



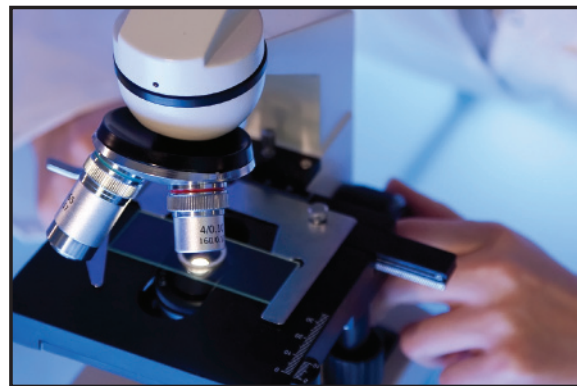
CARE BEYOND A CURE: THOSE AMAZING TYROSINE KINASE INHIBITORS

By Gregory K. Ogilvie, DVM, Diplomate ACVIM (Specialties of Internal Medicine, Oncology)
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Clinician scientists at California Veterinary Specialists Angel Care Cancer Center have joined research teams from around the world to explore the broad applications and safety of several tyrosine kinase inhibitors (TKI's) that have recently become available to veterinarians. The results of these research efforts and others like it confirm that this class of drugs can benefit animals and people with many diseases including cancer, atopic skin disease, immunologic and inflammatory disorders and asthma. These targeted therapies inhibit enzymes involved in cellular signaling pathways that regulate key cell functions and cell survival, especially in mast cells. Mast cells are notorious for producing a wide variety of mediators that can trigger and sustain an inflammatory response with profound negative clinical consequences. Hence, down-regulation of mast cell activity with these TKI's can have an effect on many other downstream signaling pathways, thus benefiting patients with oncological, dermatological, neurological and immune-mediated conditions.

The tyrosine kinase inhibitors used in the veterinary setting most often include imatinib, masitinib, and toceranib. Of these, the latter two have been approved for use in many parts of the world because of their acceptable safety profile and because they have independently been shown to be effective for the treatment of canine mast cell tumors. The governmental approval of masitinib occurred following the successful outcome of a pivotal trial evaluating outcomes of 202 dogs with grade II/III cutaneous MCT including those from the investigators at California Veterinary Specialists. This study reported that masitinib significantly delayed time-to-progression compared to placebo, with the effect being more pronounced when masitinib was used as first-line therapy, and regardless of whether the tumors expressed mutant or wild-type KIT. A follow up evaluation was performed and published on these dogs with mast cell tumors to determine the long-term impact of masitinib their survival. The data confirmed that 62.1% of dogs receiving masitinib were alive at 12 months compared to only 36% of the dogs in the placebo treated group.

Imatinib, masitinib, and toceranib are being actively researched for their use in many other malignant and non-malignant diseases in man and animals, sometimes with synergistic effects. For example, knowledge and safety of masitinib in veterinary patients recently helped accelerate a development program in human melanoma directly to a phase III randomized controlled clinical trial. An additional nine phase III studies currently or about to be underway in people with for pancreatic



cancer, GIST, mastocytosis, asthma, melanoma, multiple sclerosis, rheumatoid arthritis, Alzheimer's disease, and multiple myeloma. Work in veterinary patients has confirmed that at least masitinib can be given safely and effectively to dogs with cancer and who are also concurrently receiving chemotherapy including carboplatin and doxorubicin. Masitinib and toceranib have been shown to result in objective responses in dogs with many malignancies including but not limited to anal sac adenocarcinoma, thyroid carcinoma, malignant melanoma, T cell lymphoma, gastrointestinal stromal tumors, and osteosarcoma. Preliminary results show that masitinib and toceranib can be used safely in cats with cancer, including mast cell tumors.

Work has been done to explore the beneficial effects of masitinib and other tyrosine kinase inhibitors for the treatment of inflammatory diseases including canine atopic dermatitis and feline asthma. Indeed, in one phase III randomized controlled trial in which dogs with confirmed diagnosis of canine atopic dermatitis received oral masitinib or placebo-control for 12 weeks. This study involved 306 treatment-naïve dogs provided strong evidence that daily administration of masitinib achieved a positive clinical including in dogs resistant to Cyclosporine and/or corticosteroids, and dogs with severe pruritus, the latter two groups representing populations with high unmet medical need.

In summary, tyrosine kinase inhibitors have enhanced the ability of veterinarians to benefit dogs and cats with a wide variety of malignancies. Toceranib and masitinib are in fact the first two anticancer drugs ever marketed for the treatment of mast cell tumors in the dog. Emerging data suggest that the beneficial effects appear to extend to dogs with atopic dermatitis and cats with feline asthma. Additional research is underway to confirm these later two off label indications. These unique molecular therapies represent the first step for veterinary medicine in the field of targeted therapies.

Clinical Trials at California Veterinary Specialists

Study Title: AB09003: An open label, prospective, multicenter, randomized, 2-parallel groups, phase 2 study to compare efficacy and safety of masitinib (single agent) to human tyrosinase (huTyr) DNA vaccine (single agent), with a randomization 1:1, in the treatment of dogs with malignant melanoma expressing mutated c-kit post surgery (+/-radiotherapy)
Eligibility: All dogs in good health with confirmed
Hypothesis: We hypothesize that masitinib alone will be equal to the melanoma vaccine and that masitinib and the melanoma vaccine is superior to the vaccine alone.
Financial Obligations: Partial Financial Support

Study Title: AB08012: An open label, prospective, multicenter, randomized, 3-parallel groups, phase 2 study to compare efficacy and safety of masitinib (single agent), masitinib in combination with doxorubicin and doxorubicin (single agent), with a randomization 1:1:1, in treatment of dogs with splenic hemangiosarcoma post splenectomy
Eligibility: All dogs in good health with confirmed
Hypothesis: We hypothesize that masitinib (single agent) is not as effective as masitinib in combination with doxorubicin but superior to doxorubicin for the treatment of dogs with splenic hemangiosarcoma post splenectomy
Financial Obligations: Partial Financial Support

Study Title: AB08014: An open label, prospective, multicenter, randomized, 2-parallel groups, phase 2 study to compare efficacy and safety of masitinib in combination with doxorubicin to Human tyrosinase (huTyr) DNA vaccine (single agent), with a randomization 1:1, in the treatment dogs with malignant melanoma post surgery +/- radiotherapy
Eligibility: All dogs in good health with confirmed malignant melanoma
Hypothesis: We hypothesize that masitinib in combination with doxorubicin is superior to human tyrosinase (huTyr) DNA vaccine (single agent) for the treatment of dogs with malignant melanoma post surgery +/- radiotherapy
Financial Obligations: Partial Financial Support

Study Title: AB08016: An open label, prospective, multicenter, randomized, 3-parallel groups, phase 2 study to compare efficacy and safety of AB1010 (single agent), AB1010 in combination with doxorubicin and doxorubicin (single agent), with a randomization 1:1:1, in the treatment of dogs with advanced or not T cell lymphoma
Eligibility: All dogs in good health with confirmed T cell lymphoma
Hypothesis: We hypothesize that AB1010 will have an anti-cancer effect on her own and that AB1010 will enhance the efficacy of doxorubicin for the treatment of T cell lymphoma
Financial Obligations: Partial Financial Support

Study Title: Chemotherapy/Tyrosine Kinase Receptor antagonist Kinavet study
Eligibility: All dogs in good health with confirmed malignancies that are likely to be benefited with specific chemotherapeutic agents and a tyrosine kinase receptor
Hypothesis: We hypothesize that a novel oral molecular therapeutic will safely and effectively enhance the effectiveness of single agent chemotherapy when used to treat a wide variety of cancers in the dog.
Financial Obligations: The cost of chemotherapy and the molecular therapeutic are free.

Study Title: Therapeutic Apheresis for Canine Cancer
Eligibility: All medium to large sized dogs in good health with histologically confirmed measurable cancer, especially malignant melanoma
Hypothesis: We hypothesize that therapeutic apheresis will safely and effectively remove an inhibitor of the immune system and subsequently cure or control metastatic and non metastatic measurable cancer, especially malignant melanoma in the dog.
Financial Obligations: The cost related to the therapy and scheduled tests are free.

Study Title: Palladium/lipoic Acid Oxidative Stress Study
Eligibility: All dogs in good health with confirmed malignancies that are in remission
Hypothesis: We hypothesize that the palladium/lipoic acid complex, an oral medication designed to enhance quality of life and to have some anticancer effects, will safely and effectively benefit dogs with a wide variety of cancers.
Financial Obligations: The palladium/lipoic acid complex and the simple urine tests are free.

Study Title: OncoNutrition Kinase Inhibitor Family Study
Eligibility: All dogs and cats with cancer
Hypothesis: We hypothesize that the oral kinase inhibitor family will treat cancer effectively
Financial Obligations: The OncoNutrition Kinase Inhibitor is free.

Study Title: Vet Stem Project - Canine
Eligibility: All dogs with Osteoarthritis (OA) that are likely to be benefited with the novel therapy of autogenous stem cells applied intra-articularly.
Hypothesis: Primary hypothesis is that autogenous fat derived stem cells will undergo cellular differentiation and help regenerate diarthrodial joint cartilage in the dog. Secondary hypothesis is that autogenous fat derived stem cells will reduce the detrimental effects of inflammatory mediators in OA.

This project consists of three different studies:
1) The Elbow Joint
2) The Stifle Joint
3) The Hip Joint

Study Title: Vet Stem Project - Feline
Eligibility: All dogs with Osteoarthritis (OA) that are likely to be benefited with the novel therapy of autogenous stem cells applied intra-articularly.
Hypothesis: There are numerous potential therapeutic options for the treatment of Canine OA; few effective therapies exist for the Feline patient. Primary hypothesis is that autogenous fat derived stem cells will undergo cellular differentiation and help regenerate diarthrodial joint cartilage safely and effectively in the cat. Secondary hypothesis is that autogenous fat derived stem cells will reduce the detrimental effects of inflammatory mediators in OA.

Study Title: Total Knee Joint Replacement (TKR) study for the treatment of end-stage degenerative joint disease (DJD/OA) in the dog
Eligibility: All dogs with confirmed measurable knee joint DJD/OA.
Hypothesis: We hypothesize that total knee joint replacement will safely and effectively treat DJD/OA in the dog. Total hip joint replacement is commonplace in veterinary medicine. Cranial cruciate ligament surgery is the most common surgical procedure performed in specialty veterinary surgery. Finding a solution to address this problem would significantly enhance and improve the quality of life of thousands of dogs.

Study Title: Total Elbow Joint Replacement (TER) study for the treatment of end-stage degenerative elbow joint disease (DJD/OA) in the dog
Eligibility: All dogs with confirmed measurable DJD/OA.
Hypothesis: We hypothesize that total elbow joint replacement will safely and effectively treat DJD/OA in the dog. The elbow joint is considered one of the most unforgiving joints in both man and dog. Finding a solution for addressing this problem would significantly enhance and improve the quality of life of thousands of dogs.

Study Title: Plasma gel for enhanced wound healing in the dog
Eligibility: All dogs with skin defects secondary to trauma or surgical dehiscence
Hypothesis: We hypothesize that growth factors concentrated in autogenous plasma gel will safely and effectively enhance the rate of wound healing in the dog.

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Dear Colleagues:

We very much enjoy teaching at CVS, and each year in addition to our internship and residency programs we have scores of visitors from all over the world. It is fun for us and it keeps us on our toes. I am constantly amazed by the knowledge and commitment of these young people and it reassures me that the future of our profession is secure. As the partner in charge of coordinating our training programs I sometimes get questions from primary care doctors regarding our interns and residents, more often due to interest in employing them after graduation, but sometimes in regard to the supervision they receive.



Our internship program is offered through the VIRMP match and is highly competitive. We received 106 qualified applicants for five positions last year and we secured out top choices. Many of the graduates of our program are in general practices in Southern California and several are in residencies throughout the country. They report that they are well prepared for their residencies or to step into a busy private practice.

The program is a rotating internship with the following core rotations: 12 weeks internal medicine, 12 weeks surgery, 15 weeks ER/CC, 2 weeks cardiology, 6 weeks oncology, 1 week ophthalmology, a 2 week elective and one week of vacation. Our ER service is manned 24 hours with highly experienced emergency doctors and unlike many other internship programs CVS interns do not work overnight shifts. In fact, they are never unsupervised. The intern ER shift is a swing shift and while they do have primary care responsibility on the emergency service they are always working alongside a seasoned ER doctor. Although we keep the interns pretty busy, they are available for occasional extra shifts if you find yourself in need of a relief doctor.

CVS is a certified training facility for the American College of Veterinary Emergency and Critical Care and we currently have two residents finishing their programs. Dr. Sarah Hoggan and Dr. Jennifer Hoose have been with CVS for several years before starting their residencies.

Please contact me personally if you have any questions regarding our internship and residency programs. If you are looking for an associate, a few of our current interns have said they want to go into private practice after their June graduation and they very much want to stay in San Diego County.

We thank you all for your continued support.
Amy Carr, DVM, DACVECC

What's New at CVS?

Congratulations to Drs. Sarah Hoggan and Amy Carr for the publication of their article "Mojave toxin-type ascending flaccid paralysis after envenomation by a southern pacific rattlesnake in a dog" in the October issue of the Journal of Veterinary Emergency and Critical Care.

Congratulations to Dr. Kayla Corriveau, a member of our current intern class and a graduate of Western University, for receiving the 2011 Award for Practice Excellence from the CVMA.

Our behaviorist, Dr. Stefanie Schwartz recently participated in the TV show "Swift Justice" with Judge Jackie Glass as an expert witness in a case regarding a labrador retriever accused of biting a schnauzer.

Dr. Schwartz was also recently invited to appear as an expert witness at a recent taping in Hollywood of attorney Nancy Grace's TV show "Swift Justice" on CBS-Los Angeles. Dr. Schwartz was asked to give her professional opinion regarding a case of two mini Dachshunds who were accused of destroying the pet sitter's foam mattress.

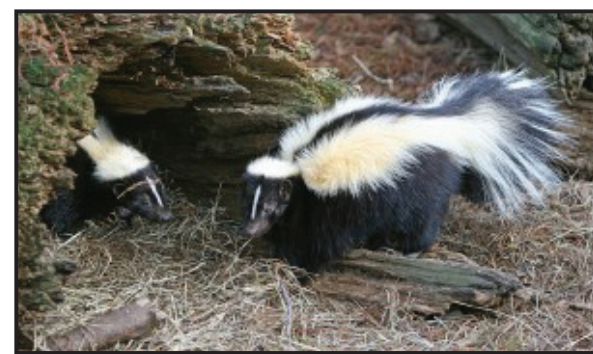
DO DOGS LEARN FROM TRAUMATIC ENCOUNTERS WITH WILDLIFE?

By Stefanie Schwartz, DVM, MSc, Dip. ACVB

Rattlesnakes, Skunks, Spiders and Porcupines, Oh My! Dogs are often repeat offenders in their contact with dangerous creatures. One would think, from our human perspective anyway, that contact with something so painful and frightening would leave an indelible mark in a dog's memory. The old adage of "curiosity killed the cat" seems to apply to dogs, too. From the dog's perspective, the pursuit of critters equipped with some of Nature's strongest defenses is simply irresistible.



Slow moving, shaggy looking porcupines probably are very tempting to dogs looking for a predatory thrill or just playful curiosity. Back East, dogs seem to run into porcupines more often than they do here on the West coast. Either way, the porcupine usually wins. Porcupine quills are not ejected, they simply embed themselves into the dog on contact; undetected quills can then migrate into remote areas much like foxtails do. Do dogs learn to avoid porcupines following this painful encounter? Nope.



I wonder if a skunk might resemble a funny looking cat to a dog, although the average dog who knows cats can probably smell a skunk at a distance, and that's before it gets too close for comfort. It's not like Nature has done much to camouflage the skunk either. Black and white is quite easily detected to any animal even without color vision like dogs. Many poisonous creatures have bright

colors and patterns that evolved in part to give potential predators an extra clue to keep away. Skunk spray is particularly noxious; did you ever deskunk a skunk when it was in style to keep them as pets, and regretted it only after the excised sacs perfumed your hospital? Anyway, the skunk's specialized anal sacs evolved to defend the skunk; unfortunately, they don't work well against motor vehicles. One would think that simple aversive conditioning (skunk = bad) would be enough to deter future inspections. Still, we all know and love dogs who go after skunks over and over again. *Why do they do that???*



Rattlesnakes usually give plenty of warning before they strike, but they don't always get the chance. Goofy dogs galloping through the woods or canyons off leash can trample or startle the snakes. What's a poor snake to do? Dogs just don't seem to understand the rattler is a warning to stay away, and instead continue to approach within striking distance. There is definitely a communication problem between rattlesnakes and dogs.

Spiders don't generally attack without provocation unless you're a fly caught in a web. It is of note that females with eggs can be more offensive than defensive. Most spider bites occur when the spider is accidentally startled by a dog, but the dog might have gone too close to investigate the spider. Dogs don't know that the venom of the black widow spider, for instance, is some fifteen times more toxic than a rattlesnake bite. Perhaps someone should tell dogs about this. In their defense, most dogs probably never saw the spider that bit them. Spiders are everywhere.

So why don't dogs learn to avoid dangerous critters? Well, it's not entirely clear. But, encounters are more likely in dogs who:

- Roam off leash
- Have strong prey drive
- Are young, playful and naïve
- Are not under reliable voice command
- Are not closely monitored during walks
- Are not easily frightened by novel stimuli

Some dog trainers offer training to teach dogs to avoid rattlesnakes. Typically, a shock collar is placed on the dog who is then set up to approach a captive live rattlesnake at which point the shock is delivered. Shock collars, in my opinion, are not humane and can create more problems. Using rattlesnakes as live bait gives me a problem, too.

Here are some tips to keep dogs safe from unfriendly neighbors:

- Dog owners should keep their dogs on leash in high risk areas (or avoid these areas completely).
- Keep yards free of habitats (e.g. piles of debris, clutter, over turned flower pots) for snakes and spiders.
- Control rodent population that might attract snakes: don't feed dogs outside or offer bird seed close to the house (this will also attract other scavengers).
- Repair breaks in your fencing.
- Block access to crawl spaces under your porch, deck or shed.
- Install floodlights in your yard to deter nocturnal creatures from entering the kill zone.
- Make some noise before you let your dog outside so any unwelcome visitor has a chance to get away. Place a strip of jingle bells on your back door, or hang wind chimes near the door. Borrow one of your kid's noise makers and give it a toot, buzz or clang before your dog goes out.

Come to think of it, we shouldn't be asking ourselves *why dogs don't learn from their mistakes with wild-life*. The question is "Why don't WE learn from our mistakes?" If we persist in setting our dogs up to come in contact with danger, then accidents are no longer accidents. The canine predatory drive may override any learning that may or may not have occurred from previous traumatic experience, but it is still our job to protect those we love from getting hurt.

"One can measure the greatness & the moral progress of a nation by looking at how she treats her animals."

Mahatma Gandhi

Be kinder than necessary, for everyone you meet is fighting some kind of battle.



TOTAL KNEE JOINT REPLACEMENT

By Sarit Dhupa, DVM, BVSc
Diplomate of the American College of Veterinary Surgeons

Total Knee Replacements (TKR) has long since been considered the standard of care for the treatment of stifle joint Osteoarthritis (OA) in humans. In veterinary medicine, we have not been able to follow this model primarily due to the lack of long-term follow up data. GREAT NEWS!! We are pleased to report that we now have five-year follow-up on canine total knee joint replacements.

Although cranial cruciate ligament disease is common, regardless of chronicity and osteoarthritis, the current standard of care in veterinary medicine, is to recommend a traditional method of stabilization. It is our strong belief that the standard of care within a few years, for any dog with significant OA will be to perform a TKR, much the same as is recommended in people. Although surgery may be challenging, there have been significant advancements made with regards to both instrumentation and implantation over time.

This rapid evolution has primarily been made possible by the extensive experience gained from the application of total hip replacements over the last almost 40 years in veterinary medicine. We are now able to apply both cemented and non-cemented prostheses to both the distal femoral exoprosthesis and the proximal tibial endoprosthesis. Surgery itself, entails the application of a cobalt chrome distal femoral exoprosthesis and an ultra high weight polyethylene proximal tibial endoprosthesis. The post operative care protocols are similar to those of a standard cruciate stabilization. Our first implantation was performed in April 2007 and our experience leads us to believe prognosis is EXCELLENT for dogs post TKR. The indications include stifle osteoarthritis, osseous malformations, current or previous fractures, certain patella luxations, and other distal femoral and proximal tibial deformities that can be corrected using a TKR. Please do not hesitate to contact Sarit Dhupa (at our Carlsbad campus) or any of the CVS surgical team to discuss any of these cases. Thank you again for your continued support. We are proud and honored to be your partner in providing continued and ever improving health care to your patients.



CVS RADIATION ONCOLOGY MILESTONES

By David Proulx, DVM, MSpVM
Diplomate, American College of Veterinary Internal Medicine, Oncology
Diplomate, American College of Veterinary Radiology, Radiation Oncology

The Radiation Oncology Department at California Veterinary Specialists has reached an important milestone this year. Since starting our radiation treatment program in 2004 we have treated more than 1000 dogs and cats with cancer. Now we treat nearly 250 patients each year at our Carlsbad treatment center and deliver more than 2500 individual treatments annually. We have also established ourselves nationally-recognized radiation treatment center with cases coming to us from San Francisco, Los Angeles, Las Vegas and the East Coast.

We have also reached our two year anniversary of performing Cyberknife Treatment. To date, more than 30 patients have received treatment using this cutting edge technology. Cyberknife Therapy is a form of radiation called stereotactic radiosurgery. This type of therapy allows for the delivery of high doses to a tumor while at the same sparing critical surrounding normal tissues.

With the coming year we are looking to expand our services even further. In collaboration with the UCSD Medical Center we are now able to offer a second form of radiosurgery for our patients using Varian Medical Systems' Trilogy. Like Cyberknife, the Trilogy is able to deliver sterilizing doses of radiation to a tumor while sparing the surrounding normal tissues from the harmful effects of radiation. We are currently the only radiation facility in the world able to offer both Cyberknife and Trilogy radiosurgery. We are optimistic that these cutting edge technologies will allow us to continue to make significant strides in fighting canine and feline cancer.



WE ARE HAPPY TO WELCOME OUR NEW BOARD CERTIFIED SURGEON

Dr. Seth Ganz
DVM, DACVS

Dr. Seth Mathus Ganz received his veterinary degree from Tufts University's School of Veterinary Medicine in North Grafton, Massachusetts. He completed a one-year rotating internship followed by a one-year surgical internship in San Diego. Dr. Ganz went on to complete a three-year small animal surgical residency at Fox Valley Animal Referral Center in Appleton, Wisconsin. He obtained board certification by the American College of Veterinary Surgeons in 2011.

Dr. Ganz has broad interests in soft tissue and orthopedic surgery, as well as in neurosurgery. He has published research on total hip replacement and thoracic trauma.

Dr. Ganz will be based in our Carlsbad location. He can be reached at (760) 431-2273.