



## VCS Mid-Year Symposium is a Big Winner in Vegas!

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Keynote speaker, Dr. Karen Milligan, (L)  
with Program Chair, Dr. Betsy Hershey

The mid-year VCS meeting was held March 7-10<sup>th</sup> 2010 in Las Vegas, Nevada at the Red Rock Casino Resort and Spa. The resort is located off the strip and is considered a "locals" casino. It had all the amenities including a casino, a spa, excellent restaurants, a 16 screen movie theater, an 11 lane bowling alley and spectacular views of Red Rock Canyon.

The topic of "Targeted Therapies" was timely with the recent marketing of Palladia and Kinavet. Dr. Cheryl London presented a discussion on the historical use of tyrosine kinase inhibitors (TKIs) in veterinary medicine, current therapies and the future of TKIs in veterinary medicine. Of particular interest was Dr. London's presentation on the use of Palladia including practical tips for dosing and management of side effects. The potential for use of Palladia for non-mast cell cancer patients was also discussed, including which cancers anecdotally have responded to Palladia. Palladia's effects against non-mast cell cancer are proposed to be due to its receptor inhibition profile, including VEGFR and PDGFR in addition to kit, resulting in anti-angiogenic activity. The

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## FROM THE GUEST EDITOR'S DESK

David Proulx, DVM, MSpVM  
Diplomate ACVIM (Oncology)

Greetings from San Diego. Welcome to the summer edition of the VCS Newsletter. Summer means that the VCS Annual Meeting is just around the corner. We are very excited to have our city as the host of the meeting. The conference committee is working feverishly to ensure a successful event. Remember to get those abstracts submitted in time!

I would like to thank all of those who have contributed to this summer edition of the VCS Newsletter. Targeted therapies are certainly the hot topic these days. While these therapies are not entirely new, the development and release of Palladia has definitely brought such therapies back to the forefront of the veterinary oncology world. The recent mid-year VCS meeting in Las Vegas was entirely focused on such targeted therapies. In this issue, Dr. Betsy Hershey has generously provided us with a written summary of the Las Vegas meeting.

Keeping on the theme of targeted therapies, Drs. Greg Ogilvie and Albert Ahn have contributed an article entitled "Masitinib – The Efficacy of Targeted Therapy in Veterinary Medicine." This article provides nice overview of Masitinib and its role in targeted anti-cancer therapy. More specifically, the authors highlight the uses of Masitinib in the treatment of mast cell disease as well as discuss other potential applications of the drug.

Additionally, in this newsletter's Tech Talk section Patricia Mata from Texas A&M provides an overview of mapping and measuring masses. Ms. Mata, highlights the importance of measuring and tracking masses -- something many of us undoubtedly overlook during our daily busy routines.

I hope you enjoy reading this issue of the VCS Newsletter. I want to thank all of our contributors to the newsletter. I look forward to seeing everyone this October in San Diego.

Best regards,

Dave Proulx, DVM, MSpVM, DACVIM (Oncology),  
DACVR (Radiation Oncology)

## WEB SITE UPDATE

[www.vetcancersociety.org](http://www.vetcancersociety.org)

Use Password1 with your email address the first time you log in and check out all the new features!

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Previous issues of VCS News  
are now available  
in the Members Only  
Section of the web site.

## GUEST EDITOR FOR THE NEXT ISSUE OF VCS NEWS

Dr. Carlos Rodriguez will be Guest Editor for the Fall 2010 Issue of VCS News. If you would like to submit a manuscript for publication, please send it to him no later than July 6, 2010.

Phone: (415) 401-9200  
Email: [thecowdoctor@hotmail.com](mailto:thecowdoctor@hotmail.com)

Graphics should be submitted as separate TIFF, EPS, or large JPEG files. Inline or embedded graphics will not be accepted.



## *A Canyon Walk with Andrew and Leann Vaughan*



VCS's first hiking excursion occurred on March 8th during the Las Vegas Mid-Year conference. Thirty-three participants of varied industrial, private practice and academic backgrounds all enjoyed a lovely walk through the Calico Tanks region of Red Rock Canyon National Recreation Area. Andrew and Leann Vaughan successfully ensured that everyone remained on the trail and that no injuries were sustained. The hike culminated with a beautiful view of the Las Vegas Valley from the 5,000ft peak of Calico Hills. Surprisingly, in spite of forecasts to the contrary, all of the hikers managed to avoid nearby passing rain storms. The trip was such a success that we are all hopeful that it might spark a tradition of incorporating hiking or other physical activities into future VCS conferences.

*continued from page 2 President's Note*

mas). In order to achieve appropriate levels of power for analysis, the project requires tumor samples from ideally 80-100 dogs of a few common individual breeds for each of these histologic tumor types. Help from the dog owning public as well as the veterinary oncology community is needed to pump up the case numbers quickly. Markers of cancer risk may be discovered that can facilitate improved purebred dogs through selective breeding, and discovery of previously unknown cancer associated genes and pathways will advance our basic knowledge as well. Data will be placed into the public domain as it becomes available, so in a sense this project will belong to all of us. All it takes to contribute are signed client consent forms along with 3 mls of EDTA blood from every tumor bearing purebred dog you see with ANY type of malignancy, and ideally 1 gram of fresh tumor tissue obtained at the time of biopsy of lymphoma, osteosarcoma, melanoma, histiocytic sarcoma, and hemangiosarcoma lesions. Pedigree information is desired but not essential for inclusion. Samples are FedExed overnight to the Van Andel Institute at no cost to the collecting institution. Please go to [www.VAI.org/helpingdogs/](http://www.VAI.org/helpingdogs/) to download contact information, forms and collection and shipping specifications.

Thanks for your time in reading this piece – I look forward to seeing you all in San Diego in October, and wish you all a lovely summer!

## **Masitinib – The Efficacy of Targeted Therapy in Veterinary Medicine**

Gregory Ogilvie, DVM, Diplomates  
ACVIM, ECVIM<sup>1</sup> and Albert Ahn, DVM<sup>2</sup>  
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Care Cancer Center, Carlsbad, CA.  
<sup>2</sup>AB Science USA, 51 JFK Parkway, First  
Floor West, Short Hills, NJ.

### **Targeted Therapy**

Masitinib, a drug being developed for numerous indications in veterinary and human medicine by AB Science ([www.ab-science.com](http://www.ab-science.com)), belongs to a therapeutic class known as targeted therapy. These small molecule drugs selectively inhibit specific tyrosine kinases or their signaling pathways. In the last decade several tyrosine kinase inhibitors (TKI) have been developed for the treatment of cancer and other diseases, the most well-known being imatinib (Gleevec, Novartis), which has dramatically improved the treatment for patients with chronic myelogenous leukemia and gastrointestinal stromal tumor. Unfortunately, resistance to imatinib tends to develop for some patients. Nonetheless, targeted therapies are still creating a buzz in human and veterinary medicine alike; including, at this year's VCS conference in Las Vegas.

### **About Masitinib**

Masitinib is arguably the most specific inhibitor of KIT available. In vitro, it has shown greater affinity and selectivity for the KIT receptor as compared to imatinib, while not inhibiting, at therapeutic doses, those tyrosine kinases or tyrosine kinase receptors attributed to possible toxicity. This highly selective nature suggests that it will exhibit a better safety profile than other TKIs (Dubreuil et al, 2009). Among

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masitinib's other claims-to-fame is that it was the first approved targeted therapy in veterinary oncology, having been registered by the European Medicine Agency in November 2008 for the treatment of non-resectable mast cell tumors (MCT)s grade II/III (EMEA approval under the trade name Masivet®; Kinavet® in the USA, pending FDA registration review).

Since Masivet's European launch in 2009 it is estimated that 480 veterinarians have used it for approximately 1390 dogs; primarily as a treatment for MCT but also as an off-label treatment for various other cancers and in a phase III study for canine atopic dermatitis. In the USA, masitinib has been available as part of a compassionate-use program with approximately 650 recipients to date.

#### **Masitinib's Anticancer Action**

Other than KIT, masitinib also potently targets platelet-derived growth factor receptors (PDGFR  $\alpha$  and  $\beta$ ), Lyn and to a lesser extent fibroblast growth factor receptor 3 (FGFR3) and the focal adhesion kinase (FAK) pathway. Altogether, these could provide a mechanism of action for masitinib's anticancer properties.

Masitinib's strong inhibitory effect on wild-type and juxtamembrane-mutated KIT receptors, results in cell cycle

arrest and apoptosis of cell lines dependent on KIT signaling. Stem cell factor, the ligand of the KIT receptor, is a critical growth factor for mast cells, essential to their survival, proliferation, differentiation, adhesion and degranulation processes. Thus, masitinib exerts a direct antiproliferative and pro-apoptotic action on mast cells through its inhibition of KIT signaling. Evidence also indicates that recruitment of inflammatory cells, especially infiltration by mast cells, facilitates the growth and spread of cancers by producing molecules that enhance tumor invasiveness. Therefore, inhibition of mast cell function may prove to be therapeutically beneficial in restraining the growth of numerous cancers, even those without a direct association with mast cell proliferation.

In addition to its antiproliferative properties, masitinib can also regulate the activation of mast cells through its targeting of Lyn and Fyn, key components of the transduction pathway leading to IgE induced degranulation (Gilfillan & Tkaczyk, 2006). This can be observed in the inhibition of Fc $\epsilon$ RI-mediated degranulation of human cord blood mast cells, the effect of which is again stronger with masitinib than compared to imatinib (Dubreuil et al., 2009). By

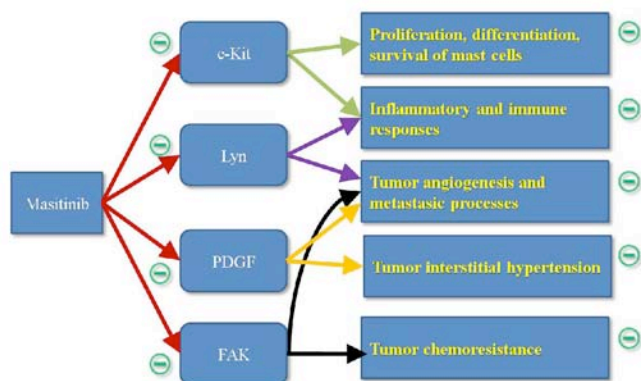
consequence of masitinib's down regulation of mast cell activity, it reduces the array of mediators released, including VEGF, which in turn is likely to disrupt as yet unidentified downstream signaling pathways and angiogenesis processes. Additionally, it is thought that inhibition of Lyn kinase activity also has potential benefits in defense against metastasis and drug-resistance.

Masitinib may reduce angiogenesis and enhance the chemotherapy sensitivity and availability at the tumor site via inhibition of PDGFR. Recent studies have suggested that PDGFR- $\beta$  inhibition reduces tumor interstitial pressure and thus, increases the uptake of concomitantly administered drugs (Jayson et al. 2005). Inhibition of PDGFR kinase activity may also result in direct tumor cell growth arrest and apoptosis if PDGFR is constitutively activated.

FAK influences cell proliferation, survival, and migration, and has been associated with tumor progression, metastasis and chemoresistance. Masitinib can block the FAK pathway in cells through the inhibition of FAK phosphorylation activity, without blocking its enzymatic activity. In vitro tests have shown that gemcitabine-resistant pancreatic tumor cell lines were resensitized to gemcitabine when used in combination with masitinib, possibly in part through inhibition of the FAK pathway (Humbert et al. 2010).



Figure 1: Main kinases targeted by masitinib and mechanisms of anticancer effect.



- Fifty percent (80/160 dogs) of the overall population treated by masitinib had their tumor decrease in size by  $\geq 50\%$  during the first 6 months, versus 12/41 dogs (29%) in the placebo group ( $p=0.02$ ).
- Masitinib demonstrated an anti-metastatic potential, reaching statistical significance ( $p=0.006$ ) in preventing the emergence of metastasis. Additionally, complete remissions in cases of metastatic MCT have been reported in a pilot study and also in post-registration cases.

### Mast Cell Tumors

MCT is the most common cutaneous malignant neoplasm in dogs, accounting for 16 to 21% of all skin tumors. Targeted therapies represent a cutting-edge new technology in the treatment of MCT. For the first time, it is possible to accurately target the cells responsible for proliferation of this potentially aggressive tumor. Masitinib was specifically designed to target mast cells, working directly at the origin of the tumor, and is therefore distinct from usual cytotoxic chemotherapies that prevent multiplication of all cells, including healthy and useful ones.

Masitinib was approved for the treatment of canine MCT following the successful outcome of a pivotal trial including 202 dogs with grade II/III cutaneous MCTs, recruited from 25 veterinary centers in the USA and France. Kevin Hahn et al. reported that masitinib significantly delayed time-to-progression (TTP), i.e. increased overall median TTP compared to placebo, with the effect being more pronounced when used as first-line therapy and regardless of whether the tumors expressed mutant or wild-type KIT. Other key results from this study included:

- For dogs with non resectable tumors and regardless of the presence of KIT mutations, masitinib induced: long-lasting tumor control; significantly improved long-term survival; and was a curative treatment, inducing complete tumor responses at 24 months in 23.8% of observed cases vs. 0% with placebo.

	Masitinib	Placebo	p-value
Best response rate (first 6 months)	50%	29%	0.020
Overall TTP for non-resectable tumors	173 days	75 days	0.001
TTP for non-resectable, non-mutated KIT tumors	140 days	75 days	0.027
TTP for non-resectable, mutated KIT tumors	241 days	83 days	0.002
12-month survival rate for non-resectable tumors	62%	36%	0.024
24-month survival rate for non-resectable tumors	40%	15%	0.040
Median overall survival for non-resectable tumors	617 days	322 days	0.121

Table 1. Masitinib is well tolerated and demonstrated significant effectiveness in large-scale, placebo-controlled clinical trial.

### MCT Case Studies

Masitinib's benefits are illustrated well by this post-registration case of a 9 year-old Shar Pei, who presented with recurrent, grade III MCT that failed standard treatment (vinblastine plus prednisolone combination, which was then followed with lomustine). A rapid improvement was observed within 14 days of treatment with masitinib (Figure 2) with complete healing observed by day 40 and a complete response that has lasted for at least 7 months. Not only did the tumor decrease in volume, but quality of life was generally improved.

### Using Masitinib

TKIs are user friendly drugs. Unlike chemotherapies, masitinib is delivered orally in tablet form and can be administered everyday directly by the owner at the point-of-care, for example, at their home. Masitinib has also been rigorously tested in clinical trials to prove its efficacy and safety, with the study follow-up in the MCT trial being longer than 4 years to date. Common

Figure 2: Complete response of grade III MCT (photography courtesy of Dr Malcolm Brearley)



side effects typical associated with this therapeutic class are diarrhea and vomiting. These reactions are usually mild to moderate in severity and typically last less than a few weeks. Moreover, such reactions are transitory, having a comparable frequency to untreated dogs after the first 3 months of treatment. Dogs being treated with masitinib must be regularly monitored by the veterinarian (bi-weekly during the first 3 months, then at least monthly) for side effects including possible protein loss syndrome. Contraindications include dogs suffering from liver or renal function impairment and in dogs with anemia or with neutropenia; in addition to pregnant or lactating bitches, dogs less than 6 months of age or less than 3.4 kg body weight.

### Masitinib Off-Label Experiences

The off-label use of masitinib in Europe has revealed some interesting case studies that are now the focus of further clinical development. These include several examples of masitinib being used for maintenance chemotherapy of dogs with T-cell multicentric lymphoma. For some of these dogs, masitinib monotherapy of T-cell lymphoma was sufficient to maintain a complete or clinical remission. These clinical observations are supported by *in vitro* data showing that canine T-cell lymphoma cell lines are particularly sensitive to masitinib, possibly due to inhibition of PDGFR.

In another case, a dog was diagnosed as having histologically confirmed neurofibrosarcoma with mast cell infiltration. This tumor recurred despite two prior surgeries, chemotherapy with doxorubicin and metronomic chemotherapy (endoxan/meloxicam). A strong relationship exists between the pathogenesis of neurofibrosarcoma and both mast cells and Schwann cells, suggesting therefore, possible benefits from treatment with targeted KIT or PDGFR inhibitors, respectively. Upon commencement of masitinib monotherapy an observed rapid tumor growth was quickly stabilized followed by a significant decrease in volume and a negligible mass after 10 weeks of treatment.

Finally, one dog presented with a histologically proven metastatic melanoma that was unresponsive to chemotherapy; however, after the introduction of masitinib a complete response was achieved. Again, these findings are supported by *in vitro* experiments, which show masitinib can sensitize canine melanoma tumor cell lines to doxorubicin, even doxorubicin-resistant (17CM98) melanoma cells.

### Masitinib as a Chemosensitizer

There is evidence that masitinib can exert an anticancer action that extends beyond its inherent tyrosine kinase inhibitory profile, e.g. *in vivo* and *in vitro* studies have shown that it can enhance the antiproliferative effects of gemcitabine in human pancreatic cancer; even in gemcitabine-resistant cell lines (Mityr et al. 2010; Humbert et al. 2010). Such chemosensitisation may allow lower concentrations of chemotherapeutic agent to be used, thereby reducing risk, or may increase drug efficacy at standard doses. How masitinib acts as a chemosensitizer is not yet clear and additional investigations are needed to elucidate the mechanism of chemosensitisation. What can be inferred, however, is that for many cancers the effect is not due to a direct inhibition of masitinib's main tyrosine kinase targets, nor by any mechanism specific to a given chemotherapeutic agent. Rather, a complex interplay within the *in vivo* environment creates synergistic effects that render the cells more susceptible to masitinib/chemotherapy combination, i.e. through the reduction of tumor progression, improved drug delivery, the inhibition of mast cell migration and activation, and/or anti-angiogenesis effects.

Douglas Thamm et al. investigated masitinib's potential as a chemosensitizer in canine combination chemotherapies, including its ability to sensitize canine cancer cell lines to several che-



Table 2: Masitinib is being developed for several oncology and inflammatory indications

<b>Targets</b>	<b>Action</b>	<b>Therapeutic potential</b>
<b>KIT</b> <b>PDGFR</b> <b>FAK pathway</b>	Inhibition of proto-oncogenic targets	MCT T-cell lymphoma Melanoma Splenic hemangiosarcoma
<b>PDGFR</b> <b>Lyn/FAK</b>	Potential of chemotherapeutic agents	Tumors treated with chemotherapies
<b>Mast Cells via</b> <b>KIT / Lyn</b>	Inhibition of mast cell activation	Atopic dermatitis Arthritis Asthma Inflammatory Bowel Disease

*This list of indications reflects the development program of masitinib in veterinary medicine and should not be interpreted as a list of indications in which masitinib demonstrated efficacy.*

motherapeutic agents (Thamm et al. manuscript submitted). These data established proof-of-concept that masitinib strongly sensitized histiocytic sarcoma cells to vinblastine; osteosarcoma and mammary carcinoma cells to gemcitabine; and to a lesser degree, several cell lines were sensitized to doxorubicin. Following this, Anthony Rusk et al. performed phase I studies in dogs with advanced tumors and showed that masitinib in combination with carboplatin or doxorubicin had acceptable and manageable safety profiles, without added toxicity (Rusk et al. manuscript submitted). Moreover, encouraging antitumor activity was observed in both combination studies with a number of dogs achieving partial or complete responses. These results have led to the implementation of several phase II studies to further investigate masitinib's potential to sensitize various canine cancer cell lines to cytotoxic agents (Table 2).

### **Masitinib for Inflammatory Diseases**

As previously mentioned, the main cellular target of masitinib is the highly influential mast cell and consequently masitinib can provide therapeutic benefit in inflammatory diseases involving mast cell dysfunction. Indeed, masitinib has recently completed a successful phase III trial for canine atopic dermatitis, and is undergoing phase II trials in canine inflammatory bowel disease and arthritis; as well as feline asthma.

Masitinib's pharmacological profile leads to numerous potential therapeutic possibilities for which the following clinical development program has been implemented to explore further (Table 2).

### **Masitinib for Cats**

Currently, masitinib is only officially authorized for use in dogs; however, AB Science is actively evaluating this drug for use in cats. Pharmacokinetics and toxicity preclinical studies of masitinib in cats has already been published (Bellamy et al, 2009), with masitinib having therapeutic potential in feline asthma, inflammatory

## Notice:

### Membership Dues Increase Effective January 2011

Veterinarians \$150  
Residents, Interns \$50  
Techs, Students \$40

*It has been at least 4 years  
since the last dues increase.*

bowel disease and of course MCT. Off-label use has again revealed some interesting case studies. These include one subject presenting with MCT who experienced rapid improvement in clinical status after 7 days of masitinib treatment and partial response in two sub-cutaneous nodules. Also, encouraging results are reported in asthmatic cats; one presenting with corticosteroid-intolerance and another with corticosteroid-resistance, who have both been treated with masitinib for over 6 months and show an improved quality of life. Masitinib's potential to treat feline asthma will be further investigated in an imminent phase II study.

### Concluding Remarks

Perhaps the most striking aspect of masitinib from a veterinarian's point-of-view is the possible diversity of its applications. Already established as a valuable treatment for MCT, masitinib could have the potential to treat a wide range of other cancers, either by itself or in combination with existing therapies. Then there are its anti-inflammatory uses, such as atopic dermatitis and asthma. So, even if this is the first time you have read about masitinib, it is fair to say that it is unlikely to be the last time you hear about this dynamic drug.

### Acknowledgements

Albert Ahn is an employee of AB Science. The authors thank Colin Mansfield, PhD who provided medical writing services on behalf of AB Science. No other conflicts of interest have been declared.

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### Medical Oncologist Position in UK

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