

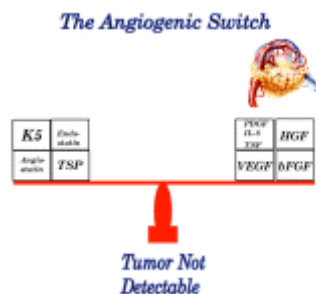
## Targeting the blood supply of cancer. Discussion of novel and non-toxic treatment available for pet dogs with lymphoma

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New, effective, and non-toxic treatments are now under investigation in both pet animals and people with cancer. These new treatments have become available through a dramatic increase in our understanding of the basic biology of cancer and the requirements for cancer growth and spread. An essential requirement for cancer growth and spread appears to be the development of new blood vessels (angiogenesis). If a cancer requires new blood vessels in order to progress, then it may be possible to prevent a cancer from growing or spreading by preventing it from creating new blood vessels. This possibility is now the basis of a novel approach to the treatment of cancer that is based on either preventing a cancer from creating new blood vessels (antiangiogenic agents) or specifically destroying the blood vessels in a cancer.

Angiogenesis is a complex and intricately controlled process. This process is based on a balance between positive factors that promote new blood vessel formation and negative factors that inhibit new blood vessel formation. The goal of new anti-angiogenic therapies is to shift this balance, which in cancer has "switched" towards new blood vessel formation, in the other direction, i.e. towards the inhibition of blood vessel formation. Many factors have been found to influence this blood vessel formation balance. Several are currently under investigation as potential anticancer agents.



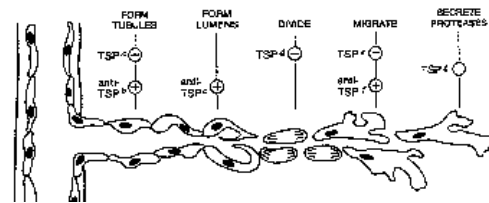
The angiogenic switch that shifts the balance towards blood vessel formation in cancer

Since most adult tissues do not require new blood vessel formation, these new anticancer agents hold the promise of effectiveness and the absence of significant toxicity. Tissues in which new blood vessel formation is needed in the adult include healing wounds, the outer surface of the eye (cornea), the uterine lining during the estrus cycle, and joints that are responding to arthritis. It appears that the normal regulation of blood vessel formation in these tissues and conditions is different from the new blood vessel formation seen in cancer. This may explain why many

antiangiogenic agents have not been associated with problems such as wound healing, arthritis, or keratitis (eye irritation).

Recent studies have demonstrated that in addition to differences in the regulation of new blood vessel formation in cancer compared with normal tissues, the actual blood vessels that are "created" in cancers are different from those created in normal tissues. These differences have allowed a number of new agents to be developed that specifically damage tumor-associated blood vessels and not normal vessels. The goal of these agents is to attack cancers by damaging their blood supply. Many agents that inhibit blood vessel formation (antiangiogenic agents) also appear to hasten the death of tumor-associated blood vessels.

Thrombospondin-1 is a large protein that has a number of biological roles including the inhibition of new blood vessel formation and the enhancement of existing blood vessels death. These biological roles have suggested the potential value of Thrombospondin-1 as a potential anti-cancer agent.



The diverse roles of Thrombospondin-1 during angiogenesis

Recent studies have focused on small fragments of Thrombospondin-1 that are thought to be specifically associated with angiogenesis. These fragments have been shown to be potent inhibitors of new blood vessel formation and appear to promote the death (apoptosis) of blood vessel cells.

Over the last 2 years the Animal Cancer Institute has been evaluating the safety and activity of these small fragments of Thrombospondin-1 in pet dogs with malignant cancers. At the onset of this ongoing trial we were hopeful that Thrombospondin-1 peptides would control the growth of measurable cancers in pet dogs and result in disease stabilization. We have been surprised to find that not only did control of disease occur in some dogs but that a small proportion of pet dogs had objective regressions of their cancers. Regressions of cancers were seen in both primary tumors and in cancers that had spread to other parts of the body (metastases). Results from a series of dogs treated with a Thrombospondin-1 fragment will be presented at the annual meeting of the American Association for Cancer Research in San Francisco in April and are expected to be presented at the annual meeting of the American Society of Clinical Oncology in Orlando in May. For more information on this ongoing clinical trial please contact Kate Cadorette at [kcadorette@animalcancerinstitute.com](mailto:kcadorette@animalcancerinstitute.com).



Barney a 13 year old black lab who was diagnosed with a nasal sarcoma. The tumor had been treated with both radiation therapy and chemotherapy but was recurrent. Prior to receiving Thrombospondin-I Barney was experiencing life threatening nasal bleeding on a daily basis. Treatment with Thrombospondin-I resulted in resolution of nasal bleeding and a complete regression of a portion of the tumor that had invaded the hard palate. Barney began breathing comfortably through his nose and continued to do well on Thrombospondin-I for approximately 8 months.

One of the interesting results from the clinical trials using Thrombospondin-I peptides has been their activity against canine lymphoma. This preliminary evidence of effectiveness against lymphoma has supported the initiation of a randomized trial of Thrombospondin-I peptides in combination with Lomustine chemotherapy for dogs with lymphoma. This trial provides conventional chemotherapy to all dogs and then the addition of the active Thrombospondin-I peptides or placebo in a randomized manner. In this way all dogs receive a standard and appropriate treatment for lymphoma (i.e. Lomustine chemotherapy) and then may additionally receive the antiangiogenic therapy. The clinical trial supports the majority of the cost for treatment, laboratory testing, and follow-up. Dogs eligible for this trial must have a relapse of B cell lymphoma that was initially treated with conventional chemotherapy. This trial is currently available through a number of veterinary referral hospitals and universities in the United States. For more information please contact Kate Cadorette at [kcadorette@animalcancerinstitute.com](mailto:kcadorette@animalcancerinstitute.com).

Agents that inhibit new blood vessel formation or specifically target tumor-associated blood vessels represent a novel, potentially effective, and non-toxic treatment for cancer. It is likely that these agents will provide the next major breakthrough in the management of pet animals and people with cancer. Antiangiogenic therapy will likely become part of the conventional treatment of cancer and will be used in combination with surgery, radiation therapy and chemotherapy. These agents are currently in clinical trials and may become available to both pet animals and people in the near future.