

ABSTRACT

Cancers are characterized by somatic mutation arising from the interplay of mutagen exposure and deficient DNA repair. Whole genome sequencing of tumours reveals characteristic patterns of mutation, known as mutation signatures, which often correspond with specific processes such as cigarette smoke exposure or the loss of a DNA repair pathway. Quantifying DNA repair deficiency can have clinical implications. Cancer chemotherapies which induce DNA damage are known to be more effective against cancers with deficient DNA repair. However, it is not yet known whether mutation signatures can serve as reliable predictive biomarkers for response to these treatments. Furthermore, the current understanding of mutation signatures stems largely from studies of primary, untreated tumours, whereas metastasis underpins as much as 90% of cancer-related mortality. This thesis aims to (1) describe the association between mutation signatures and clinical response to DNA damaging chemotherapy, (2) enable accurate personalized assessment of mutation signatures and their evolution over time, and (3) characterize the evolution of mutational processes in metastatic cancers. To assess clinical actionability, we quantified signatures of single nucleotide variants, structural variants, copy number variants, and small deletions in 93 metastatic breast cancers, 33 of which received platinum-based chemotherapy. We found that patients with signatures of homologous recombination deficiency had improved responses and prolonged treatment durations on platinum-based chemotherapy. Next, we formulated a Bayesian model called SignIT, which improves the accuracy of individualized mutation signature analysis and infers signature evolution over tumour subpopulations. We demonstrated SignIT's superior accuracy on both simulated data and somatic mutations from The Cancer Genome Atlas, and validated temporal dissection using whole genomes from 24 multiply-sequenced cancers. We highlighted a potential clinical application of mutation signature timing in a *BRCA1*-mutated pancreatic adenocarcinoma with low HRD signature but exceptional response to platinum-containing chemotherapy. Finally, we deciphered mutation signatures from nearly 500 metastatic cancer whole genomes, revealing evolution of mutational processes associated with late metastasis and exposure to cytotoxic chemotherapy. Taken together, our findings demonstrate the complex interplay of factors shaping the metastatic cancer genome. We highlight both clinical opportunities of studying genomic instability and the additional insights available from understanding their temporal evolution.

BIOGRAPHICAL NOTES

Place of Birth: Changchun, China
Academic Studies: B. Sc. University of British Columbia, 2013

GRADUATE STUDIES

Field of Study: Computational Biology and Genomics of Cancer

Courses

MEDG521	Molecular and Cell Biology of Cancer
ONCO502	Concepts in Oncology
BIOF520	Problem-Based Learning in Bioinformatics
BIOF501A	Special Topics in Bioinformatics

Instructors

Prof G. Morin
Prof S. Yip
Prof S. Jones
Prof R. Morin
Prof R. Brinkman

AWARDS

CIHR Vanier Canada Graduate Scholarship
UBC Four Year Doctoral Fellowship
BCCA-CIHR-UBC MD/PhD Studentship
CIHR Frederick Banting and Charles Best Canada Graduate Scholarship – Master's
UBC Faculty of Medicine Graduate Award
UBC Alumni Association Scholarship
UBC Student Leadership Conference Faces of Today Award
UBC Faculty of Science Achievement Award
John Bosdet Memorial Fund Graduate Student Travel Award
Translational Genomics Cluster Trainee Collaboration & Travel Award

SELECTED PUBLICATIONS

Eric Y. Zhao, Martin R. Jones, Steven J. M. Jones. Whole Genome Sequencing of Cancer. *Accepted*. **Cold Spring Harbor Perspectives** - Book Chapter.

My Linh Thibodeau, Melika Bonakdar, Eric Zhao, et al. Whole genome and whole transcriptome genomic profiling of a metastatic eccrine porocarcinoma. **NPJ Precision Oncology**. 2018.

Hui-li Wong, Kevin C. Yang, Eric Y. Zhao, et al. Molecular characterization of metastatic pancreatic neuroendocrine tumors (PNETs) using whole-genome and transcriptome sequencing. **Molecular Case Studies**. 2018.

Eric Y. Zhao, Yaoqing Shen, Erin D. Pleasance, et al. Homologous Recombination Deficiency and Platinum-based Therapy Outcomes in Advanced Breast Cancer. **Clinical Cancer Research**. 2017.

My Linh Thibodeau, Caralyn Reisle, [Eric Y. Zhao](#), et al. Genomic profiling of pelvic genital type leiomyosarcoma in a woman with a germline CHEK:c.delC mutation and a concomitant diagnosis of metastatic invasive ductal breast carcinoma. **Molecular Case Studies**. 2017.

Wendie D den Brok, Kasmintan A. Schrader, Sophie Sun, Anna V. Tinker, [Eric Y. Zhao](#), Samuel Aparicio, Karen A. Gelmon. Homologous recombination deficiency in breast cancer: a clinical review. **JCO Precision Oncology**. 2017.

SELECTED PRESENTATIONS

Evolution of Genomic Instability in Metastatic Cancer. Accepted for **Oral Presentation**. American Society of Clinical Oncology. **2018**, Chicago IL.

Clinical Translation of Genomic Scars in Advanced Breast Cancer. **Poster Presentation**. Annual Meeting of the Clinician-Investigator Trainee Association of Canada. **2017**, Toronto ON.

Homologous Recombination Deficiency & Platinum-based Therapy Outcomes in Advanced Breast Cancer. **Poster presentation**. Canadian Cancer Research Conference (CCRC). **2017**, Vancouver BC.

Breast Cancer Whole Genomes Link Homologous Recombination Deficiency with Therapeutic Outcomes. **Poster presentation**. American Association of Cancer Research (AACR). **2017**, Washington DC.

Guiding Platinum-based Chemotherapy with a Somatic Mutation Signature of BRCA1/2 Impairment. **Poster presentation**. American Society for Human Genetics. **2016**, Vancouver BC.

BRCA-Related Genomic Signature Predicts Clinical Improvement with Cisplatin. **Oral presentation**, Advances in Genome Biology and Technology. **2016**, Orlando FL.

SUPERVISORY COMMITTEE

Prof Steven Jones
Prof Inanc Birol
Prof Marco Marra
Prof Christian Steidl
Prof Stephen Yip



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)

ERIC YANG ZHAO

B. Sc. Hon. (Physiology), The University of British Columbia, 2013

Monday, May 7, 2018, 9:00 am
Room 2263, Diamond Health Care Centre
2775 Laurel St, Vancouver, BC V5Z 1M9
Latecomers will not be admitted

“The Clinical Actionability and Evolution of Mutational Processes in Metastatic Cancer”

EXAMINING COMMITTEE

Chair:

Prof John Spinelli (Population and Public Health)

Supervisory Committee:

Prof Steven J. M. Jones, Research Supervisor (Bioinformatics)
Prof Christian Steidl (Bioinformatics)

University Examiners:

Prof Cathie Garnis (Interdisciplinary Oncology)
Prof Judy Wong (Medical Genetics)

External Examiner:

Prof Susan Lees-Miller
Department of Biochemistry & Molecular Biology
University of Calgary
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