

PHD DEFENCE – Monday, May 11th, 2015

Student: Jaswinder Khattrra

Title: CHARTING BREAST TUMOR HETEROGENEITY: FROM BULK TUMOR GENOMES TO SINGLE-CELL GENOTYPES

Time and Location: 9:00am, Room 200, Graduate Student Centre, UBC Campus

Supervisor: Dr. Sam Aparicio

ABSTRACT

Traditional classifications and treatment of human cancers have operated with limitations surrounding tumor homogeneity and mutational stasis. Clinical metrics of malignant tumors focused on descriptive and behavioral properties such as tissue of origin, cellular morphologic features and extent of spread. Missing has been an understanding of the dynamics of cellular subpopulations that underpin divergent functional properties in space and time. This dissertation focused on the development and application of methods, including next generation DNA sequencing, computational modeling, and single-cell genotyping protocols to elucidate breast tumor heterogeneity and clonal evolution at single nucleotide and single-cell resolution.

First, I present advances in our knowledge of the mutational spectrum that may occur and evolve in an individual epithelial cancer, namely a lobular breast cancer metastases and matched primary tumor separated by a nine year interval. This seminal study demonstrated clonal evolution in a patient's breast cancer and the successful application of targeted deep sequencing for determining digital allelic prevalences and clonal genotypes in bulk tumors. Second, I describe the diversity of genomic sequence and clonal heterogeneity in tumors of the triple-negative breast cancer subtype. The study uncovered wide clonal diversity in these primary tumors at first diagnosis. Third, I demonstrate via genotyping single tumor cells, that computational inferences of tumor clonal architecture can be made reliably from bulk tissue-derived data sets. This was performed using both somatic point mutations and loss of heterozygosity loci as clonal marks. And fourth, I applied single-cell analysis to study the clonal evolution in breast tumor murine xenografts following engraftment and serial passaging. This research uncovered a range of outcomes in tumor clonal composition upon initial engraftment and serial passaging. The same clonal groups were found to arise independently in separate xenografts derived from the same primary tumor, suggesting selection of functionally significant genotypes.

Comprehensive capabilities in the measurement and analysis of clonal structure in cancers offers improved classification and combinatorial treatments of subpopulations in heterogeneous tumors and better use of murine xenograft models. Functionally relevant subpopulations of tumor cells, irrespective of numerical abundance or spatiotemporal persistence, can thereby be targeted using clonally informative genomic profiles.