Vita

Candidate's name: Jorian Dunphy Hapeman

Universities Attended:

University of New Brunswick (2021)
Bachelors of Science, Honours

University of New Brunswick (2022)
Masters of Science
Biology

Publications / Presentations:

Hapeman, J.D., Carneiro, C.S., Nedelcu, A.M. 2022 Phenotypic plasticity during the dissemination of circulating tumour cell clusters: A model involving TGFβ1-mediated cluster dissociation, adherence and single-cell extravasation. *Genes.* (submitted Oct 2022)

Carneiro, C.S., Hapeman, J.D., Nedelcu, A.M. 2022. Synergistic cooperation involving TGF-β1-mediated crosstalk enhances the invasiveness of genetically distant cancer clones. *Cancers.* (submitted Nov 2022)

Hapeman, J.D., Nedelcu, A.M. A New Model for the Dissemination of Circulating Tumour Cell Clusters – NBHRF Health Research Week – Poster Presentation. *Fredericton, New Brunswick* (November 2022)

Hapeman, J.D., Nedelcu, A.M. Phenotypic plasticity during the dissemination of circulating tumour cell clusters: A new model involving TGF-β1-mediated cluster dissociation, adherence, and single cell extravasation – BHCRI Cancer Research Conference – Poster Presentation Award. *Halifax, Nova Scotia* (November 2022)

Hapeman J.D., Nedelcu A.M., Investigations into the dissemination abilities of circulating tumour cell clusters. Health Research Conference – Poster Presentation. *University of New Brunswick, Fredericton, Canada.* (August 2021)

Investigations into the mechanisms involved in the dissemination of circulating tumour cell clusters

UNIVERSITY OF NEW BRUNSWICK

THESIS DEFENCE AND EXAMINATION

in Partial Fulfillment

of the Requirement for the Degree of
Master of Science

by

Jorian D. Hapeman

in the Department of Biology

U.N.B., Fredericton, N.B.

Wednesday, December 7th, 2022
1:30 p.m.

Bailey Hall, Room 27

Examining Committee

Dr. Aurora Nedelcu	Supervisor
Dr. Denise Clark	Internal Examiner
Dr. Anna Ignaszak	External Examiner
Dr. Mike Duffy	Chair of Oral Examination

Abstract

Metastasis – the ability of cancer cells to disperse and colonize distant locations in the body, is responsible for most cancer-related deaths. While in the vasculature, tumour cells are referred to as circulating tumour cells (CTCs) and can manifest either as single cells or clusters of cells, with the latter being the most aggressive. Despite their significant role in the metastatic process, the mechanisms involved in the extravasation and dissemination of CTC clusters remain largely unknown. Notably, CTC clusters have been found to contain platelets, which can secrete many factors, including the Transforming Growth Factor Beta 1 (TGF-β1) – a signalling molecule implicated in many aspects of cancer, including the extravasation of single CTCs. To address whether the interaction between platelets and CTC clusters might facilitate the extravasation of CTC clusters, I evaluated the effect of exogenous TGF-β1 on an experimentally evolved lung cancer cell line that grows as cell clusters. I found that exogenous TGF-β1 induced the dissociation and adherence of clusters. Furthermore, once adhered, cells release their own TGF-β1 and are able to migrate and invade in the absence of exogenous TGF-β1. Based on these findings, I propose a model involving TGFβ1-mediated phenotypic plasticity that enables the extravasation and dissemination of CTC clusters as single cells. To evaluate the specific pathways activated during these processes, I used transcriptomic analyses to investigate TGFβ1-induced changes in gene expression. I found that the ability to adhere in response to TGF-β1 involves the upregulation of genes associated with the TGF-β1/Smad2/3, Wnt/β-catenin and EGFR signaling pathways. The upregulation of EGFR allows for the possibility that currently available drugs targeting EGF signalling might also be effective against CTC clusters. Overall, this study highlights the need to better understand the molecular mechanisms involved in the dissemination of CTC clusters as a means to develop new therapeutic strategies to specifically affect this important step in the metastatic cascade and improve clinical outcomes.