AMERICAN ACADEMY OF OTOLARYNGOLOGY-HEAD AND NECK SURGERY FOUNDATION

ATTN: Stephanie Jones
Assistant Director, Research and Quality Improvement
1650 Diagonal Road
Alexandria, VA 22314-2857
sljones@entnet.org
PH: 703-535-3747

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
_____AHNS Pilot Grant
__X__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: 7/1/2010 **Stop date:** 7/1/2011

Principal Investigator: Vlad C. Sandulache

Institution: Baylor College of Medicine

Title of Project: Targeting glycolysis in head and neck squamous cell carcinoma.

Abstract:

Background: The management of head and neck squamous cell carcinoma (HNSCC) often requires multimodality therapy, including chemotherapy. When used alone, conventional chemotherapeutic agents provide only a marginal survival benefit, and many tumors are resistant to this type of treatment. Alternative approaches are therefore required in order to improve the effectiveness of existing strategies. Recently, anti-metabolic strategies have been explored and appear to be a promising new field in adjuvant therapy. *We hypothesize that a subset of HNSCC tumor cells exhibit elevated glycolytic activity making them particularly susceptible to chemotherapeutic strategies which include anti-glycolytic agents.* To test this hypothesis we propose the following aims: 1) to evaluate the metabolic profile of a panel of HNSCC cell lines using biochemical analysis and determine the proportion of primarily glycolytic cell lines; 2) to evaluate the cytostatic/cytotoxic effects of four previously described anti-glycolytic agents in vitro both alone and in combination with cisplatin. 3) to evaluate the anti-tumorigenic and anti-metastatic effects of anti-glycolytic agents, alone and in combination with cisplatin, using an orthotopic mouse model of HNSCC.
Methods: HNSCC cell lines will be analyzed for dependence on glycolysis for survival and energy production. Four anti-glycolytic agents will be screened against the subset of HNSCC cells with increased glycolytic activity for in vitro cytotoxicity alone and in combination with cisplatin. In vitro cytotoxicity data will be confirmed using an established orthotopic mouse model.
Conclusion: We will identify the subset of HNSCC cell lines which are particularly susceptible to anti-glycolytic strategies. We will evaluate potential synergy of novel anti-glycolytic compounds with existing chemotherapeutic agents and provide pre-clinical data to help define a role for anti-glycolytic strategies in the treatment of HNSCC.

Briefly describe progress in completing the project:
To date we have completed a metabolic analysis of 15 HNSCC cell lines and evaluated their relative sensitivity to anti-metabolic agents. In addition, we have identified wild type p53 function as an important regulator of HNSCC metabolism. We have evaluated the cytotoxic profiles of several anti-metabolic agents in combination with conventional chemotherapeutic agents under in vitro and in vivo conditions.

What work was completed?
All proposed work was completed.

What work was not completed?
All proposed work was completed.

Were all of the funds spent?
All funds were expended.

Have the results been presented? Poster? Oral? What meeting? What publication?
The results from this project were presented in poster fashion at the 2011 Combined Otolaryngology Spring Meetings, Chicago, IL. In addition, the data have been published in the following 2 manuscripts.

Sandulache VC, Skinner HD, Ow TJ, Zhang A, Xia X, Luchak JM, Wong LJ, Pickering CR, Zhou G, Myers JN. Individualizing antimetabolic treatment strategies for head and neck squamous cell carcinoma based on TP53 mutational status. Cancer. 2011 (Epub ahead of print)

Sandulache VC, Ow TJ, Pickering CR, Frederick MJ, Zhou G, Fokt I, Davis-Malesevich M, Priebe W, Myers JN. Glucose, not glutamine, is the dominant energy source required for proliferation and survival of head and neck squamous carcinoma cells. Cancer. 2011 Jul 1;117(13):2926-38.

Clinical Applications, Either Immediate or Potential, of This Research:
We have identified mutant p53 status as contributory to altered HNSCC metabolism, potentially making tumors which express mutant p53 more susceptible to targeted anti-metabolic agents. We are currently in the planning stages of additional pre-clinical studies to validate this finding prior to proposing initiation of clinical investigation.

Other Pertinent Information:
None.