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Debra Hokkanen, President
Ellie Carson, Treasurer
The American German Shepherd Dog Charitable Foundation
C/O Morris Animal Foundation
10200 East Girard Avenue, Suite B430
Denver, CO 80231

Dear Ms. Hokkanen and Ms. Carson,

I want to personally thank you and the members of the American German Shepherd Dog Charitable Foundation for supporting our project "Targeting alpha-AR signaling to inhibit cholesterol processing and arrest hemangiosarcoma growth." I also want to once again express my sincere appreciation for your long-term sponsorship. I am very grateful to sponsors like your group who have provided support for our previous grants through Morris Animal Foundation and continue to help fund our efforts to improve treatment outcomes for dogs with hemangiosarcoma.

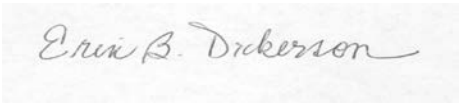
In my previous letter to you, I summarized our recent work and described how we had moved forward with some new discoveries. I described the identification of a specific cell population in hemangiosarcomas that are more drug resistant to doxorubicin, a chemotherapy commonly used to treat hemangiosarcoma. We then discovered some cancer cells survive chemotherapy because they are able to sequester drugs within intracellular structures known as lysosomes, reducing the amount of drug available to kill the cancer cells. We are now working to understand how we can block this mechanism. We found that propranolol, a beta blocker used to treat heart disease in both dogs and people, also becomes trapped in lysosomes. When propranolol is given at the same time as chemotherapy, propranolol keeps more of the chemotherapy drug out of the lysosome, exposing the internal targets of the cell to higher chemotherapy levels and killing the cancer cells. Working with our collaborator, Dr. Brad Bryan, we have now discovered that propranolol, and other beta blockers, disrupt essential cholesterol processing pathways and limit the amount of cholesterol metabolites available to the cancer cells. Because the cancer cells rely more on these products than healthy, non-cancerous cells, propranolol and other beta blockers can reduce the viability of cancer cells and eventually kill them. We are continuing to dissect these metabolic pathways in hemangiosarcoma cells and better understand how these drugs work so that we can further improve responses. Because propranolol and other beta blockers are already approved veterinary medicine for the treatment of heart disease, we should be able to rapidly transfer our findings to the clinic.

I would like to take a moment to catch you up on the research team. Dr. Brad Bryan is a professor at Texas Tech University Health Science Center and a Co-Investigator on this project. Brad and I have collaborated for several years. His original discoveries regarding the effects of propranolol on hemangiosarcoma cells and his expertise in cell biology have helped move this project forward. Dr. Ali Khammanivong is still in the laboratory, and he continues to use his background in the fields of cancer biology and bioinformatics to help us understand why hemangiosarcomas are so resistant to many therapies. Ms. Jhuma Saha is still working in the

lab as our manager extraordinaire, and she is carrying out many of the experiments for the project. She continues to keep the lab organized and running smoothly. Dr. Derek Korpela, our resident veterinarian turned graduate student, has made some exciting discoveries, and we hope that he can submit his work for publication this year. Derek also received a fellowship from Morris Animal Foundation, so that he can finish his project and obtain his PhD. We are very grateful to the donors who are supporting Derek's fellowship and his work. Kathryn Fox, our former undergraduate student, graduated in May! She recently was accepted into vet school, and she will start classes in the fall. Kathryn is working in the lab this summer as a research technician, and I am really glad to have her help for these few months. I am very proud of the research team and their accomplishments. Together we are making progress in understanding hemangiosarcoma.

Thank you once again for your continued support. If I can help to clarify anything for you or address questions related to this project, please contact me.

Sincerely,



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