Mount Sinai

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Research Focus

The newsletter of the Icahn School of Medicine at Mount Sinai Head and Neck Cancer Center, Division of Research

Targeting Inflammation To Treat Head and Neck Cancers

Cancer and inflammation are fundamentally intertwined: inflammation drives the transition of normal cells to cancer, while tumors actively induce a state of chronic inflammation to accelerate their growth and suppress anti-tumor immunity. The laboratory of Andrew Sikora, MD, PhD, is focused on understanding the role of inflammation-associated molecules in head and neck cancers, including squamous cell carcinoma and melanoma, and using this information to develop new therapeutic approaches. The ultimate goal is to shut down inflammatory signalling pathways which fuel cancer growth, while unleashing the patient's own immune system to recognize and destroy cancer cells.

Reversing tumor-mediated immune suppression

While the immune system has the potential to recognize and target cancer cells, tumors use every means at their disposal to actively suppress host immunity and escape immune-mediated destruction. Expression of inflammation associated molecules such as cyclooxygenase 2 (COX2) and inducible nitric oxide synthase (iNOS) promotes the release of soluble inflammatory mediators called cytokines into the tumor microenvironment and bloodstream. These inflammatory cytokines alter the host immune system in profound ways, including the induction of a type of immunosuppressive bone marrow derived cell called the myeloid-derived suppressor cell (MDSC).

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Andrew Sikora, MD, PhD, conducts research that straddles the gap between basic cellular and molecular studies and clinical trials for head and neck cancer.

Director's Corner

I am delighted to present the first issue of Mount Sinai Research Focus, a periodical designed to keep patients, clinicians, and those interested in the cancer research, apprised of the exciting developments in head and neck cancer research at the Icahn School of Medicine at Mount Sinai and Tisch Cancer Institute. Herein you will find some of the most compelling and cutting edge research in the areas of head, neck, and thyroid malignancy. Many of the exciting developments in basic and translational research have been made possible by our grateful patients and interested corporate donors. I hope that you find this periodical informative and consider supporting our research initiatives.

Left: Eric Genden, MD is Professor and Chairman of the Department of Otolaryngology—Head and Neck Surgery and Director of the Head and Neck Cancer Center at the Icahn School of Medicine at Mount Sinai.

Spotlight On... Julio Aguirre-Ghiso, PhD

Julio Aguirre-Ghiso, PhD

Julio Aguirre-Ghiso, PhD, has been named Director of Solid Tumor and Metastasis Research for the Division of Hematology and Medical Oncology. In his new role, Dr. Aguirre-Ghiso will be fostering the development of collaborative basic and translational studies in solid tumor and metastasis research with faculty and trainees in Hem/Onc and across programs. He will oversee the infrastructure and development of new cores to facilitate basic, translational and clinical research in solid tumors and metastasis.

Dr. Aguirre-Ghiso received his MSc and PhD degrees in molecular cell biology from the Universidad de Buenos Aires in Buenos Aires, Argentina. There he studied the signal transduction mechanisms regulating protease production and metastases in mouse mammary tumor models. He then moved to do post-doctoral training in the laboratory of Liliana Ossowski, MSc, PhD, at Mount Sinai. During this time, he investigated how the integration of adhesion and growth factor signaling mechanisms regulate the induction of tumor cell dormancy. In 2003, he was appointed Assistant Professor in the Department of Biomedical Sciences at the School of Public Health at the State University of New York at Albany and held a joint appointment at the Wadsworth Centre, New York State Department of Health. In 2008, Mount Sinai's Department of Medicine, Division of Hematology and Oncology, and the and Department of Otolaryngology, appointed him Associate Professor and Director of Head and Neck Cancer Basic Research. He received tenure in 2011. His laboratory studies how mitogenic and stress signaling pathways in concert with microenvironmental signals control cellular quiescence. This focus has led to important contributions in the fields of metastases and cancer cell dormancy.

The Sacks Fellowship — Building a Legacy of Discovery

One of the most important goals of any research program is identifying and training the next generation of researchers. Steven Sacks, MD, an alumnus of the Icahn School of Medicine at Mount Sinai, Otolaryngology Department, who continues to serve the department as voluntary faculty, understands how important exposure to research is in shaping the career choices of future otolaryngologists. To help ensure that Icahn School of Medicine medical students have the opportunity to engage in an intense, high-quality research experience in the Department of Otolaryngology, Dr. Sacks has endowed the Sacks Medical Student Clinical Research Fellowship, which will support one fellow annually.

After undergoing a rigorous selection process, the Fellow takes a dedicated research year between his or her third and fourth years of medical school. Fellows may participate in clinical research projects, or a combination of clinical and basic research. So far, two Sacks Fellows have been selected: Nathaniel "Nate" Villanueva, who participated in 2011-2012; and Brieze Keeley, who is currently in her fellowship year.

Based on Mr. Villanueva's performance as the inaugural Sacks Fellow, the program is off to a good start. His participation in several clinical research projects in Head and Neck Surgery earned him several oral presentations at national meetings, including the eighth

Nathaniel "Nate" Villanueva

Brieze Keeley

International Conference on Head and Neck Cancer, held in Toronto.

Intrigued by the clinical problem of metastatic cancer, Mr. Villanueva also had primary responsibility for developing a basic science project investigating the ability of inhibition of the cancer-associated inflammatory molecules COX2 and inducible nitric oxide synthase (iNOS) to block growth of metastatic head and neck cancer cells. This project, a collaboration between the laboratories of Julio Aguirre-Ghiso, PhD, and Andrew Sikora, MD, PhD, tested the effect of iNOS and COX2 inhibitors on growth of metastatic cells in the lung and lymph nodes of mice bearing human oral cancer xenografts after surgical removal of their primary tumor. They found that combined inhibition of both COX2 and iNOS significantly reduced tumor-associated inflammation, and inhibited growth of metastatic cancer in the lung and lymph nodes. The team's results were recently presented at the 2012 Cancer Research Institute International Cancer Immunotherapy Symposium, held in New York City.

Ms. Keeley, the current Sacks Fellow, has continued the focus on inflammation and cancer by spearheading a project designed to investigate the ability of levels of inflammatory molecules in the blood to predict development of upper aerodigestive cancers, including of the lung, esophagus, and head and neck. This collaboration between Dr. Sikora and Paolo Boffetta, MD, MPH, and Farhad Islami, MD, PhD, of Mount Sinai's Institute for Translational Epidemiology utilizes a unique collection of prospectively collected serum samples from a region of Iran that has an unusually high incidence of esophageal cancer. The samples were collected as part of the GEMINI population-based study. Results of this study may identify new serum biomarkers of cancer risk.

This is exactly the type of hands-on research experience Ms. Keeley was looking for. "I'm excited because the Sacks Fellowship gives me the opportunity to see a study through from start to finish and to take ownership of a clinically relevant project," she said. "I already have a much clearer idea what goes into designing a good clinical study, and how to make research a part of my future career."

Research program vital statistics

15 therapeutic/diagnostic clinical trials

11 NIH-funded grants

1 goal: curing head and neck cancer

If you or someone you know would like information about supporting our work, please contact **Mariko Stronach, Research Program Coordinator**.

T: 212 241 9144
email: mariko.stronach@mssm.edu
donation website: https://philanthropy.mountsinai.org/hnc

Save the Date!

Back-to-back courses:
HPV-Associated Head and Neck Cancer and INHANCE 2013 at the Icahn School of Medicine at Mount Sinai

New Developments in HPV Oropharyngeal Cancer: Immunology, Epidemiology and Clinical Management CME course will be held at Mount Sinai on May 7.

The International Head and Neck Cancer Epidemiology (INHANCE) consortium will hold its next international meeting at Mount Sinai on May 8, 2013.

For more details about either event, contact Mariko Stronach at **mariko.stronach@mssm.edu**

Targeting Inflammation To Treat Head and Neck Cancers *(continued from page 1)*

These MDSC are drawn to the tumor, where they shutdown anti-tumor T-cell responses and alter the tumor microenvironment in ways that promote cancer growth, progression, and metastasis.

In a recently published paper, Dr. Sikora and lab members Padmini Jayaraman, PhD, and Falguni Parikh, MS, described a critical role for the iNOS molecule in directing the induction of immunosuppressive MDSC, and showed in a mouse model of melanoma, showed that targeting iNOS with a well-tolerated, orally available drug blocked MDSC accumulation and activation in tumor-bearing mice. This boosted T-cell numbers and restored anti-tumor immunity, leading to immune-mediated suppression of tumor growth. These exciting results demonstrate that blocking tumor-associated inflammation alone can be enough to unmask tumor-destroying immune responses, and provide a foundation for further development of this novel approach to tumor therapy.

Targeting Inflammation

Understanding how inflammation fuels cancer growth

The very same inflammatory molecules responsible for shutting down host immunity can also act to stimulate tumor growth and treatment resistance. But how does this happen? Understanding the link between inflammation and cancer progression can lead to new therapeutic approaches that specifically target inflammatory molecules driving cancer growth and survival pathways. In a recent oral presentation at the eighth International Conference on Head and Neck Cancer, Dr. Sikora and postdoctoral fellow Esther Lopez-Rivera, PhD, described one mechanism by which iNOS expression drives unrestrained growth of malignant melanoma. The biological function of iNOS is to produce nitric oxide (NO), which at appropriate times and in appropriate quantities plays an important role in vital physiological processes such as neurotransmission and regulation of blood pressure. However, they found that when iNOS is over-expressed at high levels by melanoma cells, high NO levels can biochemically modify TSC2, a specific molecule in the mTOR signalling pathway which is an important driver of cancer growth and metastasis. This process, known as nitrosilation, results in inappropriate "full-time" activation of the mTOR pathway, and runaway melanoma growth.

Dr. Lopez-Rivera showed that mTOR activation could be reversed, and melanoma proliferation significantly slowed by blocking iNOS expression with inhibitory RNA molecules, or blocking its function with an iNOS-inhibiting drug. Since the mTOR pathway has been shown to play an important role in both melanoma and head and neck squamous cell carcinoma, iNOS inhibition is potentially an effective therapeutic strategy for both of these cancers. In fact, ongoing work in the lab is focused on determining the role of iNOS and other inflammatory molecules in promoting metastasis of head and neck squamous cell carcinoma, and developing targeted therapy approaches capable of blocking growth of metastatic cells.

Moving from mouse to man

Mounting evidence from Dr. Sikora's laboratory and others shows that pharmacologic inhibition of iNOS and other inflammatory molecules is a promising therapeutic strategy in pre-clinical cancer models. Thus, there is great enthusiasm for testing this approach in clinical trials for head and neck cancer. iNOS-inhibiting drugs have been tested in clinical trials for a number of benign inflammatory conditions, but never in cancer patients. The Head and Neck Cancer research program is ideally suited to carry out these trials, and efforts are underway to secure the necessary financial support and pharmaceutical industry partnership to make this pioneering work possible.

About the Investigator

Dr. Sikora is an Assistant Professor and Director of Translational Research in the Department of Otolaryngology at the Icahn School of Medicine at Mount Sinai.

A true surgeon-scientist, Dr. Sikora completed a postdoctoral research fellowship in Cancer Immunotherapy and clinical fellowship in Head and Neck Surgical Oncology at the MD Anderson Cancer Center in Texas before joining Mount Sinai's faculty. Dr. Sikora's laboratory group performs National Institutes of Health-funded research in tumor immunology, cancer immunotherapy, and molecular epidemiology of HPV-related head and neck cancer.

Andrew Sikora, MD, PhD

Meet Our New Members!

We believe success is built by people you surround yourself with. That in mind, we welcome a group of proficient individuals from a variety of backgrounds. **Alexis Patsias, MD,** Clinical Research Coordinator, recently graduated from medical school in Peru, and will be supporting clinical trials in head and neck cancer and other areas of Otolaryngology. **Mariko Stronach,** formerly based in the Geriatrics Department at the Icahn School of Medicine at Mount Sinai, is our new Head and Neck Cancer Research Program Coordinator. Mariko will be coordinating outreach and fundraising efforts, as well as supporting research grant submissions. **Indu Varier, MD,** Clinical Research Coordinator, will be developing and implementing an improved head and neck cancer clinical database.

Selected Accomplishments

Research Articles

Dormancy Signatures and Metastasis in Estrogen Receptor Positive Breast Cancer

Ryung S. Kim, Alvaro Avivar Valderas, Yeriel Estrada, Paloma Bragado, Maria Soledad Sosa, Julio A. Aguirre-Ghiso, and Jeffrey E. Segall .. PLoS One (2012);7(4):e35569. Epub 2012 Apr 18.

Tumor-Expressed Inducible Nitric Oxide Synthase Controls Induction of Functional Myeloid-Derived Suppressor Cells Through Modulation of Vascular Endothelial Growth Factor Release

P. Jayaraman, F. Parikh, E. Lopez-Rivera, D. Cannan, Y. Hailemichael, W. Overwijk, S.H. Chen, A. Sikora. Journal of Immunology 2012; 188:5365-5376.

Analysis of Marker-Defined HNSCC Subpopulations Reveals a Dynamic Regulation of Tumor Initiating Properties

Paloma Bragado, Yeriel Estrada, Maria Soledad Sosa, Alvaro Avivar- Valderas, David Cannan, Eric Genden, Marita Teng, Aparna C. Ranganathan, Huei- Chi Wen, Avnish Kapoor, Emily Bernstein and Julio A. Aguirre-Ghiso. PLoS One. (2012);7(1):e29974. PMCID: PMC3262798.

Sensitization to the Mitochondrial Pathway of Apoptosis Augments Melanoma Tumor Cell Responses to Chemotherapeutic Regimens

R. Anvekar, J. Asciolla, E. Rivera, K. Floros, R. Elkholi, G. Morven-Belbin, A. Sikora*, J. Chipuk*. Cell Death and Disease; 3:e420. doi: 10.1038/cddis.2012.161. *Co-corresponding authors.

Discrimination of Benign and Neoplastic Mucosa with a High-Resolution Microendoscope (HRME) in Head and Neck Cancer

P. Vila, C. Park, L. Levy, G. Goldstein, M. Teng, M. Rivera, E. Genden, R. Richards-Kortum, V. Gurudutt, A. Sikora. Annals of Surgical Oncology 2012; 19(11):3534-9.

Phase II Trial of Concurrent Sunitinib and Image-Guided Radiotherapy for Oligometastases

Tong CC, Ko EC, Sung MW, Cesaretti JA, Stock RG, Packer SH, Forsythe K, Genden EM, Schwartz M, Lau KH, Galsky M, Ozao-Choy J, Chen SH, Kao J. PLoS One. 2012;7(6):e36979. Epub 2012 Jun 27

Transoral Robotic Surgery: Role in the Management of Upper Aerodigestive Tract Tumors

Genden EM, O'Malley BW Jr, Weinstein GS, Stucken CL, Selber JC, Rinaldo A, Hockstein NG, Ozer E, Mallet Y, Satava RM, Moore EJ, Silver CE, Ferlito A. Head Neck. 2012 Jun;34(6):886- 93

Prophylactic Swallowing Exercises in Patients with Head and Neck Cancer Undergoing Chemoradiation: A Randomized Trial

Kotz T, Federman AD, Kao J, Milman L, Packer S, Lopez-Prieto C, Forsythe K, Genden EM. Arch Otolaryngol Head Neck Surg. 2012 Apr;138(4):376-82

Analysis of Marker-Defined HNSCC Subpopulations Reveals a Dynamic Regulation of Tumor Initiating Properties

Bragado P, Estrada Y, Sosa MS, Avivar-Valderas A, Cannan D, Genden E, Teng M, Ranganathan AC, Wen HC, Kapoor A, Bernstein E, Aguirre-Ghiso JA. PLoS One. 2012;7(1):e29974. Epub 2012 Jan 20

The Role of Free Tissue Transfer in Merkel Cell Carcinoma of the Head and Neck. J Skin Cancer

Londino AV, Miles BA. 2012:742303

Treatment of Oropharyngeal Squamous Cell Carcinoma with IMRT: Patterns-of-Failure After Concurrent Chemoradiotherapy and Sequential Therapy

Sher DJ, Thotakura V, Balboni TA, Norris CMN, Haddad RI, Posner MR, Lorch J, Goguen LA, Annino DJ, Tishler RB. Annals of Oncology, 2012, 23:2391- 2398

Prognostic Significance of p16 in Locoregionally Advanced Head and Neck Cancer Treated with Concurrent 5- Fluorouracil, Hydroxyurea, Cetuximab and Intensity-Modulated Radiation Therapy

Tong CC, Lau KH, Rivera M, Cannan D, Julio A. Aguirre-Ghiso, Sikora AG, Gupta V, Forsythe K, Ko EC, Misiukiewicz K, Gurudutt V, Teng MS, Packer SH, Genden EM, Kao J. Oncol Rep. (2012) May;27(5):1580-6. doi: 10.3892/or.2012.1679

p38a Mediates Cell Survival in Response to Oxidative Stress Via Induction of Antioxidant Genes: Effect on p70S6K Pathway

Álvaro Gutiérrez-Uzquiza, María Arechederra, Paloma Bragado, Julio A. Aguirre-Ghiso, Almudena Porras. J Biol Chem. (2012) Jan 20;287(4):2632- 42. Epub 2011 Dec 2

The Role of Free Tissue Transfer in Merkel Cell Carcinoma of the Head and Neck

Londino AV, Miles BA. J Skin Cancer. 2012:742303

High Resolution Optical Imaging of Benign and Malignant Mucosa in the Upper Aerodigestive Tract: An Atlas for Image-Guided Surgery

L. Levy, P. Vila, C. Park, R. Schwarz, A. Polydorides, M. Teng, V. Gurudutt, E. Genden, B. Miles, S. Anandasabapathy, A. Gillenwater, R. Richards-Kortum, A. Sikora. Minimally Invasive Surgery 2012 (in press).

Books and Book Chapters

Reconstruction of the Head and Neck: A Defect Oriented Approach

Genden EM, ed. Thieme Medical Publishers, New York, NY, First Edition; First Edition, 2012

Regulation of Tumor Cell Dormancy by Tissue Microenvironments and Autophagy

Maria Soledad Sosa, Paloma Bragado, Jayanta Debnath and Julio A. Aguirre-Ghiso. Systems Biology of Tumor Dormancy. Editors, Enderling H, Almog N and Hlatky L. (2012) Springer Science + Business Media, INC. (In Press)

Grants

"Development of Monoclonal Antibodies Targeting HPV-Infected Cancer Cells"

(PI Andrew Sikora) MSSM Center for Therapeutic Antibody Development/ Institute for Translational Sciences Developmental Grant.

"Exploring the Association Between Immune-Related Genetic Variation and Head and Neck Cancer"

1 F30 CA165615-01 NCI Mentored Training Grant for MD/PhD Students (Student PI – Chaya Levovitz; Faculty Sponsors Paolo Boffetta and Andrew Sikora).

"Regulation of Disseminated Tumor Cell Fate by RARb and NR2F1 Signaling."

(Co-PI: Aguirre-Ghiso, Bernstein, Farias) BC112380. DoD Breast Cancer Postdoctoral Fellowship Award.

"Regulation by p38 and NR2F1 Signaling of Early Dissemination and Dormancy of Breast Cancer Cells."

(PI: Maria Soledad Sosa, Mentor: Aguirre-Ghiso, J.A.). German Research Council.

"Target Organ Specific Influences of Macrophages on Dormancy of Disseminated Tumor Cells"

(Awardees – Trainee: Nina Linde, PhD. Mentor: Julio Aguirre-Ghiso).

Other Peer-Reviewed Articles

Patient-Centered Approach to Counseling Head and Neck Cancer Patients Undergoing HPV Testing: A Clinician's Guide

A. Chu, M. Posner, E. Genden, A. Sikora. *The Oncologist* 2013; 18(2): 180-189

A Local View of Cancer

Cagan RL, Julio A. Aguirre-Ghiso. Dev Cell. (2012) Mar 13;22(3):472-4.

Oropharyngeal Cancer Biology and Treatment: Insights from Messenger RNA Sequence Analysis and Transoral Robotic Surgery

Genden EM, Julio A. Aguirre-Ghiso. Mayo Clin Proc. (2012) Mar;87(3):211-2.

The Role for Surgical Management of HPV-Related Oropharyngeal Carcinoma

Genden EM. Head Neck Pathol. 2012 Jul;6 Suppl 1:S98-103.

A Systematic Review of Head and Neck Cancer Quality of Life Assessment Instruments

Ojo B, Genden EM, Teng MS, Milbury K, Misiukiewicz KJ, Badr H. Oral Oncol. 2012 Oct;48(10):923-37.

Robotic Surgery for Oropharynx Cancer: Promise, Challenges, and Future Directions

de Almeida JR, Genden EM. Curr Oncol Rep. 2012 Apr;14(2):148-57.

Time to Change the Treatment Paradigms in Anaplastic Thyroid Carcinoma

Misiukiewicz K, Posner MR. Oncology, 2012,26: 408-410.Posner M. Clinical trials in squamous cell carcinoma of the head and neck. Clin Adv Hematol Oncol. 2012;10:388-90.

Recognizing and Reversing the Immunosuppressive Tumor Microenvironment of Head and Neck Cancer

CL Tong, J. Kao, A. Sikora Immunologic Research 2012; 54(1-3):266- 74.

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