OncoPept™ interrogates the mutational landscape of tongue and buccal cancer in search of novel cancer immunotherapy targets and biomarkers

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Key features

- End-to-end platform uses tumor mutanome and expression data to interrogate identify and validate cancer immunotherapy targets
- Analyzes immune phenotype of the tumor microenvironment to predict biomarkers of response
- Applications in both pre-clinical and clinical settings

Introduction

Cancer immunotherapeutics engage the body's immune system to fight cancer. Two recently approved checkpoint control antibodies Ipilimumab and Nivolumab target the PD-1 receptor on T-cells blocking the negative signaling that attenuates T-cell activation. The release of brakes maintains the T-cells in their activated state. Activated $CD8^+$ cytolytic T-cells (CTLs) recognize and eliminate tumor cells by recognizing peptides derived from mutated cellular proteins. Identifying T-cell-activating cancer mutations will lead to the development of novel therapeutics including peptide vaccines and engineered T-cell receptors.

OncoPept is an integrated platform that combines powerful analytics to analyze exome and RNA-seq data to quantitate the epithelial, stromal and immune cell infiltration, thereby producing a holistic view of the tumor and the tumor microenvironment. By assessing the T-cell neo-epitope burden and the immune phenotype of the tumor, OncoPept helps to identify novel drug targets and biomarkers of response to cancer immunotherapy drugs.

Objectives

1. Deliver novel therapeutics in cancer immunotherapy by combining genotypic and phenotypic features of tumors
2. Provide an end-to-end solution to identify T-cell neo-epitopes in any cancer

Methods

Sequencing and Data analysis

Fifteen tongue and buccal cancer samples were analyzed to define the mutational landscape of the two cancer types. OncoPept was applied to the data to prioritize T-cell neo-epitopes in these cancers

Tumor exomes were sequenced at >150X and somatic mutations identified using MedGenome's proprietary variant calling pipeline VariMAT™. Gene expression analysis was performed on RNA-seq data (80-100 million reads/sample) and expressed as FPKM units. Differential gene expression is quantitated using Cuffdiff, DESeq2 and EdgeR. Immune cell filtration was analyzed qualitatively and quantitatively to assess the immune phenotype of the tumor microenvironment. HLA typing was done at a 4-digit resolution from RNA-seq data using Seq2HLA.

Tumor neo-antigens are taken through a series of prioritization steps to identify potential T-cell neo-epitopes. For both mouse and human tumor samples OncoPept produces greater than 2-log enrichment of T-cell neo-epitopes from tumor mutanome data.

Figure 1. Applications of OncoPept in the cancer immunotherapy space

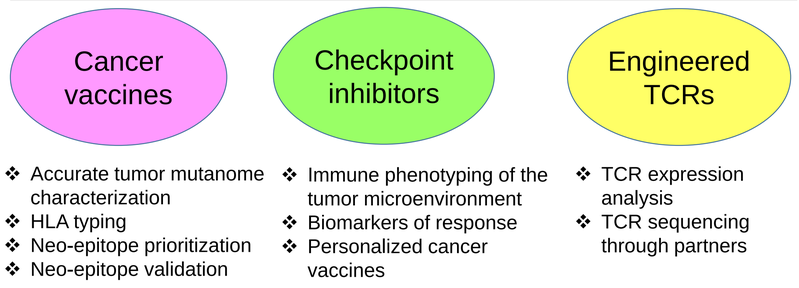

Figure 2. OncoPept Workflow: Identification of tumor-specific neo-antigens

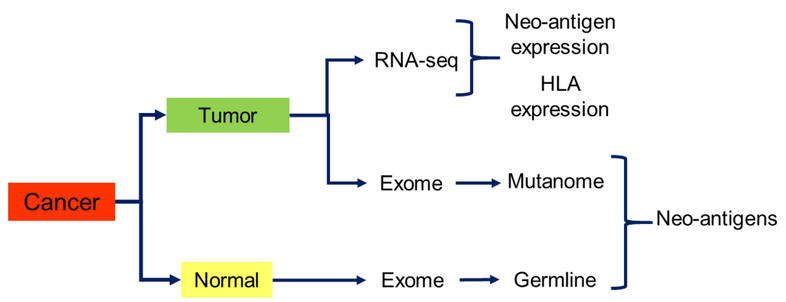

Figure 3. Clinical characteristics of Head & Neck cancer samples used in this study. Samples are **HPV, HBSAG and HIV negative**

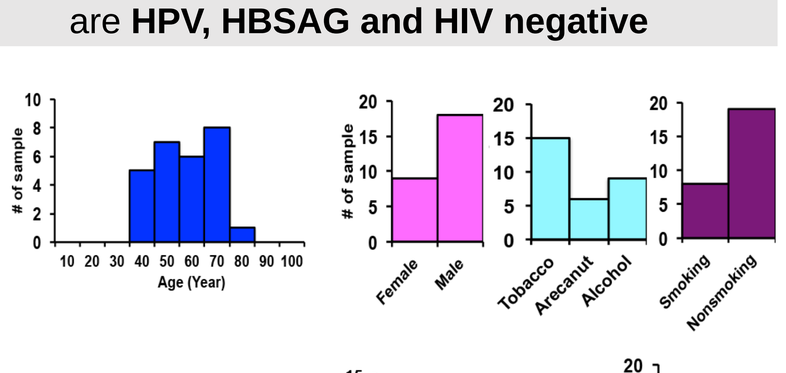

Figure 4. Mutational landscape of tongue and buccal cancer

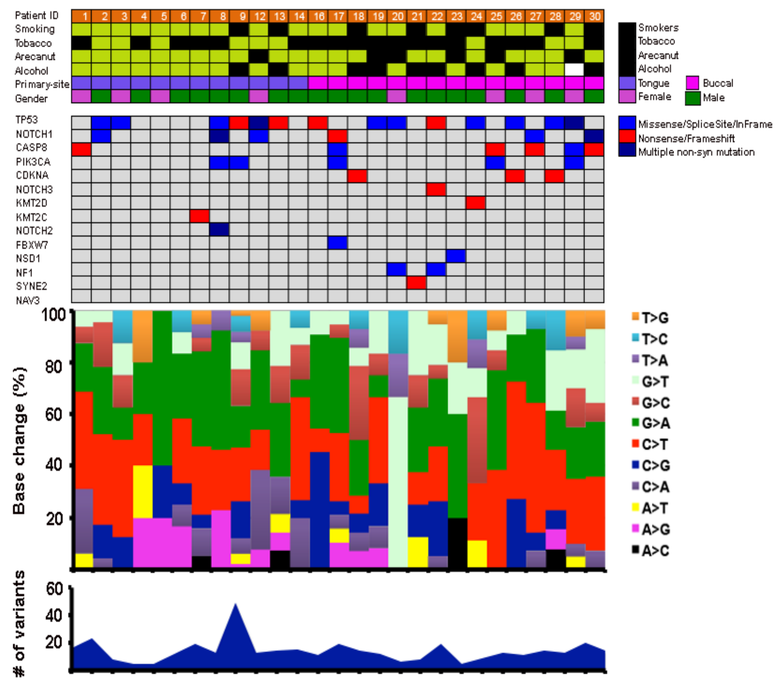

Figure 4. Tumor infiltrate analysis

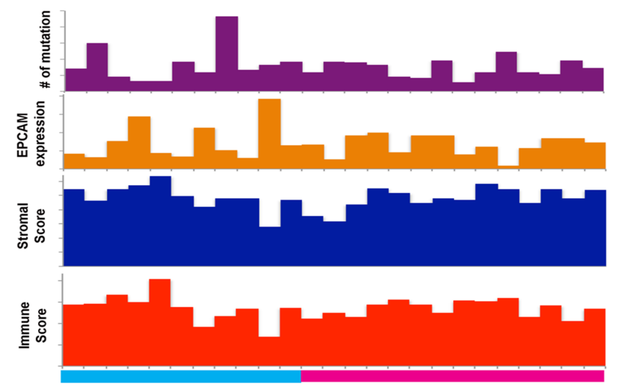

Figure 5. Differentially expressed genes contributing to T-cell neo-epitopes

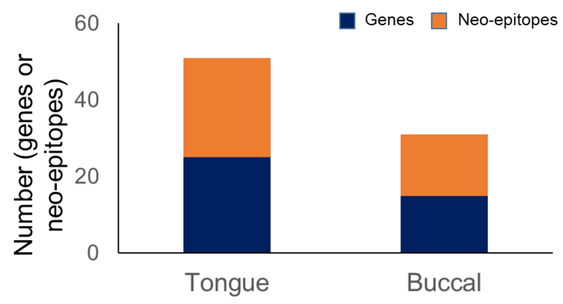

Figure 6. HLA and TCR-binding Neo-epitopes

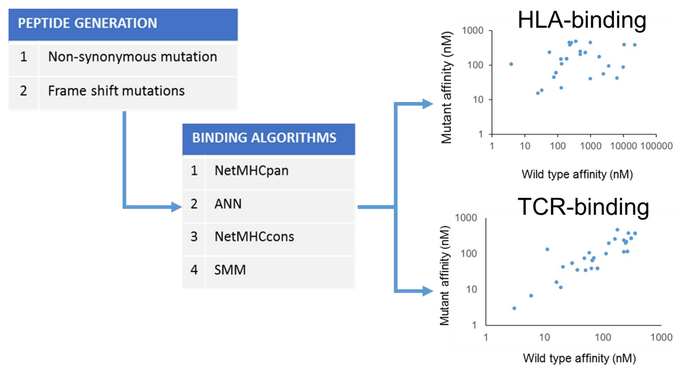

Figure 7. 2-log enrichment going from neo-antigens to neo-epitopes

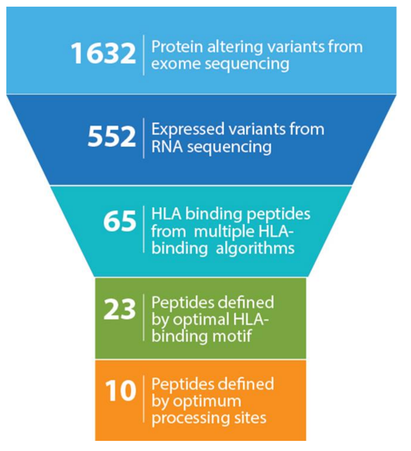

Figure 8. T-cell neo-epitopes are predominantly private