

## ABSTRACT

Neuroblastoma (NBL) is an enigmatic pediatric tumor of the sympathetic nervous system that is lethal in most children diagnosed over 18 months of age with metastatic disease. NBL is thought to originate from a differentiation arrest of the neural crest, a vertebrate-specific cell lineage with one of the most diverse developmental potentials. Genomic studies of NBL have contributed to the development of new diagnostic and prognostic markers. In addition, somatic and germline mutations in the *ALK* oncogene have been identified and are being targeted clinically. Based on this prior work, two hypotheses were developed and addressed in this thesis: (1) characterization of NBL with higher resolution genomic technologies will lead to the identification of novel loci that contribute to the disease and (2) analysis of the transcriptome of normal neural crest cells will help identify loci of relevance to NBL. To address these hypotheses I used several datasets generated from microarrays as well as RNA and DNA sequencing experiments. Two key results have emerged from this analysis including the putative role of the BRCA1/BARD1 pathway in the development of NBL, and the heterogeneity of the genetic landscape of primary NBL tumors. Potential translational avenues for the results reported in this thesis are the exploration of AURKB and MAPK inhibitors as treatment agents for NBL.

## BIOGRAPHICAL NOTES

Born: November 5, 1984, Kharkiv, Ukraine

Academic Studies: B.Sc. (Hons), University of Toronto, 2006

## GRADUATE STUDIES

Field of Study: Cancer and Developmental Genomics

## SELECTED COURSES

GENE501 Special Topics in Bioinformatics

MEDG548 Problem-Based Learning in Bioinformatics

MEDI 590 Molecular Regulation of Cell Growth and Differentiation

CHEM507 Biomolecular Simulation

MBB741 Bioinformatics

## INSTRUCTORS

Drs. F. Ouellette and F. Pio

Dr. F. Brinkman

Dr. S. Pelech

Dr. W. Scott

Dr. J. Chen

## SELECTED AWARDS

- Roman M. Babicki Fellowship in Medical Research (UBC)
- American Association for Cancer Research Women in Cancer Research Scholar Award
- Natural Sciences and Engineering Research Council Alexander Graham Bell Canada Graduate Scholarship (CGS D3)
- Natural Sciences and Engineering Research Council Julie Payette Award (PGS M),
- Michael Smith Foundation for Health Research Junior Graduate Studentship

## SELECTED PUBLICATIONS

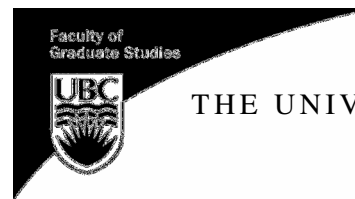
**O. Morozova**, M. Vojvodic, N. Grinshtein, L. M. Hansford, K. M. Blakely, A. Maslova, M. Hirst, T. Cezard, R. D. Morin, R. Moore, K. M. Smith, F. Miller, P. Taylor, N. Thiessen, R. Varhol, Y. Zhao, S. Jones, J. Moffat, T. Kislinger, M. F. Moran, D. R. Kaplan, M. A. Marra. (2010) Systems-level analysis of tumor-initiating cells implicates AURKB as a novel drug target for neuroblastoma. *Clinical Cancer Research* 16(18):4572-82

**O. Morozova**, M. Hirst and M. A. Marra. (2009) Applications of New Sequencing Technologies for Transcriptome Analysis. *Annual Review of Genomics and Human Genetics* 10:135-51

**O. Morozova** and M. A. Marra. (2008) Applications of next-generation sequencing technologies in functional genomics. *Genomics* 92(5):255-64.

**O. Morozova**, V. Morozov, B. Hoffman, C. Helgason, and M. A. Marra. (2008) A seriation approach for visualization-driven discovery of co-expression patterns in Serial Analysis of Gene Expression (SAGE) data. *PLoS ONE* 3(9):e3205

**O. Morozova** and M. A. Marra. (2008) From cytogenetics to next-generation sequencing technologies: advances in the detection of genome rearrangements in tumors. *Biochemistry and Cell Biology*, 86(2):81-91



## SELECTED PRESENTATIONS

**Olena Morozova**, Inanc Birol, Richard Corbett, Karen Mungall, Edward F. Attiyeh, Shahab Asgharzadeh, Yongjun Zhao, Richard A. Moore, Martin Hirst, Steven Jones, Michael D. Hogarty, Sharon Diskin, Yael P. Mosse, Maura Diamond, Richard Sposto, Lingyun Ji, Daniela S. Gerhard, Malcolm A. Smith, Javed Khan, Robert C. Seeger, Marco A. Marra, John M. Maris, the NCI TARGET Initiative. Whole genome and transcriptome sequencing defines the spectrum of somatic changes in high-risk neuroblastoma. Minisymposium presentation (15 min). 102nd Annual Meeting of the American Association for Cancer Research (AACR2011), Orlando, FL, USA, April 2-6, 2011

**Olena Morozova**, Loen Hansford, Karen Mungall, Edward Attiyeh, Richard Corbett, Nina Thiessen, Richard Varhol, Yongjun Zhao, Readman Chiu, Alexandra Maslova, Inanc Birol, Steven Jones, Martin Hirst, John M. Maris, David R. Kaplan, Marco A. Marra. Comparative analysis of primary tumors and metastases-derived tumor-initiating cells provides insights into neuroblastoma progression. Trainee talk (10 min). BC Cancer Agency Annual Cancer Conference 2010, Vancouver, BC, Canada, November 25-27, 2010. **Best Trainee Talk Award.**

**Olena Morozova**, Edward F. Attiyeh, Ryan D. Morin, Martin Hirst, Timothee Cezard, Richard, Moore, Cecelia Suragh, Nina Thiessen, Richard Varhol, Yongjun Zhao, Michael D. Hogarty, Shahab Asgharzadeh, Daniela S. Gerhard, Malcolm A. Smith, Javed Khan, Robert C. Seeger, John M. Maris, Marco A. Marra. Whole genome and transcriptome sequencing of 10 stage IV primary neuroblastoma tumors: a TARGET project report. Plenary presentation (12 min). Advances in Neuroblastoma Research (ANR2010), Stockholm, Sweden, June 21-24, 2010

**Olena Morozova**, Ryan Morin, Timothee Cezard, Nina Thiessen, Cecelia Suragh, Richard Varhol, Yongjun Zhao, Richard Moore, Martin Hirst, Marco Marra. RNA sequencing of stage IV primary neuroblastoma tumors and tumor initiating cells. Workshop presentation (20 min). 3rd Annual Translational Genomics in Neuroblastoma Meeting (TGiN-3), National Institutes of Health, Bethesda, MD, USA, November 12-13, 2009

**Olena Morozova**, Vyacheslav Morozov, Martin Hirst, Marco Marra. Defining expression signatures of known cancer genes using seriation analysis of SAGE libraries from Cancer Genome Anatomy Project (CGAP). Workshop presentation (15 min) HUGO's 13th Human Genome Meeting (HGM2008), Hyderabad, India, September 27-30, 2008

## SUPERVISORY COMMITTEE

Dr. Marco A. Marra  
Dr. Angela Brooks-Wilson  
Dr. Paul Pavlidis  
Dr. Samuel Aparicio

## PROGRAMME

The Final Oral Examination  
For the Degree of

DOCTOR OF PHILOSOPHY  
(Bioinformatics)

## OLENA MOROZOVA

B.Sc. (Hons), University of Toronto, 2006

Tuesday, May 1, 2012, 12:30 pm  
Room 200, Graduate Student Centre  
*Latecomers will not be admitted*

**“Genomic Studies of the Normal and Malignant Neural Crest”**

## EXAMINING COMMITTEE

Chair:

Dr. Lynn Raymond (Psychiatry)

Supervisory Committee:

Dr. Marco A. Marra, Research Supervisor (Medical Genetics)  
Dr. Paul Pavlidis (Bioinformatics)

University Examiners:

Dr. Phil Hieter (Medical Genetics)  
Dr. Poul Sorensen (Pathology and Laboratory Medicine)

External Examiner:

Dr. Annie Huang  
Department of Laboratory Medicine and Pathobiology  
University of Toronto  
Toronto, Ontario