

## ABSTRACT

Discovering biomarkers and molecular drivers of head and neck endocrine tumors was the inspiration for this thesis. Here, I describe the molecular evaluation of tumors of the thyroid and parathyroid endocrine glands for the purpose of identifying somatic driver alterations in these cancers. While molecular interplay of the germline genomic background of an individual and the somatic genome that emerges throughout the lifetime plays significant roles in increasing the susceptibility to cancer and in driving the malignant phenotype, the major known contributors to cancer remain the acquired somatic mutations. Analysis of a sporadic and recurring parathyroid carcinoma, with incidence of 1 per million population, revealed mutations in *mTOR*, *MLL2*, *CDKN2C* and *PIK3CA* and comparison of patient-matched primary and recurrent malignant tumors uncovered loss of *PIK3CA* activating mutation during the evolution of the tumor. Loss of the short arm of chromosome 1 along with somatic missense and truncating mutations in *CDKN2C* and *THRAP3* provided new evidence for the potential role of these as tumor suppressors. Hürthle cell thyroid carcinoma accounts for a small proportion of all thyroid cancers; however, this malignancy often presents at an advanced stage and poses unique challenges. Genomic analysis revealed large regions of copy number variation encompassing nearly the entire genomes accompanied also by near haploidization. Moreover, I identified loss-of-function mutations of the tumor suppressor gene *MEN1* in 4% of patients. Repeated alterations of the epigenetic machinery in anaplastic thyroid carcinoma, one of the most fatal of all adult solid malignancies, and novel gene fusions including *MKRN1-BRAF*, *FGFR2-OGDH* and *SS18-SLC5A11* are reported here. The transcriptomic analysis suggested known drug targets such as *FGFRs*, *VEGFRs*, *KIT* and *RET* to have low expressions in this cancer; however, through integrative data analysis, I identified the mTOR signaling pathway as a potential therapeutic target for anaplastic thyroid cancer. Molecular analysis of papillary thyroid carcinoma and benign thyroid nodules revealed very low mutation rates in these tumors with *CYP1B1*, *PTPRE*, *CTSH* and *RUNX1* emerging as promising diagnostic markers. The key somatic mutations identified in these studies can serve as novel diagnostic markers as well as therapeutic targets.

## BIOGRAPHICAL NOTES

Academic Studies: B.Sc. University of British Columbia, 2005  
B.CS. University of British Columbia, 2009

## GRADUATE STUDIES

Field of Study: Bioinformatics and Cancer Genomics

### Courses

Courses		Instructors
MEDG 505	Genome Analysis	Dr. P. Hieter
BIOF 520	Problem-Based Learning in Bioinformatics	Dr. S. Jones
MEDG 520	Advanced Human Molecular Genetics	Dr. M. Lorincz
BIOF 501A	Special Topics in Bioinformatics	Dr. F. Brinkman

## AWARDS

Canadian Cancer Society Research Institute Travel Award (2014)  
Canadian Institutes of Health Research Publication Prize (2013)  
University of British Columbia Four-Year Doctoral Fellowship (2013)  
Canadian Institutes of Health Research Doctoral Award (2013)  
Canadian Institutes of Health Research Travel Award (2012)  
Canadian Institutes of Health Research Master's Award (2010)  
BC Cancer Agency / Michael Smith Foundation for Health Research Incentive Training Award (2009)

## SELECTED PUBLICATIONS

**Kasaian K**, Chindris AM, Wiseman SM, Mungall KL, Zeng T, Tse K, Schein JE, Rivera M, Necela BM, Kachergus JM, Casler JD, Mungall AJ, Moore RA, Marra MA, Copland JA, Thompson EA, Smallridge RC, Jones SJ. MEN1 Mutations in Hürthle Cell (Oncocytic) Thyroid Carcinoma. *Journal of Clinical Endocrinology and Metabolism*. 100(4):E611-5 (2015).

**Kasaian K**, Wiseman SM, Thiessen N, Mungall KL, Corbett RD, Qian JQ, Nip KM, He A, Tse K, Chuah E, Varhol RJ, Pandoh P, McDonald H, Zeng T, Tam A, Schein J, Birol I, Mungall AJ, Moore RA, Zhao Y, Hirst M, Marra MA, Walker BA, Jones SJ. Complete Genomic Landscape of a Recurring Sporadic Parathyroid Carcinoma. *Journal of Pathology*. 230(3):249-60 (2013).

**Kasaian K**, Li YY, Jones SJ. Bioinformatics for Cancer Genomics. In Dellaire G & Berman JN & Arceci RJ (Eds.), *Cancer Genomics: From Bench to Personalized Medicine* (pp 134-152). San Diego, CA: Academic Press (2013).

**Kasaian K**, Jones SJ. A New Frontier in Personalized Cancer Therapy: Mapping Molecular Changes. *Future Oncology*. 7(7):873-94 (2011).

Choi H, **Kasaian K**, Melck A, Ong K, Jones SJ, White A, Wiseman SM. Papillary Thyroid Carcinoma: Prognostic Significance of Cancer Presentation. *American Journal of Surgery*. 210(2):298-301 (2015).

Shankar J, Wiseman SM, Meng F, **Kasaian K**, Strugnell S, Mofid A, Gowen A, Jones SJ, Nabi IR. Coordinate Expression of Galectin-3 and Caveolin-1 in Thyroid Cancer. *Journal of Pathology*. 228(1):56-66 (2012).

## SELECTED PRESENTATIONS

**Kasaian K**, Shen Y, Leelakumari S, Pleasance E, Jones M, Li YY, Mungall KL, Schein J, Mungall AJ, Zhao Y, Moore RA, Ma Y, Yip S, Gelmon K, Lim H, Renouf D, Laskin J, Marra MA, Jones SJM. *Bioinformatics Analyses Approaches for Personalized Oncogenomics*. Podium Presentation. Beyond the Genome, Boston, USA, October 2014.

**Kasaian K**, Shen Y, Leelakumari S, Eirew P, Li Y, Pleasance E, Corbett R, Mungall K, Schein J, Mungall A, Zhao Y, Moore R, Yip S, Gelmon K, Lim H, Renouf D, Roscoe R, Ma Y, Marra M, Laskin J, Jones S. *Bioinformatic Analyses Approaches for Personalized Oncogenomics*. Poster Presentation. The 105th Annual Meeting of the American Association for Cancer Research, San Diego, USA, April 2014.

**Kasaian K**, Mungall KL, Schein J, Zhao Y, Moore RA, Hirst M, Marra MA, Walker BA, Wiseman SM, Jones SJM. *Transcriptomic Analysis of Benign and Malignant Thyroid Nodules*. Poster Presentation. Pacific Symposium on Biocomputing, Big Island, USA, January 2014.

**Kasaian K**, Thiessen N, Mungall KL, Birol I, Mungall AJ, Moore RA, Zhao Y, Hirst M, Marra MA, Walker BA, Wiseman SM, Jones SJM. *Genomic Landscape of a Recurring Sporadic Parathyroid Carcinoma Case*. Podium Presentation. Mutation Detection, Lake Louise, Canada, April 2013.

**Kasaian K**, He A, Thiessen N, Mungall KL, Qian J, Varhol R, Zhao Y, Birol I, Moore R, Mungall AJ, Hirst M, Marra MA, Walker BA, Wiseman SM, Jones SJM. *Transcriptomic Landscape of Thyroid Cancers*. Poster Presentation. 11th Asia Pacific Bioinformatics Conference, Vancouver, Canada, January 2013.

**Kasaian K**, He A, Thiessen N, Mungall KL, Qian J, Varhol R, Zhao Y, Birol I, Moore R, Mungall AJ, Hirst M, Marra MA, Walker BA, Wiseman SM, Jones SJM. *Profiling Thyroid Cancers on the Molecular Level*. Poster Presentation. Genomics: The Power and the Promise, Ottawa, Canada, November 2012.

**Kasaian K**, He A, Thiessen N, Mungall KL, Qian J, Varhol R, Zhao Y, Birol I, Moore R, Mungall AJ, Hirst M, Marra MA, Walker BA, Wiseman SM, Jones SJM. *Transcriptomic Landscape of Thyroid Cancers*. Poster Presentation. BC Cancer Agency Conference, Vancouver, Canada, November 2012.

**Kasaian K**, He A, Thiessen N, Mungall KL, Zhao Y, Birol I, Mungall AJ, Hirst M, Marra MA, Walker B, Nabi IR, Wiseman SM, Jones SJ. *Molecular Characterization of a Disease of Extremes: Thyroid Cancer*. Poster Presentation. Canadian Student Health Research Forum, Winnipeg, Canada, June 2012.

**Kasaian K**, Thiessen N, Mungall KL, Fejes AP, Zhao Y, Birol I, Marra MA, Walker B, Nabi IR, Wiseman SM, Jones SJ. *Whole Transcriptome Analysis of Anaplastic Thyroid Cancers*. Poster Presentation. Advances in Genome Biology and Technology, Marco Island, USA, February 2012.

## SUPERVISORY COMMITTEE

Dr. Robert Holt  
Dr. Steven Jones  
Dr. Sohrab Shah  
Dr. Sam Wiseman



a place of mind

THE UNIVERSITY OF BRITISH COLUMBIA

## Graduate and Postdoctoral Studies

### PROGRAMME

The Final Oral Examination  
For the Degree of

DOCTOR OF PHILOSOPHY  
(Bioinformatics)

### KATAYOON KASAIAN

B.Sc. University of British Columbia, 2005  
B.CS. University of British Columbia, 2009

Wednesday, September 2, 2015, 12:30 pm  
Room 203, Graduate Student Centre  
*Latecomers will not be admitted*

**“Genomic Analysis of Head and Neck Endocrine Glands”**

### EXAMINING COMMITTEE

Chair:

Dr. Douglas Allan (Cell and Developmental Biology)

Supervisory Committee:

Dr. Steven Jones, Research Supervisor (Medical Genetics)  
Dr. Robert Holt (Medical Genetics)

University Examiners:

Dr. Wan Lam (Pathology and Laboratory Medicine)  
Dr. Calvin Roskelley (Cell and Developmental Biology)

External Examiner:

Dr. Jacek Majewski  
Department of Human Genetics  
McGill University  
Montreal, Quebec