Etiology and Pathogenesis of Oral Cancer (EPOC)

Pre-ARC Co-directors:

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Drs. Maria Kukuruzinska, Avrum Spira and Maria Trojanowska lead a pre-ARC focused on the etiology and pathogenesis of oral cancer (EPOC). This pre-ARC is a multidisciplinary collaboration involving a subset of Oral Cancer Research Initiative (OCRI) researchers. As such, EPOC meets the major goal of the ARC program of "…focusing on a research theme, explored with the aid of different disciplines and technologies to advance Research and Discovery as it applies to disease states…" The group, which includes basic scientists, clinical oncologists and surgeons, public health researchers, computational biologists and bioengineers, meets at noon on the first Monday of the month in the Molecular and Cell Biology Conference Room on Evans 4.

Oral cancer, a subtype of head and neck cancer, involves neoplasms of the oral cavity, most commonly the tongue, with close to 90% typed as squamous cell carcinoma. Oral squamous cell carcinoma (OSCC) accounts for ~2-3 % of all cancers and its hallmark is high morbidity and resistance to therapy, leading to one of the highest death rates compared to other cancers. The EPOC pre-ARC aims to decipher the molecular mechanisms underlying the origins of OSCC, identify the key metabolic and signaling networks that drive its progression and resistance to therapy, as well as factors responsible for disease morbidity. In addition, research focuses on the identification and validation of OSCC stage-specific biomarkers including malignancies of the upper aerodigestive tract. The long term goal is to expedite translation of research findings toward the design of predictive strategies for OSCC and its recurrence and to improve detection and treatment of head, neck and oral cavity cancers. Five projects are underway:

Project 1. Protein N-glycosylation, Wnt and TAZ Signaling and E-cadherin Adhesion in the Etiology and Pathogenesis of OSCC (*Kukuruzinska and Varelas*)
Emerging studies highlight pivotal roles for Wnt/β-catenin and the Hippo effector, TAZ, signaling, the loss of E-cadherin adhesion and the acquisition of mesenchymal properties in tumor development. We have documented that increased post-translational modification of

proteins with complex N-glycans promotes OSCC development. Our recent work has documented that the DPAGT1 gene, which encodes the rate limiting N-glycosylation enzyme, GPT, is aberrantly induced in OSCC. DPAGT1 acts as a key driver of Wnt/β-catenin and TAZ signaling feedback loops, and directly links the N-glycosylation pathway to OSCC signaling networks. Furthermore, DPAGT1 represses cell adhesion, promoting the transition between epithelial and mesenchymal states. The project aims to determine the mechanisms underlying altered interactions between DPAGT1, Wnt /β-catenin signaling and E-cadherin that drive cellular discohesion and cell migration in OSCC via activation of downstream signaling pathways. Additional high-throughput genomic approaches are utilized to study changes in global expression profiles as well as changes in N-glycome with OSCC tumor development and progression. Further, mathematical modeling is being developed to determine changes in signal amplitudes in response to deregulation of DPAGT1, Wnt/β-catenin, TAZ and E-cadherin and their effects on downstream signaling pathways.

Project 2. ECM Remodeling and Tumor Stroma in OSCC (*Trackman and Trojanowska*)
OSCC progression is accompanied by the remodeling of the extracellular matrix and stroma to develop a specialized tumor microarchitecture that provides microenvironment supportive for tumor maintenance and expansion. Stromal features have been shown to be predictive of disease mortality in oral cancer. This project aims to characterize myofibroblasts in OSCC and to define the molecular pathways involved in activation of stromal fibroblasts. Another focus of the project is on the role of cross-linking enzymes, lysyl oxidase (LOX) and lysyl oxidase-like protein 2 (LOXL2), known to be involved in the maturation of ECM components in OSCC pathogenesis. LOXL2 is upregulated in OSCC and it is detected at high levels at the basal epithelium of tissues with advanced cancer, suggesting that it may play a role in supporting cancer initiating cells within a niche, and that inhibition of LOXL2 enzyme activity could inhibit EMT. A cleavage product of LOX is LOX-PP which has tumor suppressive properties and has potential as an anti-proliferation/growth chemotherapeutic. Thus, another part of this project investigates the tumor suppressive role of rLOX-PP as a potential therapeutic for OSCC.

Project 3. Molecular Linkages Among Environmental Carcinogens, AhR and Oral Microbiome in OSCC (*Sherr and Genco*).
It is estimated that 60-80% of all cancers are caused by environmental carcinogens. This project focuses on environmental toxin-induced activation of AhR in oral cancer and its potential to drive oral cancer initiation and/or progression by promoting and/or collaborating with, the core signaling and metabolic pathways, studied in Projects 1 and 2, including DPAGT1/N-glycosylation, Wnt/β-catenin and Hippo effectors, TAZ and YAP, signaling. AhR is dramatically upregulated in OSCC. Constitutive AhR activity may be driven by tryptophan metabolites, particularly indoxyl sulfate, which requires the microbiome to produce indole, the indoxyl sulfate precursor. A related aspect of the project focuses on determining how oral microbiome functions in promoting OSCC progression via AhR. The goal is to establish an association between specific oral (saliva) microbiome profiles in oral cancer patients and controls using Illumina sequencing and RNA-seq of bacterial DNA and RNA. In addition, contribution of oral microbiome to molecular pathways driving OSCC via N-glycosylation, Wnt, TAZ/YAP and AhR will be determined. Tryptophan metabolism is highly active in cancer cells and the metabolites drive invasion, and bacteroidetes and other Gram-negative bacteria (i.e.,

Porphyromonas gingivalis) are examples of oral bacteria that use tryptophanase to break down tryptophan into indole.

Project 4. Molecular Mechanisms of Dysphagia in Response to Radiation Therapy (*Trojanowska and Langmore*)

Dysphagia is a morbid condition that interferes with swallowing and proper nutrition, and which develops in about 50% of head and neck cancer patients treated with radiation therapy. A key culprit of dysphagia is fibrosis, which stiffens the connective tissue. To date, little is known about the mechanisms leading to fibrosis in response to radiation, and no tools are available to predict which patients develop fibrosis. This project represents a prospective study in which biopsy specimens from patients pre-radiation and post-radiation are collected to identify genes that correlate with dysphagia, and to identify biomarkers informing of pro-fibrotic changes. The long term goal is to develop diagnostic tools to predict likelihood of fibrosis in patients undergoing radiation therapy.

Project 5. Biomarkers as Predictors of Oral Cancer Field of Cancerization and Tissue Injury (***Spira and Platt***)

The goals of the project are to use a high-throughput approach to define airway genomics in HNSCC, to increase understanding of the "Field of Injury" and to develop airway diagnostic biomarker(s) specific to the HNSCC. Current experimental strategy involves identification of a gene expression signature in cytological normal buccal, nasal and bronchial epithelium that can distinguish smokers with HNSCC from matched smokers without HNSCC. Airway gene expression in subtypes of HNSCC is compared to determine how the expression signature and the "field of injury" changes in patients with HNSCC by tumor location and HPV status and to define the relationship between the "field of injury" and HNSCC mutations in the primary tumor. Bioinformatic analysis of pathways which are found to be dysregulated in the primary tumor are compared with airway gene expression to determine if early events can be detected in airway epithelia. The hypothesis is that the airway epithelial gene expression signature of patients with HNSCC will demonstrate significant overlap with those signatures for lung cancer.

APPENDIX I

Current Members

Name / Title	***Department***	**School**	**Role in Pre-ARC**	**Email**
Maria Kukuruzinska, PhD Professor/Associate Dean for Research	*Molecular and Cell Biology*	Dental Medicine	Co-director	mkukuruz@bu.edu
Avrum Spira, MD Professor/Division Chief	*Computational Biomedicine*	Medicine	Co-director	aspira@bu.edu
Maria Trojanowska, PhD Professor	*Rheumatology*	Medicine	Co-director	trojanme@bu.edu
Radhika Chigurupati, DMD, MS Associate Professor	*Oral & Maxillofacial Surgery*	Dental Medicine	Investigator	rchiguru@bu.edu
Catherine Costello, PhD Professor	*Biochemistry*	Medicine	Investigator	cecmsms@bu.edu
Caroline Genco, PhD Professor	*Infectious Disease*	Medicine	Investigator	cgenco@bu.edu
Tony Godfrey, PhD Associate Professor	*Surgery*	Medicine	Investigator	godfreyt@bu.edu
Susan Langmore, PhD Professor	*Otolaryngology*	Medicine	Investigator	langmore@bu.edu
Virginia Litle, MD, FACS Associate Professor	*Surgery*	Medicine	Investigator	Virginia.Litle@bmc.org
Stefano Monti, PhD Associate Professor	*Computational Biomedicine*	Medicine	Investigator	smonti@bu.edu
Michael Platt, MD, MSc Assistant Professor	*Otolaryngology*	Medicine	Investigator	miplatt@bu.edu
David Sherr, PhD Professor	*Environmental Health*	Public Health	Investigator	dsherr@bu.edu
Philip Trackman, PhD Professor	*Molecular and Cell Biology*	Dental Medicine	Investigator	trackman@bu.edu
Xaralabos Varelas, PhD Assistant Professor	*Biochemistry*	Medicine	Investigator	xvarelas@bu.edu
Muhammad Zaman, PhD Associate Professor	*Biomedical Engineering*	Engineering	Investigator	zaman@bu.edu

APPENDIX II

EPOC Members Research Interests (in alphabetical order)

Radhika Chigurupati

Dr. Radhika Chigurupati is Associate Professor in Oral and Maxillofacial Surgery. She joined the Boston University Henry M. Goldman School of Dental Medicine in March 2013 after spending 9 years at University of California San Francisco (UCSF) and one and half years at University of Maryland, Baltimore. During that time, she practiced at UCSF Moffitt Medical Center, UCSF Benioff Children's Hospital and University of Maryland Shock Trauma Center.

Dr. Chigurupati specializes in surgical reconstruction of developmental and acquired jaw and facial deformities. Her primary focus in clinical practice is pediatric maxillofacial surgery. Her clinical expertise is surgical management of craniofacial growth disturbances, tooth eruption disturbances and jaw tumors in children. She also provides consultation for adults with sleep disorders/ obstructive sleep apnea (OSA), maxillofacial injuries, and pathology of the jaws and mouth. She works with her colleagues in other medical and dental specialties to provide interdisciplinary care for these patients. She and her surgery associates consult and provide surgical care for patients at Boston Medical Center and Beth Israel Deaconess Medical Center.

Dr. Chigurupati completed her Oral and Maxillofacial Surgery training at University of Washington (UW), Seattle and subsequently a fellowship in Pediatric Maxillofacial Surgery at the Royal Children's Hospital (RCH) in Melbourne, Australia. She has been an active member of the cleft and craniofacial teams at UW, UCSF and RCH. She is board certified in Oral and Maxillofacial Surgery.

Dr. Chigurupati also holds a master's degree in Global Health Science from UCSF (2009). She has contributed to teaching and surgical activities in academic institutions in several developing countries (Peru, Guatemala, India). Her research interests include clinical informatics and telemedicine. Her current research focuses on identifying solutions for early diagnosis of oral cancer in resource-restricted settings.

Catherine Costello

Catherine Costello came to Boston University in 1994. That year she established the Center for Biomedical Mass Spectrometry, which has become an internationally recognized research center. She holds her primary appointment in the MED Biochemistry Department, with secondary appointments in the Department of Physiology & Biophysics and the Department of Chemistry. Her research, which focuses on determining the structures and functions of biologically important polymers, has revolutionized an important area of biochemistry by providing insights into the structures of molecules responsible for human disease. She is the author or co-author of more than 300 scientific papers, serves on a number of editorial boards of major journals, and has received numerous awards and honors, including the 2010 Field and Franklin Award from the American Chemical Society, one of the highest honors in her field.

Caroline Genco

Innate Immune Responses to Mucosal Pathogens

Dr. Genco's lab is examining the interactions of several mucosal pathogens with both phagocytic and non-phagocytic cells. Work with N. gonorrhoeae has established that distinct proinflammatory responses are observed in different compartments of the female lower genital tract (endocervical, ectocervical and vaginal cell lines). Using these cell lines Dr. Genco has demonstrated that infection with N. gonorrhoeae inhibits the apoptotic response of these cells. N. gonorrhoeae may thus establish infection by inhibiting the apoptotic response to infection, thereby resisting killing from both the host cell and the innate immune response. Current studies are focused on defining the role of toll-like receptors and intracellular signaling receptors in N. gonorrhoeae induced proinflammatory responses in epithelial cells. Work with P. gingivalis has demonstrated the invasive capabilities of these organisms for endothelial cells and has defined specific cell signaling pathways involved in this response. Dr. Genco shown that 2 adhesins of this organism, the major and minor fimbriae proteins bind to and signal through TLR2 for an inflammatory response in human aortic endothelial cells. Furthermore both the major and minor fimbriae proteins can signal through TLR4 if the accessory proteins MD2 and CD14 are present. Dr. Genco's recent studies are focused on defining intracellular signaling receptors and pathways utilized by P. gingivalis to induce IL-1ß secretion in endothelial cells.

Regulatory Mechanisms in Bacterial Pathogens

This work is focused on understanding mechanisms utilized for bacterial colonization, and in particular in the ability of in vivo environmental factors to modulate bacterial gene expression. Transcriptional regulatory mechanisms have been defined on a global level in the pathogenic Neisseria species. Dr. Genco has established that the expression of virulence factors in these organisms is controlled by a global regulatory protein (ferric uptake regulator protein, Fur). Dr. Genco has established that the transcriptional regulatory protein Fur controls the expression of numerous genes that are required for the virulence of N. meningitidis and N. gonorrhoeae and have established that many of these genes are expressed in vivo during mucosal gonococcal infection in both men and women. Current studies are aimed at examining the regulation and expression of Fur-regulated genes in vitro, and in vivo directly in clinical specimens. Dr. Genco also recently identified a novel mechanism for Fur-mediated regulation through small regulatory RNAs (sRNA) in both N. meningitidis and N. gonorrhoeae. Dr. Genco has established that in N. meningitidis the sRNA, NrrF functions independently of the cofactor RNA-binding protein, Hfq. Current studies are focused on defining how NrrF functions independently of Hfq and on identifying additional sRNAs using high-density oligonucleotide microarrays together with computational analysis.

Pathogen Induced Chronic Inflammatory Disorders

Chronic inflammation culminates in devastating events, results in significant host pathology, and is associated with a number of human diseases including autoimmune diseases, infectious diseases, neoplastic diseases, and inflammatory atherosclerosis. Dr. Genco's studies focus on two pathogens associated with chronic inflammation, Chlamydia pneumoniae and Porphyromonas gingivalis. C. pneumoniae is a respiratory pathogen that causes a mild, usually asymptomatic pneumonia. P. gingivalis induces a local host inflammatory response that results in inflammatory bone destruction, which is manifested as periodontal disease. Normally, the acute

inflammatory response is self-limited, working to contain these infections until the adaptive immune response is activated. However, under some circumstances, a chronic inflammatory state can ensue, resulting in additional host pathology. Recently, both C. pneumoniae and P. gingivalis have been implicated in the pathogenesis of chronic inflammatory plaque formation although how these pathogens induce and maintain chronic inflammation is not well defined. Dr. Genco's laboratory has defined the role of specific innate immune signaling pathways in immune cells that contribute collectively to pathogen-induced chronic inflammation. Dr. Genco is examining in vitro model systems for platelets, endothelial cells, and macrophages. Using defined animal models of inflammation Dr. Genco's lab is characterizing the roles of innate immune pathways in inflammatory processes in vivo. Enhanced understanding of the roles of specific innate immune signaling pathways, which participate in proinflammatory mediator expression and functional immune responses will provide a promising avenue for novel therapies for chronic inflammatory disorders.

Tony Godfrey

Tony E. Godfrey, PhD, Associate Chair, Surgical Research and Associate Professor of Surgery, Boston University School of Medicine, earned a bachelor's of science degree in biochemistry from Brunel University in England, followed by a doctorate in molecular biology and biochemistry, also from Brunel. He attended the University of California, San Francisco, for postdoctoral fellowships and managed UCSF's Genome Analysis Core Facility.

Most recently, Dr. Godfrey was a Research Associate Professor in the Department of Surgery at the University of Rochester Medical Center in Rochester, NY. Prior to this he was an Associate Professor of Pathology at Mt. Sinai School of Medicine in New York, NY.

Dr. Godfrey's research is focused on cancer genetics and molecular pathology. Research projects use state-of-the-art genetic and genomic approaches to address clinical needs in the areas of cancer diagnosis, prognosis and therapy. Currently the major focus of Dr. Godfrey's research is on Barrett's esophagus and esophageal adenocarcinoma; a tumor with rapidly increasing incidence in the United States and other western countries. The Godfrey lab works closely with translational research teams comprised of surgeons, pathologists and oncologists in order to develop new molecular approaches to cancer detection, staging and treatment.

Maria Kukuruzinska

The long term goal of Dr. Kukuruzinska's work is to elucidate the regulatory mechanisms underlying the interactions between the metabolic pathway of protein N-glycosylation and intercellular adhesion in tissue development and disease.

Cross Talk Between Protein N-glycosylation, E-cadherin-mediated Cell-Cell Adhesion and Canonical Wnt Signaling. Studies in Dr. Kukuruzinska's laboratory have unveiled a critical role for N-glycosylation in the function of E-cadherin, a major epithelial cell-cell adhesion receptor that forms adherens junctions (AJs). These studies have shown that N-glycosylation affects the maturity of AJs and the assembly of tight junctions (TJs), as well as cytoskeletal dynamics. On a molecular level, the N-glycosylation status of E-cadherin is controlled by the DPAGT1 gene, the

first gene in the N-glycosylation pathway and its key regulator. At the same time, E-cadherin junctions regulate DPAGT1 expression, indicating the existence of a bidirectional feedback loop between the metabolic pathway of protein N-glycosylation and cell-cell adhesion. Current studies in Dr. Kukuruzinska's laboratory are aimed at elucidating the molecular mechanism via which AJs regulate N-glycosylation.

Molecular Basis of Oral Cancer. The conceptual framework of Dr. Kukuruzinska's mechanistic studies is being applied to investigation of the development and progression of oral cancer. Dr. Kukuruzinska's recent work has shown that aberrant activation of cellular N-glycosylation promotes the development and progression of oral squamous cell carcinoma (OSCC). Partial inhibition of cellular N-glycosylation in oral cancer cell lines leads to the stabilization of intercellular adhesion, which then drives the mesenchymal to epithelial transition. Current studies examine the molecular basis of over-expression of DPAGT1 in OSCC and its relationship to the downstream signaling pathways that impact E-cadherin's tumor suppressive function.

Molecular Basis of Sjogren's Syndrome. Recently, Dr. Kukuruzinska has initiated studies on Sjogren's Syndrome, an autoimmune disease that affects salivary and lacrimal glands. Although Sjogren's disease has long been thought to be caused by lymphocytic infiltration, Dr. Kukuruzinska's recent work has suggested that defective intercellular adhesion is one of the underlying causes of this disease. To expedite the deciphering of the molecular basis of SS and to promote the development of new diagnostics, Dr. Kukuruzinska co-founded an international collaboration, the Norwegian-United States Initiative on Sjogren's Syndrome (NUSSIS), that brings together basic researchers and clinicians from the University of Oslo, the University at Albany - SUNY, University of Florida and from the Boston University School of Dental Medicine.

<u>Susan Langmore</u>

Clinical Interests

- Swallowing problems associated with head & neck cancer and with neurologic disease, including vocal cord dysfunction
- Speech and voice disorders associated with Parkinsonian problems, ALS, fronto temporal dementia
- FEES: developed the procedure; holds workshops to teach the procedure

Research Interests

- Predictors of Swallow function after HNC
- Efficacy of behavioral treatment for swallowing and voice disorders
- Use of electrical stimulation for swallowing problems
- Predictors of aspiration pneumonia
- Prevention of aspiration pneumonia

Virginia Litle

- Management of benign and malignant esophageal diseases including Barrett's esophagus, achalasia and esophageal cancer
- Minimally invasive esophageal surgery and endoscopic procedures including minimally invasive esophagectomy, endoscopic resection and Barrx ablation of Barrett's esophagus
- VATS lobectomy for lung cancer, airway and esophageal stenting and laser treatment for palliation of lung and esophagus cancer

Stefano Monti

Dr. Monti's research centers on the development and application of computational approaches for the dissection and characterization of the molecular machinery of human malignancies and their response to environmental insults. This multidisciplinary effort relies on the generation, analysis, and integration of high-throughput genomic data, and it is aimed at the identification of novel therapeutic targets and the development of diagnostic and prognostic markers.

Dr. Monti's lab is involved in several projects, with collaborators in the School of Medicine, the School of Public Health, Harvard Medical School, and the Broad Institute. These projects include:

- Development of gene expression-based clinical classifiers for prognosis and clinical trial patient stratification.
- Molecular characterization of lymphoma malignancies: genome, transcriptome, epi-genome, and their cross-talk.
- Molecular characterization of the transcriptional program in lung cancer based on high-throughput RNA-sequencing.
- Computational genomic models of environmental and chemical carcinogenesis.

Michael Platt

Michael Platt is an Assistant Professor in the Department of Otolaryngology-Head and Neck Surgery at Boston University. His primary research interests include the study of airway gene expression in the spectrum of diseases that affect the head and neck, including chronic sinusitis, allergic rhinitis, polyp forming inflammatory diseases, and malignancies of the upper aerodigestive tract. Dr. Platt uses computational methods to profile airway epithelium and define normal and abnormal states. Understanding changes in gene expression allow for identification of biomarkers that can be targets for diagnostic and therapeutic modalities. Application of these methods to patients with head and neck cancer is important for understanding the "field of injury" response that is used for early detection of airway malignancies.

David Sherr

Since 1993, David Sherr's laboratory has conducted research on how common environmental pollutants, such as dioxins, polycyclic aromatic hydrocarbons and PCBs, adversely affect the growth and behavior of several different types of normal and malignant cells. In previous work, the Sherr laboratory studied how environmental chemicals affect the development of the immune

system. In specific, his laboratory demonstrated that aromatic hydrocarbons (generated by the combuston of any carbon source) compromise the function of bone marrow cells required for the development of antibody-forming cells. These cells are critical for immune protection against viruses and bacteria. This work had its orignis in Dr. Sherr's graduate studies on the ontogeny of lymphocyte development.

More recently, Dr. Sherr's laboratory has focused on the molecular mechanisms that initiate and maintain breast cancer and on the effects of environmental chemicals on these processes. The laboratory has shown that a cellular protein receptor, referred to as the aryl hydrocarbon receptor (AhR), plays an important role in the initiation and progression of human breast cancer. The results explain, in part, the association between environmental chemical exposure and breast cancer risk. Perhaps most importantly, these studies demonstrate that the AhR drives human breast cancer cells to invade and, presumably, metastasize even in the absence of environmental chemicals. These observations have led to the development of AhR inhibitors which block AhR activity and prevent tumor cells from invading. One immediate goal of the laboratory, therefore, is the development of potent AhR inhibitors as novel, targeted therapeutics to be used for treatment of all breast cancers but especially for treatment of "triple negative" or chemotherapy-resistant breast cancers. Interestingly, preliminary studies suggest that these AhR inhibitors could be useful for treatment of several other cancer cell types.

A new area of study in Dr. Sherr's laboratory is the analysis of the role of the AhR in blood cell development. These studies are important from both an environmental science and medical science point of view. Studies performed to date suggest that the AhR plays an important role in the normal development of blood cells. The results suggest the intriguing possibility that common environmental pollutants can alter normal blood cell development by interfering with AhR signaling.

Dr. Sherr came to BUSPH from the faculty of Harvard Medical School, where he had earlier been a postdoctoral fellow in the department of Nobel Laureate Baruj Benacerraf. The Sherr Laboratory is funded by research grants from the National Institute of Environmental Health Sciences, the NIH Superfund Basic Research Program, and the Art BeCAUSE breast cancer foundation. Dr. Sherr is the Director of the Boston University Immunology Training Program, and a member of the Amyloid Treatment Research Program, the BU Cancer Center, the Hematology/Oncology Training Program, and the BU Hormone-dependent Cancer Center. He has trained 21 postdoctoral (M.D. or Ph.D.) and 11 predoctoral (M.D. and/or Ph.D.) fellows.

Avrum Spira

Dr. Spira is a Professor in the Departments of Medicine, and Pathology and Bioinformatics and is founding Chief of the Division of Computational Biomedicine in the Department of Medicine at BUSM. He attends in the Medical Intensive Care Unit at Boston Medical Center and directs the Translational Bioinformatics Program in the Clinical and Translational Science Institute at Boston University.

Dr. Spira’s laboratory research interests focus on applying genomic and bioinformatics tools to the translational study of lung cancer and Chronic Obstructive Lung Disease (COPD), with the

ultimate objective of developing novel diagnostics and therapeutics that can directly impact clinical care. He is funded as a Principal Investigator through three institutes at the NIH including the NCI, NHLBI, and NIEHS as well as the Department of Defense. His research program centers around the concept that inhaled toxins create a “field of injury” in all exposed airway epithelial cells, and that by measuring gene expression in a relatively pure population of these cells, one can develop a gene-expression profile that reflects the physiological response to and damage from the toxin. The importance of the “field-of-injury” concept is that it allows for the detection of lung disease in tissues that are more readily assayed than the diseased lung itself.

His lab has characterized the impact of cigarette smoking on intra-thoracic (lobar bronchi) and extra-thoracic (mouth and nasal) airway epithelial cell gene expression, and he has leveraged this approach to develop a bronchial airway gene-expression biomarker for the early detection of lung cancer that is currently being validated in a multicenter clinical trial. His lab has also extended this “field of injury” paradigm to the premalignant and lung cancer screening settings, potentially allowing personalized genomic approaches to lung cancer chemoprophylaxis and therapy. This disease-specific airway “field of injury” concept is also being applied to Chronic Obstructive Lung Disease (COPD), to better understand the molecular diversity of COPD, both for developing subtype-targeted therapies and for developing biomarkers that would allow identification of biologically distinct forms of COPD. Most significantly, his lab has identified airway gene-expression biomarkers that can be used to monitor disease activity and response to therapy in COPD, and they have connected gene expression signatures of disease in clinical samples to in vitro small molecule perturbations to move from bedside to bench and identify new uses for existing drugs as potential COPD therapeutics. Finally, we are exploring gene-expression profiles in nasal and buccal epithelium as biomarkers of the physiological response to inhaled toxins and their potential role as lung disease biomarkers in large-scale population studies.

Philip Trackman

Research in Dr. Trackman’s laboratory is focused on the regulation of extracellular matrix accumulation in mineralized and non-mineralized normal tissues, and in pathologies in which extracellular matrix accumulation is affected. Studies, which utilize cell culture, animal models, and human tissues, encompass a wide range of experimental approaches derived from the disciplines of biochemistry, enzymology, cell biology, and quantitative biology. Goals of these studies are to obtain a greater understanding of the molecular and cellular basis for gingival overgrowth and other fibrotic diseases, and to understand mechanisms of osteopenia that occurs as a complication of type I diabetes. Recent important findings show that oral fibroblasts are resistant to the effects of certain inflammatory factors, and that this resistance contributes to the elevated expression of connective tissue growth factor (CCN2/CTGF). This growth factor, in turn, contributes to gingival overgrowth and oral fibrosis. In addition, the biological process of epithelial to mesenchymal transition has been identified as a contributor to gingival overgrowth. These understandings provide new avenues for therapeutic approaches to prevent and treat gingival overgrowth.

The mechanism by which lysyl oxidase acts as a tumor suppressor is under investigation. Dr. Trackman’s laboratory has made the novel discovery that the tumor suppressor function of lysyl

oxidase resides in the propeptide (LOX-PP) region of a proenzyme precursor. This propeptide is released from the proenzyme by extracellular proteolytic processing, and the released propeptide inhibits growth of tumor cells and tumor formation. A focus of the laboratory is to identify mechanisms by which the lysyl oxidase propeptide can suppress tumor formation or tumor growth and tumor metastasis. A major target of LOX-PP was found to be the fibroblast growth factor receptor-1 (FGFR1). Intracellular targets are now under investigation. A polymorphism in LOX-PP was found to have impaired ability to suppress tumors in mice, and is a risk factor for breast cancer in estrogen receptor-negative breast tumors in humans. rLOX-PP is effective as an inhibitor of tumor growth in xenograft models. Dr. Trackman's laboratory works on this project in collaboration with the laboratories of Dr. Gail Sonenshein (Tufts University School of Medicine) and Dr. Kathrin Kirsch of Boston University School of Medicine, Department of Biochemistry. The potential use of LOX-PP as a pharmacologic agent has been submitted and is pending in the U.S. patent office; and preclinical studies continue.

Maria Trojanowska

Dr. Trojanowska's research is aimed at understanding the molecular and cellular mechanisms that regulate ECM synthesis in healthy tissues and in pathological conditions such as fibrosis and tumorigenesis. The majority of her studies focus on the pathogenesis of scleroderma, an autoimmune disease characterized by vascular abnormalities and a prominent fibrosis of the skin. Her laboratory uses molecular and cellular approaches and various experimental models to elucidate the mechanisms responsible for uncontrolled ECM deposition and vessel degeneration in scleroderma. The second area of investigation is related to activation of tumor stroma. These studies examine the molecular mechanisms that mediate controlled regulation of ECM turnover in healthy connective tissue and are responsible for dysregulation of this process during tumorigenesis. Recent studies together with Dr. Lafyatis are examining the role of ER stress in systemic sclerosis.

Xaralabos Varelas

The research objective of Dr. Varelas' lab is to understand the molecular mechanisms by which cells coordinate growth with cell fate during animal development and the onset of disease. His lab is particularly interested in the role of the Hippo tumor suppressor pathway in controlling these processes. The Hippo pathway has emerged as a major regulator of tissue growth and organ size, and has a crucial role in directing signals that are transmitted by secreted growth factors, such those initiated by TGFß and Wnt. Deregulation of the Hippo pathway is linked to many diseases, including several forms of cancer. Dr. Varelas is incorporating both directed and systems-based approaches to understand the roles and regulation of the Hippo pathway, with an emphasis on defining deregulated events that impact on tumor initiation and progression.

Muhammad Zaman

Research in Dr. Zaman's lab is focused at the interface of cell biology, mechanics, systems biology and medicine. Dr. Zaman is interested in understanding and decoupling the integrated chemical, biological and mechanical basis of tumor invasion that precedes metastasis. Dr. Zaman utilizes computational and experimental tools rooted in cell biology, chemistry, mechanics and

imaging to ask how cells process external information and use it to develop specific responses in native like 3D environments. Dr. Zaman's work is also aimed at developing multi-scale models, integrating both first principle and data driven approaches to quantify cell signaling, adhesion and motion in 3D environments.

The second main thrust of Dr. Zaman's research is focused on developing computational and experimental tools to improve the quality of life, education and the practice of medicine in the developing world. In this regard, Dr. Zaman is working closely with the Center for Global Health and various medical schools and engineering institutions around the globe to develop cheap, robust and easy to use solutions to develop improved diagnostics and tools for data analysis.