EVALUATING THE IMMUNOGENICITY OF THE OVARIAN CANCER MUTANOME

Spencer D. Martin[1,2,4], Scott Brown[2], Darin Wick[1], John R. Webb[1,3], Robert A. Holt[2], Brad H. Nelson[1,3,4]

[1]Trev and Joyce Deeley Research Centre, BC Cancer Agency, Victoria, BC, Canada, [2]Genome Sciences Centre, Vancouver, BC, Canada, [3]Department of Biochemistry and Microbiology, University of Victoria, Victoria, BC, Canada, [4]Department of Medical Genetics, University of British Columbia, Vancouver, BC, Canada

A hallmark of cancer is the accumulation of mutations that allow cells to proliferate uncontrollably. A small proportion of tumor mutations can give rise to mutant peptides bound to MHC I or II, enabling recognition by host T cells. While mutations are a significant source of tumor antigens in cancers with high mutation loads, such as melanoma, far less is known about cancers with average mutation loads, such as ovarian cancer (mean 12.9 versus 1.7 coding mutations/megabase, respectively). Moreover, most studies to date have evaluated pre-existing T cell responses to mutations. Far less is known about mutation-specific vaccine-induced T cell responses. **We hypothesized that mutation-specific peptide vaccines can elicit therapeutic T cell responses towards ovarian cancer**. To test this concept, ID8-G7 mouse ovarian tumor cells underwent exome and RNA sequencing. We identified 114 somatic point mutations, 44 of which were non-synonymous and transcribed. Expressed mutations were ranked according to predicted MHC class I binding scores (NetMHCpan). 29-mer peptides encompassing the 21 top-ranked mutations were individually co-injected with poly(I:C) into naive mice. 15/21 mutated peptides elicited peptide-specific CD4+ and/or CD8+ T cell responses. For 9 peptides, T cell responses were specific for the mutated (versus wild type) peptide. However, none of the T cell lines recognized ID8-G7 tumor cells by ELISPOT. Furthermore, neither prophylactic nor therapeutic vaccination with mutated peptides extended survival of ID8-G7 tumor-bearing mice. We conclude that none of 21 evaluated mutations gave rise to naturally processed MHC class I or II epitopes to confer tumor cell recognition by CD4+ or CD8+ T cells. Using the epitope prediction parameters from this study as a guide, we are currently analyzing data from The Cancer Genome Atlas to determine the average number of potentially targetable mutations in human ovarian cancer with the goal of developing mutation-specific immunotherapies for this disease.