Ashley Adile Brain Tumour Foundation of Canada Final Progress Report

Previous findings from Dr. Singh's lab identified novel therapeutic targets, BMI1 and STAT3, both of which play an important role in medulloblastoma (MB) development and metastasis. During both terms of my studentship, I conducted a multitude of *in vitro* and *in vivo* experiments, demonstrating that the most efficacious BMI1 inhibitory agent significantly diminished protein levels of the target in preclinical models. With a gain in BMI1 expression levels associated with resistance to ionizing radiation, this studentship allowed further investigation into the prospect that a reduction in BMI1 may circumvent challenges of current therapeutic modalities for treatment of pediatric MB.

Following vigorous *in vitro* testing in the first term, the BMI1 inhibitor was validated in the lab's established mouse adapted patient-derived therapy models. The small molecule inhibitor was found to be highly effective at minimizing tumour burden, while also prolonging mouse survival. Specifically, introduction of the BMI1 inhibitor, in combination with chemoradiotherapy - the best current standard of care protocol - resulted in a significant survival benefit. Such data has resulted in the commencement of a North American clinical trial for children with newly diagnosed diffuse intrinsic pontine glioma (DIPG) and recurrent MB. With no treatment options beyond palliative care, the main objective of my research is to discover new therapeutic avenues for those suffering from pediatric brain tumours, while striving for a cure, but valuing contributions made towards lengthening patients' survival and quality of life.

As an active lab member, I have presented at various conferences, as well as authored book chapters and refereed papers. For such commitment and research expertise, I was honoured to be the recipient of the 2017-2018 Brain Tumour Foundation of Canada, allowing me to further explore innovative work in pediatric brain cancer research. Connection to the foundation also presented me with opportunities, like participating in the 2017 Pam And Rolando Del Maestro Family Undergraduate Student Research Competition, where I mentored a fellow undergraduate student in the Singh lab. Here, student teams across Canadian institutions created and presented an innovative proposal based on the case study given, which was judged by a panel of physicians and researchers. As the only team representing McMaster, we presented on novel agents targeting therapy-resistant stem cells of glioblastoma, the most common malignant primary brain tumor in adults. Having come first place in this competition, we were given the opportunity to present at the Join the Movement to End Brain Tumours National Conference, along with a monetary award. The ability to connect with individuals who have lost, currently fighting or supporting a loved one with brain cancer, at the national conference was a truly invaluable experience; one that I continue to cherish. Most recently, I participated in the 2018 Hamilton-Niagara Brain Tumour Walk, where I walked alongside patients and their families, marching in support of this community and with the hope to make a difference in the field of pediatric brain cancer.

Published Refereed Papers

Bakhshinyan D, **Adile AA**, Venugopal C, Singh SK (2017). BMI1: a path to targeting cancer stem cells. *European Oncology and Haematology*.

Accepted Refereed Papers

Bakhshinyan D, Venugopal C, **Adile AA**, Garg N, Manoranjan B, Hallett R, Wang X, Mahendram S, Vora P, Vijayakumar T, Subapanditha M, Singh M, Kameda-Smith MM, Qazi M, McFarlane N, Mann A, Ajani OA, Yarascavitch B, Ramaswamy V, Farooq H, Morrissy S, Cao L, Sydorenko N, Baiazitov R, Du W, Sheedy J, Weetall M, Moon YC, Lee CS, Kwiecien JM, Delaney KH, Doble B, Cho YJ, Mitra S, Kaplan D, Taylor M, Davis T, Singh SK (2018). BMI1 is a therapeutic target in recurrent medulloblastoma. *Oncogene.*

Refereed Papers in Preparation

Shouksmith A, Shah F, Grimard ML, Gawel JM, Raouf Y, Geletu M, Berger-Becvar A, de Araujo ED, Luchman HA, Heaton WL, Bakhshinyan D, **Adile AA**, Venugopal C, O'Hare T, Deininger MW, Singh SK, Konieczny SF, Weiss S, Fishel ML, Gunning P (2017). Identification and Characterization of AES-135, a Potent HDAC Inhibitor that Prolongs Survival in an Orthotopic Mouse Model of Pancreatic Cancer. *Journal of Medicinal Chemistry*.

Accepted Refereed Book Chapters

Adile AA, Bakhshinyan D, Venugopal C, Singh SK (2017). *In vitro a*ssays for screening small molecules. In: Methods in Molecular Biology, Springer.

Poster Presentations (*Presenter)

Adile AA*, Bakhshinyan D, Venugopal C, Subapanditha MK, Weetall M, Davis TW, Singh SK (2017). Small molecule inhibitor targeting self-renewal as a therapeutic option for medulloblastoma. 2018 Let's Talk Cancer Hamilton - Let's Talk Science Outreach, Hamilton, ON, Canada.

Adile AA*, Bakhshinyan D, Venugopal C, Subapanditha MK, Weetall M, Davis TW, Singh SK (2017). Small molecule inhibitor targeting self-renewal as a therapeutic option for medulloblastoma. 2018 Students Advancing Brain Cancer Research (SABCR) Research Symposium, Hamilton, ON, Canada.