（様式５）Form 5

学位論文内容の要旨
Abstract of the dissertation

博士の専攻分野の名称：博士（獣医学）氏名：グライケヴィンクリスチャンモンテシリオ
Name: Gulay, Kevin Christian Montecillo

学位論文題名
The title of the doctoral dissertation

The role of histone lysine demethylase 2B in the pathology of canine hemangiosarcoma

(イヌ血管肉腫の病態におけるヒストンリジン脱メチル化酵素 2B

の役割に関する研究)

Epigenetic regulators have been implicated in tumorigenesis of many types of cancer; however, their roles in endothelial cell cancers such as canine hemangiosarcoma (HSA) have not been studied. In this study, we find that lysine-specific demethylase 2b (Kdm2b) is highly expressed in HSA cell lines compared to normal canine endothelial cells. Silencing of Kdm2b in HSA cells results to increased cell death *in vitro* compared to the scramble control by inducing apoptosis through the inactivation of the DNA repair pathways and accumulation of DNA damage. Similarly, doxycycline-induced Kdm2b silencing in tumor xenografts results to decreased tumor sizes compared to the control. Furthermore, Kdm2b is also highly expressed in clinical cases of HSA. We hypothesize that pharmacological Kdm2b inhibition can also induce HSA cell death and can be used as an alternative treatment for HSA. We treat HSA cells with GSK-J4, a histone demethylase inhibitor, and find that GSK-J4 treatment also induces apoptosis and cell death. In addition, GSK-J4 treatment decreases tumor sizes. Therefore, we demonstrate that Kdm2b acts as an oncogene in HSA by enhancing the DNA damage response. Moreover, we show that histone demethylase inhibitor GSK-J4 can be used as a therapeutic alternative to doxorubicin for HSA treatment.