AMERICAN ACADEMY OF OTOLARYNGOLOGY-HEAD AND NECK SURGERY FOUNDATION

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COVER SHEET FOR FINAL PROGRESS REPORT

Type of Grant:

___ AAFPRS Leslie Bernstein Grant
___ AAFPRS Leslie Bernstein Resident Research Grant
___ AAFPRS Leslie Bernstein Investigator Development Grant
___ AAOA Foundation/AAO-HNSF Combined Research Grant
___ AAO-HNSF Resident Research Award
___ AAO-HNSF Maureen Hannley Research Training Award
___ AAO-HNSF Percy Memorial Research Award
___ AAO-HNSF Health Services Research Grant
___ AAO-HNSF Rande H. Lazar Health Services Research Grant
__ X __ AHNS Pilot Grant
___ AHNS Alando J. Ballantyne Resident Research Pilot Grant
___ AHNS/AAO-HNSF Young Investigator Combined Award
___ AHNS/AAO-HNSF Surgeon Scientist Combined Award
___ AHRF Wiley H. Harrison Memorial Research Award
___ ALA/ALVRE Award
___ ANS/AAO-HNSF Herbert Silverstein Otology and Neurotology Research Award
___ ARS New Investigator Award
___ ARS Resident Research Grants
___ ASPO Research Grant
___ ASPO Daiichi Innovative Technology Grant
___ PSEF/AAO-HNSF Combined Grant
___ The Triological Career Development Award
___ XORAN Resident Research Grant

Start date: ______March 2009_______  Stop date: ______March 2010_______

Principal Investigator: __ Raewyn Marie Seaberg ____________________________

Institution: ___ University Health Network, Toronto ON ________________________

Title of Project: _____ MECT1-MAML2 fusion transcript in patients with mucoepidermoid carcinoma __________________
Abstract:

Mucoepidermoid carcinoma (MEC) is the most common type of malignant salivary gland tumour. It can arise from major salivary glands as well as from the minor mucous/serous glands that are scattered throughout the upper aerodigestive tract. These cancers display variable histopathologic differentiation and unpredictable clinical behaviour. Because of this, the identification of a surrogate tumour marker to aid in the prediction of tumour behaviour and ultimately clinical prognosis is highly desirable.

Of the cases reported in the literature to date, approximately 40-50% of MECs have a t(11;19)(q21;p13) translocation involving the genes mucoepidermoid translocated 1 (MECT1) (also known as CREB-regulated transcriptional coactivator, CRTC1) and a member of the mastermind-like gene family (MAML2) located at 19p13 and 11q21, respectively. This translocation, which can be the sole cytogenetic alteration, generates a MECT1-MAML2 fusion oncogene that disrupts the normal mechanism of the Notch and CREB signaling pathways to induce tumorigenesis.

Several recent reports have suggested that the MECT1-MAML2 translocation may be associated with low-grade tumour histology, although others have found the translocation in both low and high-grade MECs. Interestingly, there is also emerging evidence that patients with the MECT1-MAML2 translocation may have a lesser incidence of local recurrence, metastases, as well as longer disease-free and overall survival than patients in whom the translocation is not detected.

This project aims to determine the utility of routine testing of MECs for the MECT1-MAML2 translocation. This will be accomplished by determining the incidence of the translocation in patients that were treated surgically at the University Health Network by undertaking RT-PCR analysis of banked tumour specimens, and the relationship between the presence of the translocation and histopathological features and clinical outcome.

Briefly describe progress in completing the project:

Seventy-three (73) MECs were retrieved from the pathology files of the University Health Network. The tumors were resected between 1992-2007. All the slides available were reviewed and the tumors were graded using the Healey's system. RNA was extracted from representative formalin-fixed, paraffin-embedded tissue from each case and the presence of the t(11;19) translocation was investigated by reverse transcriptase polymerase chain reaction (RT-PCR).

Twenty-three cases (32%) were positive for the t(11;19) translocation with 22 containing the CRTC1-MAML2 chimeric gene and 1 the CRTC3-MAML2 gene indicating a likely t(11:15) translocation. The t(11;19) translocation was found in 8/23 (35%) grade I tumors, 11/35 (31%) grade II tumors, 3/12 (25%) grade III tumors, and 1/3 (33%) of oncocytic MECs. The tumor with the CRTC3-MAML2 gene was grade I. Clinical follow-up of fusion-positive MECs ranged from 2-331 months with a mean of 52. At last follow-up 18 patients were alive with no disease, 3 were alive with widely recurrent disease (22, 23, and 331 months), and 1 had died with disease (10 months). The patient that died had a T3N2Mx lesion of the base of tongue whereas those with recurrent disease had advanced sinonasal tumors at presentation.

What work was completed?

All of the work, which consisted of pathological review and RT-PCR analysis as well as clinical chart review, was completed.
What work was not completed?

n/a

Were all of the funds spent? If no, then the remaining funds will need to be return with a hard copy of the final financial report. If an AAO-HNSF grant, these can be sent to Stephanie Jones. If one of the sister society grants, contact Stephanie to obtain the name and address of the organization to whom the funds should be returned.

Yes, all of the funds have been spent.

Have the results been presented? Poster? Oral? What meeting? What publication?

The results were presented as a poster at the 99th USCAP Annual Meeting in Washington DC, in March 2010.

Clinical Applications, Either Immediate or Potential, of This Research:

The t(11;19) translocation was more common in grade I-II MECs but was also seen in 25% of grade III tumors. MECs arising in the sinonasal tract may have an adverse outcome despite the presence of t(11;19) underscoring the importance of primary tumor site and stage in the prognosis of MEC. Given the variable detection of t(11;19) using RT-PCR, there is a need to assess its incidence and clinical significance using fluorescence in-situ hybridization. Rare MECs have a variant CRTC3-MAML2 chimeric gene.

Other Pertinent Information:

We feel that our work needs to be verified with fluorescence in-situ hybridization (FISH) for it to be meaningful. This work is ongoing. We have some evidence that our RT-PCR assay missed some of the MECT1-MAML2-positive tumours; we are investigating whether this is an assay sensitivity issue or whether there is a more complicated rearrangement of these two genes that our assay is missing in these particular tumours.

Additionally, we have at least one case that is MECT1-positive and MAML2-negative by FISH analysis. Again, we are investigating whether this is an issue with the MAML2 FISH or whether MECT1 may have an undiscovered gene partner in this tumour.