Abstract ID: 10522

Title: The effect of two BRM promoter variants on the risk of Stage I/II upper aerodigestive tract cancers.

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Background: BRM is a key subunit of the chromatin remodeling complex SWI/SNF and a putative tumor suppressor gene that is silenced in 15-20% of many solid tumors (PMID 15722796). Evidence suggests that it is epigenetically regulated, as two BRM promoter insertion variants (BRM-741 and BRM-1321) may lead to gene silencing by recruiting histone deacetylases. The presence of both homozygous BRM-741 and BRM-1321 highly correlate with loss of BRM expression and function in lung tumors, while increasing smoking-related lung cancer by two-fold (PMID 21478907). Also, the pharmacologic reversal of epigenetic changes of BRM offers a potential novel therapeutic approach (PMID 21478905). We assessed whether these BRM variants are associated with the risk of upper aerodigestive tract cancers, focusing on Stage I/II tumors that would most benefit from new screening and prevention strategies.

Methods: BRM was genotyped by qPCR using TaqMan probes. 1,008 controls were matched to 595 cases by frequency distribution based on age, gender and smoking status. Multivariate logistic regression generated adjusted odds ratios (aOR).

Results: The 595 cases were: 115 esophageal, 278 lung, and 202 head and neck cancers. 51% were adenocarcinomas; 60% were Stage I. The frequency of homozygozity was: BRM-741, 26%; BRM-1321, 23%; both variants, 15%. In the combined analysis, there was significant correlation between malignancy and homozygous BRM-741 (aOR 1.91 (95%CI 1.3-2.4); p=0.001) or BRM-1321 (aOR 1.94 (95%CI 1.4-2.7; p=3x10E-4). Being homozygous for both BRM variants carried an even greater risk (aOR 2.45 (95%CI 1.6-3.9); p=1x10E-5). This correlation was similar for adenocarcinomas (aOR 2.53 (95%CI 1.4-4.2); p=6x10E-4) and squamous cell carcinomas (aOR 2.33 (95%CI 1.3-4.4); p=8x10E-4). The increased cancer risk was also similar between these subgroups: head and neck, esophageal and lung cancers; Stage I and II patients; smokers and non-smokers.

Conclusions: The two homozygous BRM variants increase the risk of early stage upper aerodigestive tumors by more than two-fold independent of smoking status. BRM promoter variants and their potential epigenetic effect may be early events in the evolution of these cancers.

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March 28, 2012

Dear Awards Committee,

Re: Letter of support for Kit Man Wong for the Novartis Oncology Young Canadian Investigator Award

I have known Kit for more than two years now, and have rarely been so impressed by a medical resident (now an accepted Oncology Fellow in our training program). On paper, she has a most enviable academic record, and one that is considered top of the field in a Canadian medical training setting. She graduated with a B.Sc. *sum laude* Gold Medal and a Cumulative GPA of 3.99 from the University of Toronto. She followed this success with a *Sum Laude* Cody Silver Medal in Medicine, out of over 250 students at the University of Toronto. She has a long trail of awards for her academic achievement, teaching and research.

Despite going into Medicine straight after completion of her undergraduate degree, Kit has developed a broad experience in a multitude of research areas (including both surgical and medical fields) before settling down to a decision in the past year to pursue Medical Oncology. Along the way, she has worked in some of the top research laboratories at the University of Toronto, including the laboratories of Drs. Tom Hudson (Cancer Genetics), Kathy Siminovitch (Immunology), Gary Levy (Organ Transplantation), and Peter Liu (Cardiology). Her resident evaluations, both formal and informal, properly describe her as functioning well beyond her level of clinical training. These achievements reflect a highly intelligent, dedicated, focused, and driven individual in pursuit of performing at the highest level in both clinical and research fields.

Throughout her medical training, Kit has focused on research, experiencing many facets through various clinical and laboratory projects. To her credit, she did not aim at "low hanging fruit" by focusing only on working with researchers simply to publish peer-reviewed first-author papers. Instead, Kit took advantage of the Canadian system where there are a few opportunities to have brief, yet intense experiences in a research field. She rapidly immersed herself in various research projects to not only acquire fundamental knowledge and skills as a young scientist, but also make solid decisions regarding her research and clinical interests. Her willingness to explore and learn from a variety of experiences has strengthened her critical thinking ability while maintaining a broad perspective.

Kit writes brilliantly. I have not had a resident or fellow synthesize a topic (in this case, extremes of weight and chemotherapy dosing) so clearly and concisely, such that I had minimal

comments and suggestions when she wrote entire protocols for submission for approval to access data and samples for analysis within the National Cancer Institute of Canada Clinical Trials (Cooperative) Group (NCIC CTG), and for ILCCO (the International Lung Cancer Consortium). Last year, she attended the ILCCO meeting, and now has budding projects in both a cooperative group and an international epidemiological consortium.

Her enthusiasm for research, motivation and dedication are truly exceptional. She brings to completion what she sets her mind to perform. She also sets high standards and works diligently to attain them. These qualities, in addition to those previously mentioned, are certainly the reasons for her ongoing successes. She has completed her project on myelofibrosis and hepatocellular injury after allogeneic bone marrow transplantation (with Dr. Vikas Gupta) within the span of one year, and had the opportunity to give an oral presentation of her research findings at the 6th International Congress on Myeloproliferative Diseases and Myelodysplastic Syndromes (November 3-4, 2011, New York). Her abstract was also presented at the 2011 American Society of Hematology annual meeting (December 10-13, 2011, San Diego). She was a winner of the 2011 PSI Foundation Resident Research Prize for Excellence in Research Papers, which awards only the top research projects done by residents across the Universities of Ontario. This research was performed PRIOR to her entry into the Oncology Fellowship.

As for the current ASCO abstract, Kit has worked on an extension of novel findings that my group and my colleague`s group (Dr. Reisman, Medical Oncology Clinician Scientist) initially published in Oncogene in back to back papers in 2011. She evaluated the role of two functional promoter polymorphisms in BRM, a gene involved in chromatin remodelling. These two polymorphisms regulate transcriptional activity of the gene through the creation of a MEF2 promoter binding site, and increase the risk of cancer development. Kit decided that we needed more data on the association of these BRM polymorphisms in early stage upper aerodigestive tract cancers, since we are developing pharmacological agents to reverse the epigenetic suppression of BRM2. She determined that our best chance for using BRM markers in the clinical setting was to identify subsets of patients at risk for cancers that are still in a curable state. The resultant research extends our initial findings to focus on a clinically relevant group where this marker could be translatable in the clinical setting. The current research was performed after Kit was accepted into the Medical Oncology fellowship training program at the University of Toronto.

It is rather unique that someone so early in their career has completed so much oncologic research. She will be a strong Oncology fellow with respect to both clinical and research aspects. She has my highest recommendation for the Novartis Oncology Young Canadian Investigator Award. If you have any additional questions, please feel free to contact me at Geoffrey.Liu@uhn.on.ca .

Sincerely,

Geoffrey Liu, MD FRCPC (Medical Oncology)
Alan B. Brown Research Chair in Molecular Genomics
Cancer Care Ontario Chair in Experimental Therapeutics and Experimental Medicine
Associate Professor, Dalla Lana School of Public Health, and University of Toronto.
Princess Margaret Hospital and Ontario Cancer Institute

KIT MAN WONG

I conducted a literature review for this project, and participated in the design of the study and planning of data analyses. I was also responsible for interpreting the results, drawing clinically meaningful and relevant conclusions, and formulating potential future research directions. Finally, I was primarily responsible for writing the abstract and manuscript of the study for publication.

Contribution percentage: 70%