Notice of the Final Oral Examination
for the Degree of Master of Science

of

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BSc (University of Victoria, 2013)

“Investigating the Co-Evolution of Tumor Antigens and the Anti-Tumor Immune Response”

Department of Biochemistry and Microbiology

August 21, 2017
1:00 P.M.
Clearihue Building
Room B017

Supervisory Committee:
Dr. Brad Nelson, Department of Biochemistry and Microbiology, University of Victoria (Supervisor)
Dr. Robert Burke, Department of Biochemistry and Microbiology, UVic (Member)
Dr. Perry Howard, Department of Biology, UVic (Outside Member)
Dr. Megan Levings, Department of Surgery, University of British Columbia (Additional Member)

External Examiner:
Dr. Jeremy Wulff, Department of Chemistry, UVic

Chair of Oral Examination:
Dr. James Nahachewsky, Department of Curriculum and Instruction, UVic

Dr. David Capson, Dean, Faculty of Graduate Studies
Abstract

Background: High-grade serous carcinoma (HGSC) can exhibit high intratumoral heterogeneity (ITH). Despite a strong association between tumor-infiltrating lymphocytes (TIL) and survival in HGSC, ITH may have profound impacts on the anti-tumor T cell response. Yet, it is unknown how anti-tumor T cell responses contend with ITH over time in HGSC. Previous studies in melanoma and HGSC both showed tumor-reactive T cell clones emerge over time with their cognate tumor-antigens. Therefore, I hypothesized patients would share a common mechanism of T cell evolution to contend with ITH in HGSC. If so, I expect to see similar patterns of tumor recognition between primary and recurrent disease.

Methods: Tumor-associated lymphocytes (TAL) were expanded from primary and recurrent ascites samples using high-dose IL-2 and a rapid-expansion protocol (REP). Following expansion, TAL were assessed for recognition of autologous tumor by IFN-γ ELISPOT and flow cytometry for CD137. CD137+ tumor-reactive TAL were FACS-purified and the tumor-reactive T cell repertoire was profiled by deep sequencing of TCRβ chains (TCRseq). Tumor-reactive TCR clonotypes were compared between primary and recurrent disease to elucidate differences in tumor-reactive populations over time in HGSC.

Results: Patient TAL recognized tumor in two out of three cases. In patient IROC 060, the tumor became more immunogenic between primary and recurrent disease, which may reflect expression of new antigens and/or loss of an immunosuppressive phenotype. In patient IROC 106, the tumor remained immunogenic between primary and recurrent disease, which may reflect maintenance of stable antigen expression and an immune-sensitive phenotype. Patient IROC 034 did not exhibit any tumor-reactivity, suggesting tumor-reactivity is not ubiquitous in HGSC. FACS-purification of CD137+ T cells followed by TCRseq was successfully performed on T cell populations of both high- and low-abundance, suggesting TCRseq can be performed on populations containing very few T cells. I am currently awaiting TCRseq results that profile the clonal repertoire of tumor-reactive TAL from primary and recurrent disease in two patients, IROC 060 and IROC 106.

Conclusions: Anti-tumor T cell responses from ascites are both diverse between patients and dynamic within a patient, suggesting various mechanisms of T cell evolution to contend with ITH in HGSC. I developed a pipeline for the identification of tumor-reactive TCR sequences without the need for a priori knowledge of specific antigens. Additionally, this pipeline is feasible for very low-abundance samples, such as tumor-reactive T cells.

Significance: This study provides early insights into how TAL contend with ITH in HGSC. Ultimately, these results will inform the design of adoptive T cell therapy for recurrent HGSC.