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BSc (Microbiology & Immunology), University of British Columbia, 2011

DEPARTMENT OF PATHOLOGY

TITLE OF THESIS:	PROFILING RETINOID SIGNALING IN TRIPLE-NEGATIVE BREAST CANCER: TOWARDS PRECISION APPLICATIONS
TIME/DATE:	9:30 am, Tuesday, March 13, 2018
PLACE:	Room 3107, The Mona Campbell Building, 1459 LeMarchant Street

EXAMINING COMMITTEE:

Dr. Lorraine Gudas, Department of Pharmacology, Weill Cornell Medical College (External Examiner)

Dr. Karen Bedard, Department of Pathology, Dalhousie University (Reader)

Dr. David Waisman, Department of Pathology, Dalhousie University (Reader)

Dr. Graham Dellaire, Department of Pathology, Dalhousie University (Supervisor)

Dr. Paola Marcato, Department of Pathology, Dalhousie University (Supervisor)

DEPARTMENTAL REPRESENTATIVE:	Dr. Wenda Greer, Department of Pathology, Dalhousie University
CHAIR:	Dr. Gerald Johnston, PhD Defence Panel, Faculty of Graduate Studies

ABSTRACT

Breast cancer is the most common malignancy diagnosed in women, affecting approximately one in eight Canadian women in their lifetime. Clinical decision-making for breast cancer focuses on targeting growth factor signals through the estrogen receptor and human epidermal growth factor receptor 2. Tumors which lack expression of the progesterone receptor, ER, and HER2 (known as triple-negative breast cancers, TNBCs), cannot be effectively treated with these agents and patients often face worse prognoses. This illustrates a need for novel therapeutic approaches for the management of TNBC. One potential agent, all-*trans* retinoic acid (atRA) is already used clinically in the treatment of acute promyelocytic leukemia with a limited side-effect profile. I hypothesized that atRA would be an effective treatment for some patients with TNBC following the identification of determinants of sensitivity.

This study characterizes the response of TNBC models to atRA using *in vitro*, *in vivo*, and *in silico* methods. I demonstrate that atRA signaling contributes to expression of a new-age tumor suppressor, RARRES1, and describe the related contributions of DNA methylation and key regulatory factors in establishing its wide range of expression across TNBCs. This formed the basis for large-scale transcriptional profiling of two distinct models of TNBC, in which I identify that the transcriptional response to atRA is largely non-classical and independent of the classical retinoic acid response element; the largely-independent profiles of the two models illustrate the contribution of additional regulatory factors. I further explored the transcriptional response to atRA and the regulatory contributions of DNA methylation across 13 TNBC cell lines and utilized this to describe a predictive profile which can be used to identify TNBC patients who will benefit from atRA therapy. This was validated against four patient-derived xenografts. Finally, using an *in vivo* genome-wide RNAi screen, I identify SCN1A and GABRA3 as putative mediators of the pro-tumorigenic effects of atRA and suggest that GABAergic signaling may mediate primary or secondary resistance. This research describes non-canonical pathways mediating cellular responses to atRA and provides convincing pre-clinical evidence to supports the precision use of atRA for patients with TNBC.