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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Research Focus

Targeting Inflammation To Treat Head and Neck Cancers

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, 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 2005, 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

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
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.

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

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

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

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

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

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

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

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

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

The Role of Free Tissue Transfer in Merkel Cell Carcinoma of the Head and Neck. J Skin Cancer
Londino Av, Miles BA. 2012;724303

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

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

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

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

Books and Book Chapters

Reconstruction of the Head and Neck: A Defect Oriented Approach

Regulation of Tumor Cell Dormancy by Tissue Microenvironment and Autophagy

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”
1F30 CA185615-01 NCI Mentored Training Grant for MD/PhD Students (Student PI – Chaya Leovitz, Faculty Sponsor Paolo Boffetta and Andrew Sikora).

“Regulation of Disseminated Tumor Cell Fate by RARβ and NR2F1 Signaling.”
(Co-PI Aguirre-Ghiso, Bernstein, Farias) BC112880. 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”

Other Peer-Reviewed Articles


A Local View of Cancer

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

The Role for Surgical Management of HPV-Related Oropharyngeal Carcinoma

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

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

Time to Change the Treatment Paradigms in Anaplastic Thyroid Carcinoma

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

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