisner emphasized that veterinary clinical trials should not be viewed as “animal experimentation.” Veterinary trials are nearly identical to human clinical trials, he explains, in that the primary goal is to conduct safe and ethical clinical research with positive outcomes for animal patients. Veterinary trials involve a veterinarian-patient-owner relationship with the owner serving as the custodian of the companion animal. In this regard, veterinary clinical trials have many similarities to human pediatric trials in which a parent serves as the advocate and spokesperson for the child.

Similar to human clinical trials, companion animal protocols require approval in advance, but from the Institutional Animal Care and Use Committee (IACUC) and the Veterinary Medicine Teaching Hospital Clinical Trials Review Board, which is similar in function to the Institutional Review Board (IRB) for human clinical trials. Companion animal owners provide informed consent and can withdraw their pet from participation at any time.

Some 60 to 70 animal clinical trials are ongoing at any one time. Information about current veterinary clinical trials can be accessed at the Veterinary Center for Clinical Trials website (https://bit.ly/2N5ZAWA), and will soon be available on the CTSC study recruitment website.

Using spontaneous companion animal models of human disorders can inform our understanding of disease and response to novel therapies, particularly those involving longitudinal studies. Because animals live shorter lives, there is often a much faster natural progression of disease, according to Wisner. As the barriers to initiating clinical trials can be lower in companion animal patients and the costs of conducting veterinary trials are substantially lower than human clinical studies, they have the potential to both inform and accelerate the conduct of subsequent human clinical trials.

An institution rich in resources

In addition to veterinary and medical resources within a single institution, UC Davis offers extensive expertise in other fields that inform human research, according to Jenna Burton, assistant professor of clinical oncology at the School of Veterinary Medicine. For example, the College of Biological Sciences and Department of Biomedical Engineering provide tremendous resources for investigators.

“The capabilities we have at UC Davis are exceptional and, enhanced by our collaborative culture, it is an ideal research environment,” said Burton, who also serves as associate director of the Veterinary Center for Clinical Trials.

Recognition of this unique positioning of medical and veterinary research was a key driver in the grant-initiated collaboration underway.

Striving towards One Health

UC Davis is one of only 15 institutions in the United States – and the only one west of Colorado – that is a member of the Clinical and Translational Science Award One Health Alliance (COHA). Membership in the consortium is composed of veterinary schools partnered with medical research institutions that have a Clinical and Translational Science Award (CTSA). COHA promotes research on naturally occurring animal models of human disease and veterinary-medical collaboration to advance translational research.

“The increasingly close ties between the UC Davis veterinary and medical schools fit perfectly into the One Health concept,” added Wisner, referring to the global initiative that calls for expanding interdisciplinary collaborations and communications with the goal of attaining optimal health for people, animals, and the environment. “Health care researchers in the human and animal arenas can advance and accelerate medical knowledge and clinical care by working collaboratively far better than working on their own.”

UC Davis Clinical and Translational Science Center  •  2018  •  Volume 8, Issue 1
Collaboration offers new hope for oral inflammatory disease

“MEETING EACH OTHER was purely serendipitous!” said Dori Borjesson, director of the Veterinary Institute for Regenerative Cures and professor of pathology, microbiology and immunology at the UC Davis School of Veterinary Medicine, speaking of finding her collaborator, Nasim Fazel, professor of clinical dermatology at UC Davis Health, a few years ago.

While attending a grant-writing conference, Fazel happened to overhear one of Borjesson’s postdoctoral students discussing feline gum disease, and her ears perked up. A physician with dual board certification in dermatology and dentistry, Fazel is uniquely qualified to treat uncommon inflammatory diseases that involve both oral mucosal and skin manifestations.

Borjesson was working with Boaz Arzi, associate professor of dentistry and oral surgery at the School of Veterinary Medicine to study feline oral disease. Fazel, a human disease researcher, was exactly who they needed.

Cat trials inform diseases in people

“To obtain NIH funding for animal studies, we need to show that there is a disease in people for which it is relevant. So having a human medicine collaborator can be critical,” said Borjesson. In addition, researchers of human disease also tend to have more cutting-edge equipment and therapeutics available to them. “Veterinary researchers are always seeking out human medicine counterparts to collaborate with for the animal diseases we want to investigate.”

Borjesson, Arzi, and Fazel joined forces 5 years ago and recently added Natalia Vapniarsky Arzi – a current CTSC KL2 scholar and assistant research scientist with the School of Veterinary Medicine’s Department of Pathology, Microbiology and Immunology – to study feline chronic gingivostomatitis, a painful and debilitating inflammatory condition of unknown etiologic origin in cats.

The current standard of care for feline gingivostomatitis is removal of all the teeth. To date, this UC Davis School of Veterinary Medicine-School of Medicine collaboration produced three publications in two years, with another currently in preparation.

The first study demonstrated that two infusions of mesenchymal stem cells isolated from a feline’s own fat tissue (autologous cells) resulted in complete clinical remission or a substantial clinical improvement in five of seven cats that completed the study. This study also identified two biomarkers that were possibly predictive of successful response to treatment.

In a second study, the team turned their attention to allogeneic (donor) stem cells. These cells are more readily available, more easily standardized, and provide other practical advantages when compared to the use of autologous cells. Using allogeneic stem cells, and following the same protocol as the previous study, the team reported that four of seven cats experienced complete clinical remission or a substantial clinical improvement. However, there was a delayed response to therapy as compared to cats in the earlier study.

A third study offered the first comprehensive comparison of human and feline adipose-derived mesenchymal stem cells. The data resulting from this study serve as a resource for investigators who use cats with naturally occurring diseases as a model for human diseases.

A fourth study, currently underway, is focused on assessing similarities between serum biomarker profiles and histopathologic features of feline gingivostomatitis in comparison to chronic oral inflammatory diseases in humans, including recurrent aphthous stomatitis, pemphigus vulgaris, bullous pemphigoid and oral lichen planus.

Companion species research

The encouraging results from the cat trials prompted Fazel to pursue investigation into stem cell therapy for patients with oral lichen planus, which, like feline gingivostomatitis, is a chronic, debilitating, idiopathic inflammatory disease of the gums. “Treatment options are limited in refractory cases of oral lichen planus,” she explained, “with an unmet need for novel therapies.” Thus, this sort of research collaboration provides a powerful opportunity to advance cures for both humans and companion animals.

Fazel – a former CTSC Mentored Clinical Research Scholar (2007-09) – is a clinician who works with the director and support staff of the UC Davis Institute for Regenerative Cures, and together they are seeking FDA approval to pursue a clinical trial investigating this novel therapy in oral lichen planus patients.

“Some of my patients read about our collaboration in the Sacramento Bee and are excited over the prospect for results that might help them,” said Fazel. “I’m hopeful that this novel therapy will become a viable option for them in the not-too-distant future.”

§
Joint rounds and conferences

Driven by curiosity and a desire to understand the manifestations of disease and how such conditions may be diagnosed and treated – both across species and across the causeway – UC Davis scientists are building networks to advance the research enterprise. Animal research has been a longstanding avenue on the map of medical research, but the One Health initiative raises the bar to include co-clinical trials. As described elsewhere in this newsletter, a growing number of medical and veterinary researchers have identified collaborators through various modalities, both formal and informal. One burgeoning pathway has been through joint rounds, journal clubs, and conferences.

Ophthalmology

The faculty members and trainees of the Department of Ophthalmology and Vision Science in the School of Medicine and the Ophthalmology Service at the School of Veterinary Medicine share a close and unique relationship despite physical separation. Two of the driving forces behind this relationship are veterinarian Christopher Murphy and physician Mark Mannis, whose own friendship and collaborative activities span more than 20 years.

Veterinary residents attend the School of Medicine’s weekly ophthalmology rounds and veterinary faculty attend monthly grand rounds in Sacramento. Mannis also initiated a monthly collaborative corneal conference that provides a forum for medical and veterinary ophthalmologists to discuss challenging cases in a small group environment.

In addition to the Sacramento-based rounds, the School of Veterinary Medicine hosts an annual Veterinary Ophthalmology Grand Rounds that is well attended and eagerly anticipated by clinical ophthalmologists from UC Davis Health. At this unique event, medical ophthalmologists have the opportunity to examine the eyes of a variety of live creatures, both large and small.

In 2016, UC Davis veterinary and medical ophthalmologists created a comprehensive, yearlong joint microsurgical training curriculum for residents from the Schools of Medicine and Veterinary Medicine. Residents attend lectures together 2-3 times a year, along with joint time in a wet lab working on suturing techniques under the supervision of the faculty from both schools. By combining the groups of residents, this joint activity enabled ophthalmology faculty members to leverage their wealth of knowledge and experience to the mutual benefit of the residents.

Anatomic pathology

Anatomic pathologists and residents from the UC Davis Schools of Medicine and Veterinary Medicine come together in Sacramento for a few hours twice monthly over in an informal venue to discuss interesting cases they encounter. These bimonthly, evening gatherings attract 20 to 30 attendees and have been taking place for approximately 15 years.

Lively case discussions that leverage the combined expertise of the medical and veterinary pathologists ensue through comparisons of disease presentation in humans and nonhuman species, the specificity and utility of tissue tumor markers across species, and the characteristics of zoonotic diseases. Sessions evoke curiosity and provide opportunity to learn. In addition, the conference serves as a convenient resource when looking for a guest speaker from the other side of campus.

Clinical pathology

Shared activities, including multiple research projects, between the veterinary and medical clinical pathologists at UC Davis prompted the launch of quarterly joint rounds. With the goal to create a relaxed atmosphere, clinical pathologists share their research findings, learn about comparative clinical pathology, and develop ideas for new collaborations. The rounds include case discussions and a special focus on transfusion medicine and hematopathology.

Craniomaxillofacial disorders

A group of like-minded colleagues decided to take the concept of a joint journal club to a statewide level. In 2016, they organized the inaugural “Craniomaxillofacial Disorders and Solutions in Man and Animals Conference.” Hosted at UCLA, and supported by funds from the National Institutes of Health, the UCLA School of Dentistry, the UC Davis School of Veterinary Medicine and others, the two-day conference attracted more than 70 investigators and clinicians from human and veterinary medicine. Visit https://bit.ly/2K9AjNo to read more about this conference in the Journal of Dental Research.
Partnering in animal-human eye research  Continued from page 3

Veterinary Medicine. Christopher Murphy, professor of ophthalmology in the veterinary school, and Mark Mannis, professor and chair of ophthalmology in the medical school, have been consulting with one another for decades. It was only natural that Murphy, one of Thomasy’s early mentors, and Mannis, Li’s former mentor, brought the two together.

The departments of both schools share grand rounds and a corneal conference to discuss difficult cases. They also have a joint microsurgical training program, which Thomasy believes is unique in the country.

“In terms of applicability, there’s nothing particularly special about the eye – many animal organs could serve as models for human research,” Thomasy said. “What is unique is the strong collaborative culture between our ophthalmology departments that has been developed over so many years.” §