Sinai Health System

Rhinology/Skull Base Research
Ian Witterick, Allan Vescan, Eric Monteiro and John de Almeida

There are ongoing clinical research projects in rhinology and the skull base program. These include:

- Development of quality indicators for chronic rhinosinusitis

- Virtual reality simulators (Neurotouch) with validation trials

- Virtual reality sinus simulators to establish learning curves

- Validation of the skull base inventory quality-of-life instrument

- A ten year outcomes study of non-squamous cell sinonasal malignancies

Education research continues with the OtoSim™ in undergraduate medical education as well as the development of quality and safety measures for our specialty.

Head & Neck Oncology Research
Ranju Ralhan, Ian Witterick, Paul Walfish, Jeremy Freeman, Allan Vescan and Eric Monteiro

Our research interests primarily focused in the areas of translational research in applying proteomic findings and novel digital imaging technologies to development of biomarkers based algorithms that can be used in early detection, risk assessment, and management of oral cancer and precancers, as well as in community screening. The goal of this knowledge translation research has been to develop better cancer diagnostics based on subcellular quantitation of biomarker proteins expression in oral premalignant lesions for stratifying their risk of cancer development that brings fundamental change to the management of these patients. Our biomarkers can identify head and neck lesions that have a high risk of becoming cancer, permitting more effective and less traumatizing treatment.

1. Proteomics based biomarkers for predicting oral pre-malignant lesions at high risk of cancer development. Our most significant contributions have stemmed from our biomarkers research using oral pre-malignant lesions leading to development of new biomarkers to predict the risk of malignant transformation in patients with oral lesions. Currently, we are focusing on developing an Oral Cytology Test using oral cytosmears for protein biomarkers analyses for widespread use of our technology in dental clinics for patient care.

2. Prediction of recurrence-free survival using a protein expression–based risk classifier for head and neck cancer. Head and neck cancer prognostic biomarker panel has also been identified using tissue proteomics and independently validated in Canada and India for their global use for predicting the risk for recurrence of the disease in oral cancer patients (Chauhan SS et al., Prediction of recurrence-free survival using a protein expression–based risk classifier for head and neck cancer. Oncogenesis. 2015;4:e147. doi: 10.1038/oncsis.2015.7). As a powerful predictor of 3-year recurrence-free survival in head and neck cancer patients, the newly developed biomarker panel risk classifier will facilitate patient counseling for personalized treatment.

3. Developing novel molecular therapeutics for oral cancer. Two novel small molecule inhibitors identified in high throughput chemical screens have being investigated for their therapeutic efficacy, drug targets, mechanism of action using in vitro, in vivo, and clinical oral cancer samples for development of targeted therapy for oral cancer (Srivastava et al., Anticancer activity of Pyrithione Zinc in oral cancer cells identified in

small molecule screens and xenograft model: Implications for oral cancer therapy. *Molecular Oncology* 2015. 9 (8), 1720–1735; Guodong et al., ER maleate is a novel anticancer agent in head and neck cancer cells: Implications for cancer therapy. *Oncotarget* 2016 Feb 26. doi: 10.18632/oncotarget.7751).

Knowledge translation of our biomarkers into clinical settings for patient care has unraveled gaps in understanding of molecular mechanisms implicated in head and neck cancer development. Intense efforts are focused on unraveling molecular mechanisms involved in malignant transformation of oral epithelial dysplasia using indigenously established in vitro and in vivo experimental models to get deeper insight into development and progression of oral cancer.

Endocrine Oncology Research
Ranju Ralhan, Paul Walfish, Jeremy Freeman, Ian Witterick, Allan Vescan and Eric Monteiro

The endocrine oncology research laid major thrust on translational research aimed at applying proteomic findings and digital pathology to development of biomarkers based algorithms for improving thyroid cancer diagnostics.

Clinically integrated diagnostics for thyroid cancer is being developed with four major themes:

1. Use of protein biomarkers for predicting aggressive thyroid cancers.

2. Molecular signature for distinguishing benign from malignant thyroid nodules in ultrasound guided fine needle aspiration biopsies to improve surgical selection.

3. Biomarker based selection of aggressive thyroid cancer patients for immunotherapy.

4. Reference clinical database set up for cataloging the clinical course in different subtypes of thyroid cancer and correlating pre–operative FNA cytology with final surgical pathology.

1. Histology and digital pathology based biomarker panel test for predicting aggressive thyroid

cancers. Using proteomics and immunohistochemistry, our laboratory identified protein biomarkers that are differentially expressed in thyroid benign tissues and cancers. Our results demonstrated the clinical significance of increased nuclear Ep-ICD (i.e. intra-cellular domain of EpCAM) in aggressive thyroid cancer tissues. Interestingly, loss of membranous ALCAM and EpEx (extracellular domain of EpCAM) correlated with progression of disease and predicted poor prognosis in thyroid cancer patients. A digital pathology platform is being developed based on image analysis of immunostained biomarkers to derive a robust algorithm for predicting aggressive thyroid cancers.

2. Thyroid US-FNAB biomarker panel test. It is of critical clinical importance to accurately select for surgery thyroid nodules at risk for malignancy and avoid surgery on those that are benign. Using alterations in sub-cellular localization for seven putative biomarker proteins (identified by proteomics), we defined a molecular signature which could distinguish benign from malignant nodules to assist in future surgical selection by FNAB (Ralhan et al., Immunohistochemical Subcellular Localization of Protein Biomarkers Distinguishes Benign from Malignant Thyroid Nodules: Potential for Fine-Needle Aspiration Biopsy Clinical Application. Thyroid. 2015 Nov;25(11):1224–34). Our molecular signature had high efficiency for distinguishing benign from malignant thyroid nodules and could improve surgical selection for thyroid cancer among indeterminate nodules. Further validation in prospective pre-operative FNAB is in progress for its clinical application. Thus, using surgical pathology and preliminary FNAB, this panel of protein biomarkers is being validated for clinical application to improve pre-surgical selection of thyroid nodules at risk for malignancy. This is of paramount importance in not only avoiding unnecessary surgery on benign nodules with its associated morbidity but also in reducing healthcare costs through selection for surgery those nodules at risk for malignancy.

3. Programmed Death-Ligand 1 Overexpression Predicts Poor Prognosis in Papillary Thyroid Cancer (PTC) and its Variants. Programmed death ligand 1(PD-L1) expression on tumor cells is emerging as a potential predictive biomarker in anti–PD-L1 directed cancer immunotherapy. We evaluated the prognostic potential of PD-L1 in PTC and its variants and determined whether PD-L1 represents a therapeutic target in aggressive or metastatic PTCs that could be amenable to antibody-based immunotherapy. Our findings showed that PD-L1 expression in tumor cells correlates with aggressive metastatic PTC and shortened survival thereby favoring the possibility that anti PD-1/ PD-L1 axis immunotherapy could be a potential target for the treatment of advanced refractory PTC (Chowdhury et al., Programmed death-ligand 1 overexpression is a prognostic marker for aggressive papillary thyroid cancer and its variants. Oncotarget 2016 Apr 12. doi: 10.18632/oncotarget.8698).

4. We have established one of the largest clinical databases that have been developed for cataloging the clinical course in different subtypes of thyroid cancer. This database will also be useful for comparing the current pre-operative ultrasound and FNAB cytology based diagnosis with the final surgical pathology. It will therefore serve as a unique invaluable resource for comparative evaluation of new molecular diagnostic techniques with the current cytology based diagnostics to improve future surgical selection of patients for hemi-thyroidectomy vs total thyroidectomy and distinguishing benign from malignant thyroid nodules by pre-operative FNAB techniques.