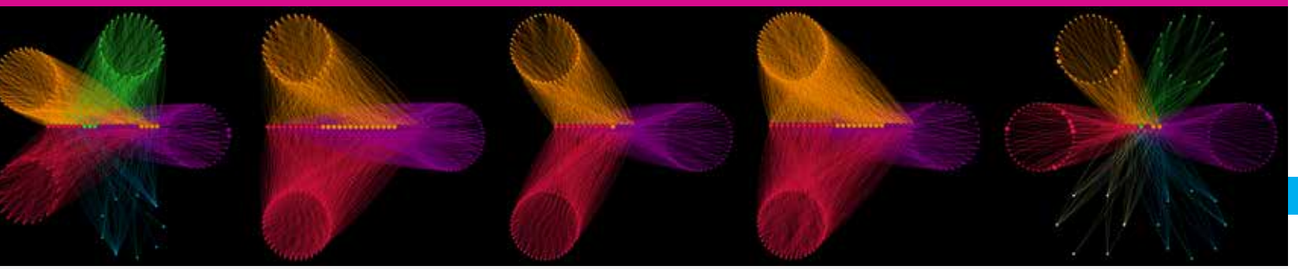


The Pathophysiology of Spasmodic Dysphonia: Dystonia and Motor Control Laboratory Dormancy via SOX9-and RARb-Driven Quiescence Programs

Kristina Simonyan, MD, PhD. Associate Professor of Neurology and Associate Professor of Otolaryngology

The pathophysiology of spasmodic dysphonia has eluded investigators. New techniques in neuroimaging, neuropathological, clinical, genetic and environmental correlates, led by Dr. Simonyan at Mount Sinai, have begun to identify the causes and potential therapies for spasmotic dysphonia. Using a variety of neuroimaging methods, including structural and functional MRI as well as positron emission tomography (PET) with radioactive ligands, Dr. Simonyan applies these research tools with clinical, behavioral and genetic testing in order to fully characterize the underlying causes and pathophysiology of SD and other focal dystonias. Recent advances in understanding dystonia included the first report of a group of patients with negative dystonia of the palate, which represents a novel and rare form of focal dystonia, impairing speech production (Sinclaire, Simonyan, Brin and Blitzer in the June issue of the Laryngoscope). In this study, the group has defined the neural correlates of this form of dystonia in comparison with healthy subjects and patients with spasmotic dysphonia, identifying a unique pattern of brain abnormalities associated with negative dystonia of the palate.

Another paper by Kirke, Frucht and Simonyan in the June issue of the Journal of Neurology examined in depth the curious clinical phenomenon of alcohol responsiveness of dystonic symptoms in a large population of patients with SD and identified that more than 55% of SD patients have at least some positive benefits on their voice symptoms following alcohol consumptions.

This study opens potential new avenues of research for the development of novel therapeutic options for dystonia, in general, and spasmotic dysphonia, in particular.

In addition, as a longstanding research direction, Dr. Simonyan and her Dystonia and Motor Control Laboratory continue studies on normal motor control during speech production. Together they combine the available neuroimaging tools with computational neural modeling approaches in order to elucidate the organization of functional and structural brain networks underlying production of a spoken word in healthy individuals. Additionally, the laboratory uses graph theory to analyze function MRI data recorded from speakers as they produce single syllables to whole sentences, revealing the complexity of the brain network machinery that controls speech and language. (Study by Stefan Fuertinger, Barry Horwitz, and Kristina Simonyan.)

Mount Sinai

Department of Otolaryngology – Head and Neck Surgery

Head and Neck Cancer Research Program, at the Icahn School of Medicine at Mount Sinai

Icahn School of Medicine at Mount Sinai

One Gustave L. Levy Place
Box 1189
New York, NY 10029-6754

Leslie Waters-Martin
Research Program Coordinator
Leslie.waters-martin@mountsinai.org
212-241-7107

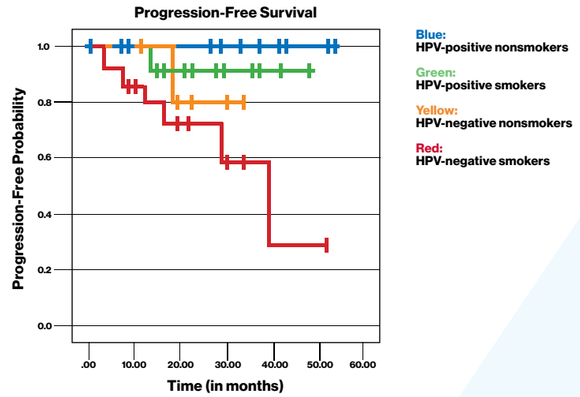
Mount Sinai | **Research Focus**

Volume 2 : Spring 2016 — Head and Neck Research Focus Letter

How Tobacco use Impacts Prognosis in HPV-Associated Oropharyngeal Cancer Patients

While rates of laryngeal, oral, and hypopharyngeal squamous cell carcinoma have been decreasing as smoking has decreased in the US, the incidence of oropharyngeal squamous cell carcinoma has been rising. Commensurate with this change, there has also been a change in the patient demographics. Worldwide, there has been a shift from a population of older patients (>60 years of age) with a strong history of tobacco and alcohol use to a younger population (<60 years of age) of patients with no or limited history of tobacco and alcohol use. These trends are a result of an epidemic of human papillomavirus (HPV)-associated oropharyngeal cancer. The significance of this epidemic is highlighted by the fact that HPV-associated oropharyngeal cancer in men will likely become more common than cervical cancer in women within the next 5-7 years.

Data suggests that the best survival rates are achieved in non-smoking HPV-positive patients (82.4%), followed by HPV positive smokers, HPV-negative non-smokers, and finally HPV negative smokers (57.1%). Investigators at Mount Sinai report new data demonstrating the TransOral Robotic Surgery (TORS) yields outstanding out comes in the groups of patients that are at the high risk for recurrence and death, tobacco users. Researchers found smokers and nonsmokers had locoregional control rates of 96.3% and 94.4% and progression-free survival rates



Caption for Artwork above would go here

83% and 94.1%, respectively. HPV-negative and HPV-positive patients had locoregional control rates of 87.1% and 100% and progression-free survival rates of 74.2% and 95.2%, respectively. Locoregional control rates for HPV-negative smokers, HPV negative nonsmokers, HPV-positive smokers, and HPV-positive non-smokers were 90.9%, 80.0%, 100%, and 100%, where-as progression-free survival rates were 72.2%, 80.0%, 92.3%, and 100%, respectively. Researchers conclude TORS may be beneficial for the management of HPV-associated oropharyngeal cancer irrespective of smoking status.

Eric Genden, MD MHA, FACS
Isidore Friesner Professor and Chairman, Otolaryngology – Head and Neck Surgery Icahn School of Medicine at Mount Sinai

A note from Eric Genden, MD MHA, FACS

Over the past decade, the worldwide prevalence of oropharyngeal cancer and thyroid cancer has increased at an alarming rate. It is estimated that our multidisciplinary team of basic scientists, clinicians, and translational scientists have established a series of unique clinical trials designed to achieve optimal cure rates with minimal treatment toxicity. In this edition of Research Focus we highlight just a few of the unique programs that have contributed to a better understanding of these diseases. I hope that you find this update informative as we strive toward curing this disease in a way that maintains the patient's quality of life.

Advances in the Effort to Cure Thyroid Cancer: Personalized Medicine

Ross Cagan, PhD

Aggressive forms of thyroid cancer, including medullary thyroid carcinoma and certain forms of papillary thyroid carcinoma, have proven resistant to many targeted therapies. The Cagan Laboratory at Mount Sinai is using the fruit fly Drosophila to develop novel approaches to several cancer types including medullary thyroid carcinoma and papillary thyroid carcinoma.

Expressing an oncogenic form of the Ret receptor in the fly, the Cagan Laboratory has developed a screening platform that helped identify vandetanib as a candidate therapeutic for medullary thyroid carcinoma. Vandetanib was subsequently approved as the first standard of care for medullary thyroid carcinoma.

The figure above is an example of targeting an oncogene to the fly eye. More recently, the laboratory has collaborated with multiple other laboratories to develop a new generation of lead therapeutic compounds for thyroid cancer. Combining fly genetics plus medicinal and computational chemistry, in collaboration with the laboratories of K. Shokat, Arvin Dar,

In contrast to the smooth control eye (left), expressing the Ras oncogene (right) led to 'tumors' that emanate from the eye. This phenotype is useful to screen for new drugs.

and Avner Schlessinger, they have developed new kinase inhibitor-class drugs that address several targets. In short, initial lead compounds were identified using a robotics-based whole animal fly screen; genetic screens then identified additional targets to be 'dialed into' the lead hit. Medicinal and computational approaches were then used to improve the lead hits, creating a multi-targeting lead compound. Both fly and mouse studies indicate that this 'balanced polypharmacology' approach may prove more successful at addressing tumor progression, resistance, and heterogeneity than currently available drugs. These new candidate compounds are currently being explored for their clinical potential. We are now working on fully computational methods with the Mount Sinai Minerva Supercomputer to build truly novel compounds that act in novel chemical space; our initial efforts have yielded a new class of drugs and we are now working to improve overall therapeutic index.

Sinai Robotic Surgery Trial in HPV Positive Oropharyngeal Cancer Yields Promising Results

Brett Miles, MD DDS, **Marita Teng,** MD, **Marshal Posner,** MD, **Eric Genden,** MD MHCA

In general, patients with human papillomavirus-positive oropharyngeal squamous cell carcinoma (HPV+) are curable, young and will live for prolonged periods. They are at high risk for long-term toxicity and mortality from therapy. High-dose radiotherapy (RT) and chemoradiotherapy (CRT) substantially impact on local tissues and organ function and result in a significant rate of late mortality and morbidity in patients. There are currently few trials examining the role of de-escalation using surgery alone in intermediate and early T-stage HPV-related disease. New surgical techniques have broadened the range of patients capable of achieving a complete resection and the functional outcomes in such patients are outstanding. Studies such as the ECOG 3311 and the Sinai Robotic Surgery (SIRS) trial aim to evaluate the oncologic efficacy and function morbidity when TransOral Robotic Surgery (TORS) is employed to stratify patients for appropriate adjuvant therapy.

Patients with intermediate stage HPV-positive oropharyngeal cancer are screened for poor prognostic features and undergo robotic surgery. Patients in whom pathology demonstrates good prognosis features are then followed without postoperative radiotherapy. Patients with poor prognostic features (ECS, LVI, PNI) receive reduced dose radiotherapy or chemoradiotherapy based on pathology. It is expected that more than 50% of patients treated with surgery will have had a curative treatment and 25-30% will avoid radiation therapy entirely and long-term survival will not be changed by withholding radiation therapy to good prognosis patients after surgery.

Furthermore, the sensitivity of HPVOPC to chemotherapy and radiotherapy raise the possibility that delayed or salvage treatment in early stage patients would be highly effective, would result in similar survival outcomes and radiotherapy could be applied to a much smaller population then current standards. Looked at from a different perspective, the need for post-operative radiotherapy in this younger, HPV+ and more functional population have not been validated in clinical trials to date. The value of the SIRS trial and similar trials such as the ECOG 3311 will be to answer questions about the role of robotic surgery and pathologic staging for HPV-related oropharyngeal cancer.

Molecular Epidemiology of Head and Neck Cancer Director Institute for Translational Epidemiology

Paolo Boffeta, MD, MPH

Dr. Boffetta's research group is leading the INHANCE (International Head and Neck Cancer Epidemiology) Consortium, a collaboration comprising the principal investigators of more than 40 large molecular epidemiology studies of head and neck cancer that are ongoing or have been recently completed. Overall, clinical and questionnaire data on over 26,000 cases & 34,000 controls, and biological samples from a majority of the study populations are available for collaborative projects. These studies have been conducted in various regions of the world.

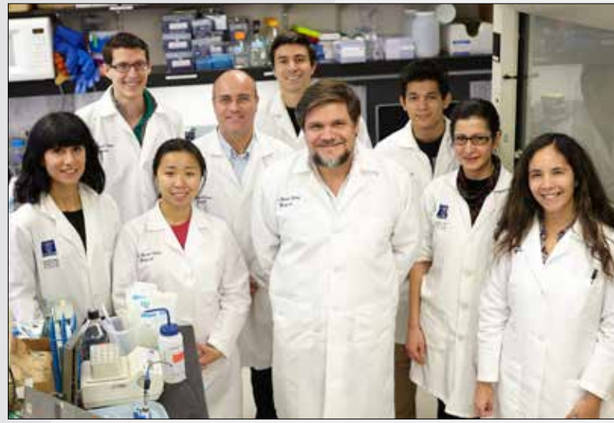
Worldwide, an estimated more than 600,000 head and neck cancer cases and 325,000 deaths due to head and neck cancer occur each year. Head and neck cancers are a related group of cancers that involve the oral cavity, pharynx and larynx. While it is well established that tobacco and alcohol account for at least 75% of head and neck cancers on a global scale, important etiologic questions remain to be addressed: (i) the role of genes and their interactions with environmental factors, (ii) etiology in rare subgroups including young age at onset, and nonsmokers and nondrinkers, and (iii) a precise characterization of the role of human papillomavirus (HPV).

Dr. Boffetta's research group has conducted pooled analyses of lifestyle risk factors such as alcohol beverage type and concentration, and also pooled analyses in rare groups such as early onset head and neck cancer cases, and nonsmokers/nondrinkers. They have participated in genotyping projects based both on a list of priority variants and on genome-wide scans, and have assessed the effect of HPV infection.

Among the recent publications are (i) an analysis of low-level tobacco smoking, demonstrating an increased risk for smoking less than 3 cigarettes/day, and (ii) a pooled analysis of data on mouthwash use, showing little evidence of an excess of risk among users.

Researchers at Mount Sinai Determine NR2F1 Controls Tumor Cell Dormancy via SOX9-and RARb-Driven Quiescence Programs

Julio A. Aguirre-Ghiso, PhD Professor, Director of Head & Neck Cancer Basic Research and Hematology and Oncology



Julio A. Aguirre-Ghiso, PhD (Center)

In head and neck squamous cell carcinoma (HNSCC) metastasis originate from disseminated tumor cells (DTCs). The team led by Dr. Aguirre-Ghiso recently published in Nature Communications a breakthrough study revealing how a transcription factor, NR2F1, and signals in the bone tissue induce dormancy of disseminated HNSCC cells. They took these findings and discovered that by combining two FDA-approved drugs, azacytidine and all-trans retinoic acid (a form of vitamin A) they restored the NR2F1-driven dormancy program stopping the expansion of HNSCC cells. In collaboration with colleagues at the University of Washington they used the HNSCC model information and identified for the first time markers that pinpoint prostate cancer single DTCs that were dormant or actively proliferating. This work has led to the development of a clinical trial for metastatic prostate cancer and the approach can be applied to other cancers, such as head and neck and breast.

More information can be found at **icahn.mssm.edu/headneckresearch**