



## Testing Strategies to Treat Drug-Resistant Hemangiosarcomas

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### **RESULTS: Researchers identify a chemotherapy resistance mechanism in hemangiosarcoma tumor cells**

Hemangiosarcoma is a common and deadly tumor of dogs. Growing in areas with a rich blood supply, such as the spleen or heart, many dogs die suddenly, secondary to massive blood loss when tumors rupture. Hemangiosarcomas also are quick to spread to other areas of the body, so even when tumors are discovered early, the tumors have already spread. Prognosis for this cancer hasn't improved in nearly two decades, and new treatment options are desperately needed.

Morris Animal Foundation-funded researchers at the University of Minnesota felt that by gaining a better understanding of the underlying biology of this aggressive tumor, they could discover new ways of improving long-term prognosis in dogs with hemangiosarcoma. Their targets were cells important in tumor growth, spread and drug responses.

The research team successfully identified a drug-resistant cell population within hemangiosarcoma tumors that may be an important player in chemotherapy resistance. The cells identified are extremely efficient at isolating cancer drugs in compartments called lysosomes. By trapping the drug within lysosomes, cancer cells were able to prevent the chemotherapy from reaching its target, effectively neutralizing the drug. This new information helps explain why some hemangiosarcoma tumors become chemotherapy resistant.

The Minnesota team also found that hemangiosarcoma cells with a high surface expression of a protein called colony-stimulating factor 1 receptor (CSF-1R) were the culprits in this process. The lysosomes in the cells with higher expression of CSF-1R were trapping the chemotherapy drug, preventing it from reaching its target, the nucleus of the cancer cells, in sufficient quantities to be effective. The team started searching for a drug that could prevent the accumulation of chemotherapy in the lysosomes, and found that the common beta blocker propranolol was effective in competing with the doxorubicin for lysosomal space. The researchers speculate that if the doxorubicin can't be taken into the lysosome (essentially because propranolol got there first), it will be free to reach its target.

The next research step is to further investigate propranolol and other beta blockers to see if they will work in combination with chemotherapy drugs, and then move to testing this new treatment approach in dogs with hemangiosarcoma.

This study identified a key mechanism in chemotherapy resistance in hemangiosarcoma tumors. Understanding how cancer cells hijack and block drugs from reaching their targets will help researchers develop more effective treatments for this difficult-to-treat cancer in dogs.