Building Momentum

Two Years of Discovery at the Giovanis Institute for Translational Cell Biology

December 2025

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MEDICINE

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A Message from the Director

Dear Ted,

It is a pleasure to share this report on progress made during the formative years of the Giovanis Institute for Translational Cell Biology.

Our shared vision for what the Institute could be became a roadmap that helped us define ambitious goals: to uncover the mechanisms of cancer metastasis, and to develop and advance therapies against metastatic disease. Our mission is attainable thanks to your investments and to the Institute's agile structure and emphasis on collaboration. By centering progress over tradition, we've created an environment where discovery can thrive.

Over the course of the past two years, a major area of focus has been recruitment, welcoming three new faculty and naming a new investigator. This update will continue to familiarize you with their work and their motivations, and I hope you will agree that this team is poised to lead the charge to dismantle metastasis through bold and fundamental science.

As the Giovanis Institute matures, we pivot from the team building phase and forging transdisciplinary partnerships to focus on the work ahead. Our immediate next steps are to begin funding research within and beyond our team, and we look forward to initiating calls for interdisciplinary proposals from across the Johns Hopkins research sphere.

Expanding our understanding of cancer metastasis is a gift that benefits the world. I know how personally significant this work is to you and your family. On behalf of all of us at the Giovanis Institute, please know this work is personal to us as well. As you read on, know that we feel fortunate to be so closely associated with you and your passion for reorienting how cancer research is organized and conducted. Know that we are proud to do this work in your name.

With appreciation,

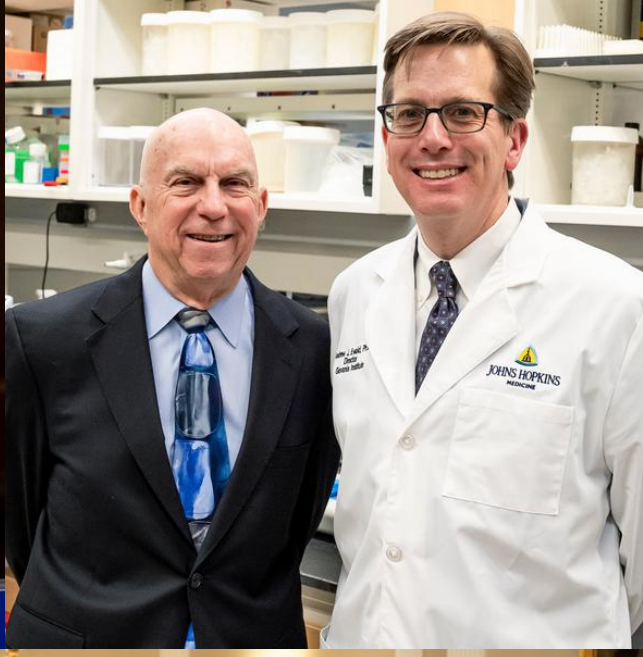
Andrew Ewald, PhD
Director and Professor, Department of Cell Biology Johns Hopkins Medicine
Director, Giovanis Institute for Translational Cell Biology
Virginia De Acetis Professor in Basic Cancer Research
Co-Leader, Cancer Invasion and Metastasis Program

Dedication of the Giovanis Institute for Translational Cell Biology

November 13, 2023

"The future is very, very bright for the basic sciences at Johns Hopkins, and I am so glad that the Giovanis name is associated with that future."

Theodore L. DeWeese, MD
Dean of the Medical Faculty and CEO, Johns Hopkins Medicine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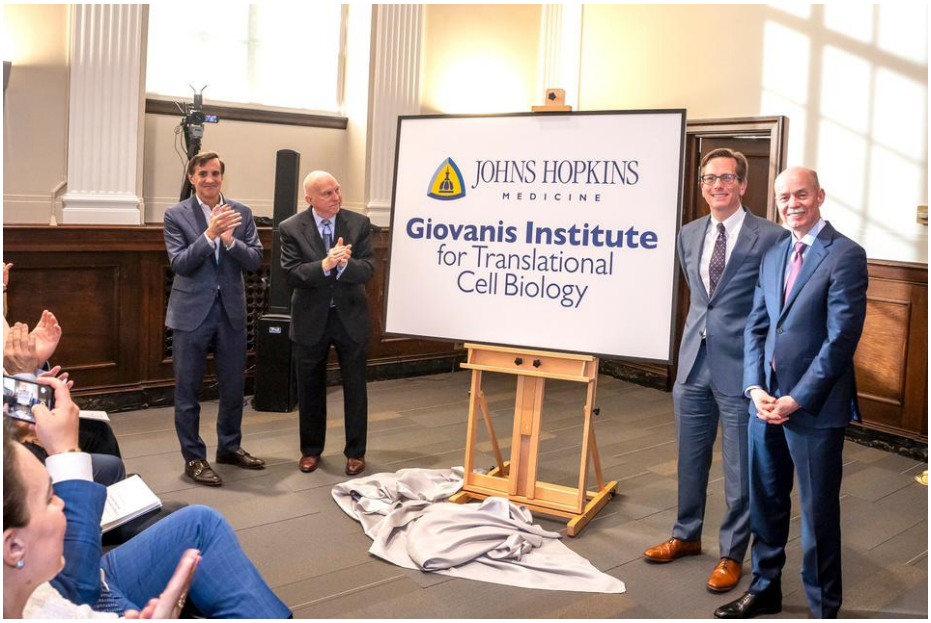
"Ted, by taking this momentous step, you are continuing the finest traditions of partnership on which the School of Medicine has been built from day one."

Andrew J. Ewald, PhD,
Inaugural Director of the Giovanis Institute for Translational Cell Biology

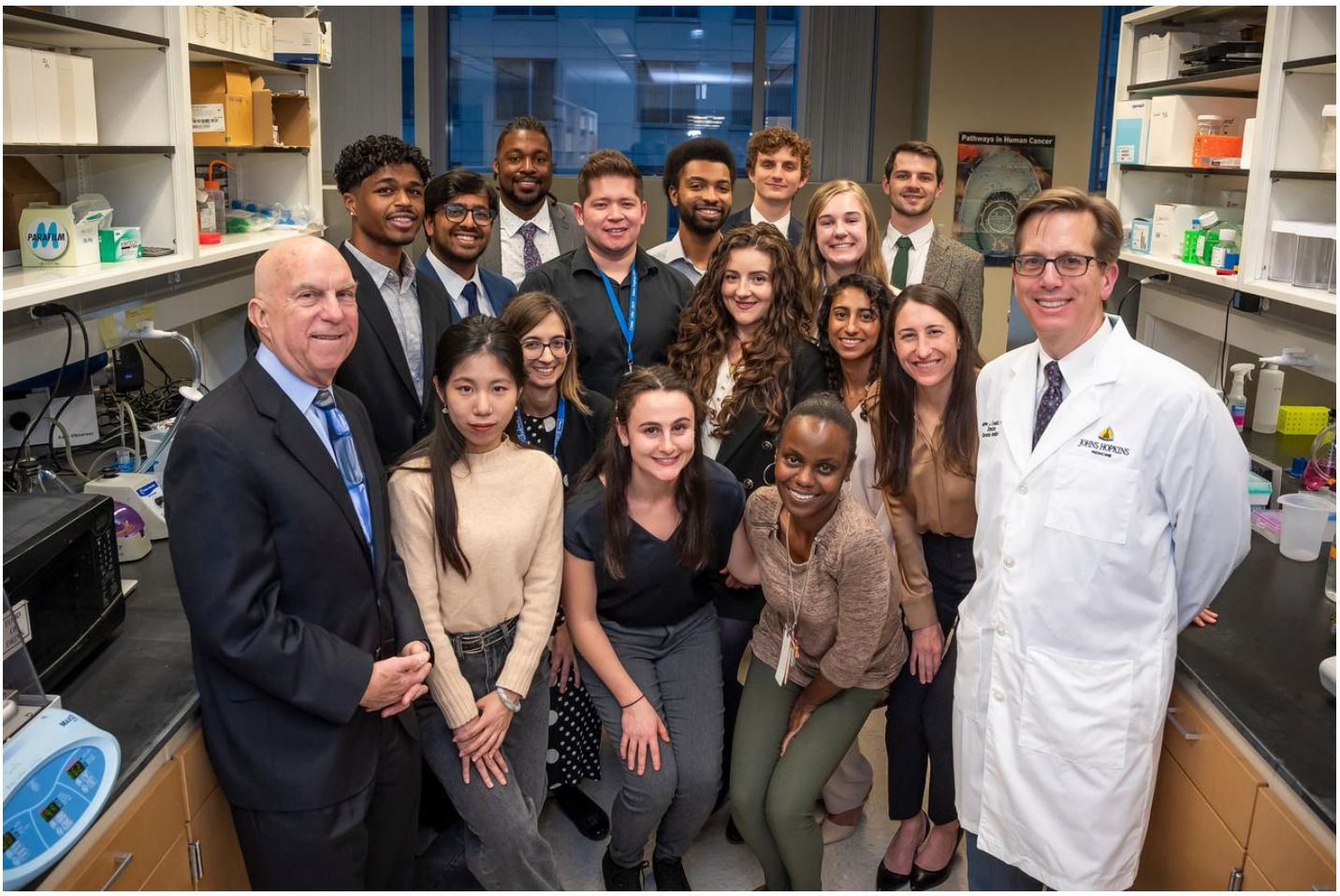


"Smart, motivated people that have the ability to explore will yield great results."

Ted Giovanis, FHFMA, MBA
President and Founder,
Jayne Koskinas Ted Giovanis (JKTG) Foundation for Health and Policy

"The Giovanis Institute is an opportunity to make huge leaps. It is built to be nimble, to reward curiosity, and to adapt to new information and new discoveries."

Ronald J. Daniels, JD, LLM
President, Johns Hopkins University



Above: Dr. Ewald and Mr. Giovanis with members of the Ewald Lab

"Institutes like this fuel discovery and are often the connective tissue that brings everyone from the University together around key scientific discoveries and the promise of the future. Institutes like this are a critical component of maintaining our continued excellence at Johns Hopkins."

William G. Nelson V, MD, PhD, DSc
Director, Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins
Marion I. Knott Director and Professor of Oncology

Founders Wall Celebration

April 7, 2025

Johns Hopkins University's tradition of celebrating visionary donors began with a $7 million bequest in 1873 that established the university and hospital. Over the years, as other generous benefactors meet or exceed this threshold, their contributions are honored by carving their names onto the Founders Wall. In a ceremony held in April 2025, institutional leaders gathered with members of the Giovanis family to honor their extraordinary commitments to basic science research at Johns Hopkins. Pictured above, Mr. Giovanis, with his friends, family, and the Giovanis Institute Director, Dr. Ewald, pose at the dedication.

From left to right: Dean of the Medical Faculty Dr. Theodore L. DeWeese, Ted Giovanis, Dr. Andrew Ewald, and Provost Ray Jayawardhana gathered to view the wall after the dedication ceremony

Dr. Andrew Ewald greets Mr. Giovanis at the Founders Wall symposium

Left: Mr. Giovanis with his JKTG Foundation team

Building the Team

A Look at the Scientists Behind the Research

Senior Faculty

The senior faculty at the Giovanis Institute for Translational Cell Biology have established their teams and are now focusing on accelerating the pace of their research. Their commitment to collaboration as a key to discovery and dismantling silos is advancing the world's understanding of the biological bases of metastatic cancer.

Andrew Ewald, PhD

Career Overview

Dr. Ewald received his undergraduate degree in physics with honors from Haverford College. He earned his PhD in biochemistry and molecular physics from the California Institute of Technology. He completed postdoctoral work with Zena Werb in mammary biology and cancer at the University of California, San Francisco. Dr. Ewald joined the Johns Hopkins faculty in 2008.

Director and Professor, Department of Cell Biology Johns Hopkins Medicine
Director, Giovanis Institute for Translational Cell Biology
Virginia De Acetis Professor in Basic Cancer Research
Co-Leader, Cancer Invasion and Metastasis Program

Dr. Ewald is the director of the department of Cell Biology, director of the Giovanis Institute for Translational Cell Biology and holds the Virginia De Acetis Professorship in Basic Cancer Research. He is a BCRF Investigator and a lifetime fellow of the American Society for Cell Biology. He is also the recipient of the Metastatic Breast Cancer Network Research Leadership Award and the Theresa's Research Foundation Research Leadership Award.

Research Interests

Dr. Ewald seeks to understand how cells build organs and how these same cellular processes can contribute to cancer metastasis. His research lab recently identified a unique class of breast cancer cells that lead the process of invasion into surrounding tissues—a first step in cancer metastasis. Further research is planned to examine if these cells are viable targets for therapy.

"The one thing I didn't expect when launching the Giovanis Institute was the degree to which it has already served as a model for how to bring together philanthropic, federal, and university support in pursuit of ambitious goals. We need to succeed in our own metastasis mission. We also need to build the template for a new, more risk-tolerant, collaborative, and innovative style of science."

Dr. Andrew Ewald

Mikala Egeblad, PhD

Career Overview
Dr. Egeblad received her undergraduate B.Sc. degree in Medicine at University of Copenhagen, and her Ph.D. in Cancer Biology from Copenhagen University/The Danish Cancer Society. She completed her postdoctoral training at the University of California, San Francisco, with Zena Werb. She joined the faculty at Cold Spring Harbor Laboratory in 2009 and was recruited to Johns Hopkins and the Giovanis Institute in 2023.

Bloomberg Distinguished Professor, Departments of Cell Biology and Oncology, Johns Hopkins Medicine
Co-Director, Breast & Gynecologic Cancer Program
Associate Director, Giovanis Institute for Translational Cell Biology
Co-Leader, Cancer Invasion and Metastasis Program

Dr. Egeblad is the co-director of the Breast & Gynecologic Cancer Program in the Department of Oncology and holds the Bloomberg Distinguished Professorship in Tumor Microenvironment. She is also a member of the Board of Directors of the American Association for Cancer Research. Her work ranks in the top 1% by citations as determined by Clarivate, and was most recently recognized in 2024 with the I.J. “Josh” Fidler Innovation in Metastasis Research Award from the Metastasis Research Society.

Research Interests
Dr. Egeblad’s research focuses on understanding how cancer interacts with the body. By studying the “ecosystem” or microenvironment that cancer cells inhabit, she has shown that the body’s responses—such as inflammation, stress, and signals from the nervous system—can sometimes aid cancer’s spread. At the Giovanis Institute, Dr. Egeblad and her team recently discovered that tumors containing necrotic regions, or areas of dead cancer cells, are paradoxically more likely to metastasize. They found that cancer cells near the necrotic regions adapt to the harsh environment and become more aggressive. Dr. Egeblad’s ultimate goal is to turn these scientific insights into real benefits for patients and families.

Peter Espenshade, PhD

Career Overview
Dr. Espenshade received his BA in Molecular Biology from Princeton University, PhD from MIT, and performed postdoctoral training with Dr. Michael Brown and Dr. Joseph Goldstein at UT-Southwestern Medical Center in Dallas.

Professor, Department of Cell Biology
Associate Dean for Graduate Biomedical Education
Interim Vice Dean for Education, Johns Hopkins School of Medicine

Since joining Johns Hopkins in 2002, Dr. Espenshade's research has focused on (1) how cells measure the concentration of nutrients in their environment with a focus on cholesterol and oxygen and (2) the mechanisms by which cells adapt to changes in these nutrients to promote cell growth. This work has important implications for tumor biology and cancer as well as heart disease.

In 2014, Dr. Espenshade became the Associate Dean for Graduate Biomedical Education. In this role, he supports graduate education for ~900 graduate students in 20 different masters and PhD programs in the School of Medicine. In 2025, Dr. Espenshade was named Interim Vice Dean for Education at the School of Medicine.

Research Interests
Alterations to normal cells result in uncontrolled cell growth and cancer. This uncontrolled growth of cancer cells ultimately affects healthy organs in the patient, leading to death. In order to divide, cancer cells must duplicate their DNA, and many successful cancer treatments target this requirement to prevent or slow cancer cell growth. Likewise, cancer cells must generate lipids, such as cholesterol and fat, to serve as building blocks for cell membranes and as a source of energy. The Espenshade Lab studies a cell signaling pathway (SREBP pathway) that is required for cancer cells to produce the lipids needed for growth. Current experiments focus on (1) demonstrating the requirement for the SREBP pathway in breast and pancreas cancer and (2) developing a SREBP pathway inhibitor as a cancer therapeutic.

New and Incoming Faculty

As the Giovanis Institute expands, recruiting top faculty prospects has been a key priority. The recruitment phase of the Institute's launch is now largely complete with the addition of two exceptional faculty members. Dr. Arja Ray, who joined the team as an assistant professor of Cell Biology earlier this year, is a T cell and macrophage-focused immunologist who specializes in breast cancer metastasis. Dr. Veena Padmanaban, who will officially join the team as an assistant professor of Cell Biology in January 2026, received her doctorate at Johns Hopkins, where she was a member of Dr. Ewald's lab group. Dr. Padmanaban has done groundbreaking work to further the understanding of whether and how sensory nerves innervate a tumor and how this can help determine the likelihood of metastasis, boosting our understanding of connections between the nervous system and cancer.

Arja Ray, PhD

Dr. Ray earned his undergraduate and master of technology degrees from the Indian Institute of Technology (IIT). He then pursued his doctorate in biochemical engineering at the University of Minnesota Twin Cities with an emphasis in cell-ECM interactions and cancer cell migration. In 2018, he joined the Department of Pathology at the University of California, San Francisco, where he remained until joining the faculty this year as an Assistant Professor in the Department of Cell Biology.

Assistant Professor, Department of Cell Biology

Research Interests

Immunotherapy has revolutionized the treatment of cancer. Most modalities of cancer immunotherapy work by enabling killer immune cells (CD8 T cells) to recognize and kill cancer cells. However, these cells do not work in isolation and are shaped by the unusual environment in a tumor. This environment includes other immune cells like macrophages and structural proteins like collagen, which scaffold the space between cells.

Dr. Ray's lab seeks to understand how the cancer-killing CD8 T cells can be made to work effectively in tumors. To achieve this goal, they study not only the CD8 T cells themselves, but also other environmental factors like those listed above. To study these processes, the lab benefits from unique tools including genetically modified mice developed by Dr. Ray. Based on his cross-disciplinary training, their work brings together immunology, mechanobiology, engineering and live imaging to tackle some of the most pressing issues in cancer treatment.

Veena Padmanaban, PhD

Dr. Padmanaban received her undergraduate degree in Biotechnology from SRM University in Chennai, India. She went on to receive her MS in biotechnology and PhD in Cell Biology at Johns Hopkins University. From 2019-2025, she served as a postdoctoral fellow at Rockefeller University.

Assistant Professor, Department of Cell Biology (January 2026)

Research Interests

Cancer doesn't just grow on its own—it interacts constantly with the body. Dr. Padmanaban's research focuses on one surprising partner in crime: the nervous system. Specifically, she studies how cancer cells "hijack" nerves and use them to grow and spread. She wants to understand how this communication happens, and whether blocking it can stop cancer from metastasizing to other parts of the body.

Dr. Padmanaban has discovered that sensory nerves growing into breast tumors actively release a molecule called substance P, which cancer cells exploit to spread through the body. Blocking this communication using an existing FDA-approved drug reduced tumor growth and metastasis in experimental models. This discovery opens a new and unexpected avenue for anti-metastasis treatment: targeting nerve-tumor communication. It also explains why so many tumors are surrounded by nerves—and how they might be using those nerves to their advantage.

Recent Major Awards

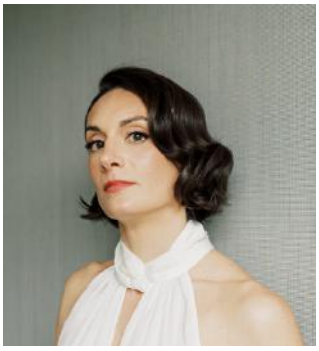
Laureate, Life Sciences, Blavatnik Regional Awards
Winner, Tri-I Breakout Prize
Susan G. Komen Career Transition Award

"My work in cancer neuroscience aims to reshape how we study, treat, and manage metastatic cancer, driving transformative advances in patient outcomes. I am excited to join the Giovanis Institute faculty and contribute to its mission of preventing metastatic disease, building on a shared commitment to changing the future of cancer research. I look forward to sharing my expertise and learning from colleagues whose diverse perspectives will inspire me, while mentoring the next generation of scientists in this dynamic community."

Veena Padmanaban, PhD

Collaboration Spotlight

Genevieve Stein-O'Brien, MHS, PhD



Terkowitz Family Rising Professor of Neurology
Bloomberg Assistant Professor of Neuroscience
Departments of Neuroscience, Neurology, and Genomic Medicine, Brain Science Institute
Kavli Neuroscience Discovery Institute

Research Interests

Dr. Stein O-Brien works on determining how an individual's unique existence affects the fundamental molecular programs that drive development and diseases. In breast cancer, there are key genetic subtypes, but that is not the entire story. Who a person is and the life they have lived influence how they will experience disease—particularly metastatic disease. Using machine learning and high-throughput molecular profiling techniques developed in her lab, Dr. Stein-O'Brien and her team are tackling the question of how a person's unique existence impacts both normal healthy development and disease progression. In breast cancer, this directly maps to puberty, pregnancy, lactation, precancer, and cancer. They have previously demonstrated that disease processes often coopt normal developmental pathways. Thus, the team takes a whole person, whole multiome approach to studying disease, with the goal of transition from precision to predictive medicine.

In collaboration with Dr. Ewald, Dr. Stein-O'Brien's team has shown that breast cancer co-ops normal developmental programs to metastasize. Moreover, they have begun to pinpoint the exact time and place at which these programs occur. This will enable them to understand the entire microenviroment in service of developing targeted interventions. Further, they have discovered novel roles during metastasis for neuropeptides that are known to play a role in pregnancy and lactation, potentially explaining their protective effect. In collaboration with Dr. Macklin, they have developed a multiscale agent-based modeling framework, which was recently published in *Cell*.

"I am tremendously excited by the potential of the team of investigators we've assembled in the Giovanis Institute. They bring together expertise on how cancer cells acquire the ability to metastasize and how the immune system, nervous system, and systemic health of the patient all contribute to disease progression and patient outcomes. We are working tirelessly and collaboratively to understand how metastasis works and to develop new therapeutic strategies to prevent and treat metastasis."

Dr. Andrew Ewald

Cultivating Tomorrow's Investigators

A guiding purpose of the Giovanis Institute is to foster new generations of cancer metastasis experts, supporting them on their journey to becoming senior investigators. Reflections and updates from current and former trainees working in the labs follows.

Research Associate

Chiaki Ishida, PhD

My research focuses on the requirement of the SREBP pathway in pancreatic ductal adenocarcinoma, the most common form of pancreas cancer. To date, I have demonstrated that the pathway is required for pancreas tumor growth, validating it as a therapeutic target. Currently, I am studying exactly why cancer cells fail to grow when the pathway is inhibited. To advance therapies for cancer, I have also identified candidate inhibitors of the SREBP pathway through a large-scale drug screen. I am working to improve the potency of these drugs for testing in mouse models.

I am pleased to share that after working as a postdoctoral fellow in the Espenshade Lab for six years, I have been promoted to Research Associate, a faculty rank in the Department of Cell Biology.

Current Postdoctoral Fellow

Virangika Wimalasena, PhD

After completing my doctorate in Dr. Andrew Ewald's lab, I am happy to share that I am continuing my work investigating breast cancer metastasis as a postdoctoral fellow in the lab. My research focuses on understanding the epigenetic underpinnings that dictate breast cancer invasion and metastasis. Thus far, I have demonstrated that two histone acetyltransferases, P300 and CBP, regulate luminal breast cancer invasion by orchestrating the required luminal to basal cell state transition. To determine the clinical relevance of these targets, I have shown that an FDA-approved P300/CBP inhibitor significantly reduces tumor growth and metastasis in a mouse model of luminal breast cancer. Currently, I am performing a screen to identify the transcription factors recruited by P300/CBP activity that coordinate the expression of genes required for both the cell state transition and invasion. Ultimately, the goal of this project is to provide a pre-clinical rationale for P300/CBP as a novel therapeutic target for metastatic breast cancer.

Current Doctoral Candidate

Celia Hallinan

Path to the Giovanis Institute

As an undergraduate at the University of Virginia, I researched peripheral nerve regeneration in the lab of Dr. Sarah Kucenas. After graduating with a degree in Neuroscience in the spring of 2021, I joined the lab of Drs. Geoff and Caroline Burns at Harvard Medical School and Boston Children's Hospital. During my two years in Boston as a research assistant, I studied heart development with a focus on cardiovascular disease modeling. In 2023 I matriculated into the Biochemistry, Cellular and Molecular Biology Program (BCMB) at Johns Hopkins School of Medicine where I became a member of the Egeblad Lab.

Current Research Focus

A cancer diagnosis often comes with intense emotional stress that affects more than just mental health. Prolonged stress can also take a toll on the body. Research has shown that long-term stress is linked to worse outcomes in cancer patients, including higher chances of metastasis and lower survival rates, but the reasons behind this connection remain unclear. My research explores the intersection of mind and body during cancer progression: I want to know how a patient's psychological state influences tumor growth and treatment response. Understanding this relationship is critical for developing more effective care strategies for patients coping with stress.

Current Doctoral Candidate

Rohan Panaparambil

My research focuses on the requirement of the SREBP pathway in breast cancer metastasis in a project that is joint between the Espenshade and Ewald Labs. Thus far in my doctoral studies, I have demonstrated that the SREBP pathway is required in a model of breast cancer metastasis due to its ability to supply cells with cholesterol. Currently, I am working to confirm this observation in mice and to understand the specific reason that cholesterol is limiting for metastasis with the goal of identifying drug or dietary interventions that will improve patient outcomes.

From Postdocs to Faculty

Former postdoctoral trainees share the impact of the formative time they spent at the Giovanis Institute.

Assistant Professor, Department of Molecular, Cellular, and Developmental Biology

University of Michigan

Junior West, PhD

As a postdoc at Johns Hopkins, I had the incredible privilege of working with world renowned scientists like Drs. Andrew Ewald and Mikala Egeblad, who are leading the charge at understanding and curing metastatic breast cancer. A common theme that I learned through my work with them was how critical it is to innovate and improve our understanding of fundamental cell and molecular biology in order to make real impacts that will improve patient outcomes in metastatic breast cancer. During my time at the earliest days of the Giovanis Institute for Translational Cell Biology, I learned that we can create meaningful and impactful spaces that push the boundaries of what we know about the biology of cancer. Witnessing the creation of the Giovanis Institute greatly expanded my view of what a career as a cell biologist could look like, and this continues to inspire me to pursue my dreams of leading a world-class research group that makes impactful discoveries with the goal of conquering this disease.

Group Leader, Cancer Macroenvironment Lab
Francis Crick Institute, London

Jose M. Adrover, PhD

My time at the Giovanis Institute at Johns Hopkins Medicine was an incredibly formative experience; it wasn't just about conducting research but learning to identify promising areas of research that align with clinical needs and how to tackle them effectively. I benefited immensely from close collaboration with faculty and trainees at the Giovanis Institute – their insights were consistently sharp and motivating. That collaborative spirit, honed within the Institute's dynamic environment, has proven critical in securing my current role as Group Leader at the Francis Crick Institute and in honing my skills to perform effective research centered on clinical needs.

Research Spotlight

An In-Depth Look at Choice Faculty Research Projects

Mapping Metastasis at the Cellular Level

Study: Mapping the breast tumor microenvironment reveals spatial relationships between macrophage subtypes and metastasis-initiating cancer cells

Investigator: Andrew Ewald

This groundbreaking breast cancer study reveals how certain cancer cells collaborate with their cellular "neighbors" to spread throughout the body. Dr. Ewald and his team used imaging mass cytometry—a technique that identifies 36 proteins simultaneously—to analyze tissue samples from 24 breast cancer patients, studying over 1.4 million cells from both primary tumors and metastases in organs like brain, lung, and liver.

The study focused on two breast cancer types: luminal (hormone-responsive) and triple-negative (more aggressive). Findings suggest that specific cancer cell populations drive metastasis: cells expressing both CK14 and E-cadherin proteins in luminal cancers, and cells expressing E-cadherin and vimentin in triple-negative cancers. Crucially, these dangerous cells don't act alone, rather they consistently cluster near CD163+ macrophages and specific fibroblasts. Surprisingly, these macrophages help cancer spread rather than fight it. This cellular arrangement remained consistent between primary tumors and distant metastases, indicating these relationships are fundamental to cancer spread.

These findings suggest profound clinical implications. For treatment development, targeting these cancer-supporting macrophages and fibroblasts could prove more effective than focusing solely on cancer cells. Combination therapies disrupting these cellular neighborhoods may prevent metastasis. For patient care, these cellular patterns could serve as biomarkers to identify high-risk patients. Patients with high levels of these cell combinations developed metastasis more quickly and had poorer survival.

Looking forward, clinical tests could be developed to detect these high-risk patterns, similar to current hormone receptor testing. Clinical trials targeting tumor-supporting cells could lead to new drugs that prevent metastasis by disrupting these cellular alliances. This research fundamentally shifts understanding from viewing cancer as isolated rogue cells to recognizing it as a complex ecosystem where disrupting the support network may be as important as attacking cancer cells themselves.

Molecular Brake on Cancer Invasion Identified

Study: Claudin 7 suppresses invasion and metastasis through repression of a smooth muscle actin program

Investigator: Andrew Ewald

This research reveals how Claudin-7 (Cldn7) prevents breast cancer metastasis by suppressing smooth muscle actin (SMA) genes, explaining why "claudin-low" breast cancer—characterized by reduced Cldn7 levels—is particularly aggressive. The group studied organoids from genetically engineered mouse models, comparing normal Cldn7 levels to knocked-down conditions, and validated findings using human breast cancer cell lines, fresh tumor tissue, and patient RNA sequencing data.

When breast cancer cells lose Cldn7, they activate specific SMA-related genes (Myh11, Acta2, Actg2, Mrtfa), triggering epithelial-mesenchymal transition (EMT). This transformation causes cells to lose their normal connections and gain invasive capabilities, enabling them to move through tissues and enter blood vessels. This research revealed a consistent inverse relationship across all models: low Cldn7 corresponds to high SMA gene expression. Genetic manipulation confirmed these SMA genes directly promote cancer invasion.

These findings provide a molecular explanation for claudin-low breast cancer aggressiveness—Cldn7 loss unleashes an invasive gene program. This positions Cldn7 as a potential biomarker to identify patients at higher metastatic risk. Second, the SMA gene program represents a new therapeutic target. Understanding that Cldn7 normally suppresses these genes enables development of strategies to block their activation in Cldn7-deficient tumors. Additionally, maintaining Cldn7 expression could serve as a preventive strategy against metastasis, and monitoring Cldn7 in circulating tumor cells might predict metastatic progression.

This work establishes Cldn7 as a metastasis suppressor that functions by negatively regulating SMA-related and mesenchymal gene expression. Future research should focus on developing therapies that either maintain Cldn7 expression or block the downstream SMA program when Cldn7 is lost, potentially improving outcomes for patients with aggressive claudin-low breast cancer.

Decoding the Language of Cell Behavior

Study: Digitize Your Biology! Modeling multicellular systems through interpretable cell behavior

Investigator: Genevieve Stein-O'Brien; Collaborator: Andrew Ewald

This research presents a groundbreaking computational framework for studying how immune cells and tumor cells interact in cancer tissue. The group developed "Cell Hypothesis Grammar," a system that allows scientists to describe cell behaviors in standardized terms, similar to language grammar rules. Integrated into the open-source PhysiCell platform, this tool makes sophisticated cancer modeling accessible to researchers without extensive programming experience.

The framework uses "agent-based modeling," where individual cells act as autonomous agents following specific rules. This approach enables researchers to simulate millions of scenarios quickly and cost-effectively, capturing rare but critical events that traditional lab experiments might miss. The system can incorporate cutting-edge genomics data and was validated through five comprehensive examples, including models of how tumors evade the immune system and develop resistance to immunotherapy.

By creating "digital twins" of patient tumors—virtual replicas that behave like actual cancers—doctors could test treatment options computationally before administering them to patients. This is particularly valuable for evaluating combination therapies and understanding why some patients respond to immunotherapy while others don't. The framework could significantly reduce trial-and-error in treatment selection, potentially improving outcomes while minimizing side effects.

Beyond individual patient care, this open-source tool democratizes computational modeling in cancer research. While these models cannot replace clinical trials, they serve as powerful tools for generating testable hypotheses and guiding research directions. As precision oncology evolves, this approach represents a promising avenue for accelerating the development of personalized cancer treatments while potentially reducing drug development costs and timelines. The work exemplifies how computational innovation can complement traditional research methods to advance our understanding of cancer and improve patient outcomes.

Dead Cancer Cells Help Tumors Spread

Study: Clot-Forming Immune Cells Drive Necrosis That Fuels Metastasis

Investigator: Mikala Egeblad

Patients whose tumors contain regions of dead cancer cells—known as necrotic regions—tend to have poorer outcomes and a higher risk of metastasis. For decades, researchers believed these regions formed passively, as aggressive tumors outgrew their blood supply. Because of that assumption, necrosis was rarely studied. But new research from Dr. Mikala Egeblad's team has revealed that tumor necrosis can be an active—and therefore targetable—process.

Dr. Egeblad's team discovered that certain immune cells, called neutrophils, can trigger blood clot formation inside tumors. These clots block circulation, starving tumor tissue of oxygen and causing cell death. Normally, neutrophils act as first responders to infection, leaving the bloodstream to attack pathogens by releasing DNA "webs" coated with toxic proteins. However, the team identified a previously unknown type of neutrophil that remains inside tumor blood vessels. These cells release their DNA webs—known as neutrophil extracellular traps (NETs)—within the vessels themselves, promoting clotting, halting blood flow, and driving tumor necrosis.

The researchers then asked why necrosis is linked to a higher risk of metastasis. They found that cancer cells near necrotic areas adapt to the harsh, oxygen-poor environment by becoming more mobile and aggressive. Importantly, when Dr. Egeblad's team blocked NET formation and clotting in mouse models, both necrosis and metastasis were reduced.

This discovery reframes how scientists view necrosis—not as a passive byproduct of tumor growth, but as an active process that can drive cancer spread. By uncovering this mechanism, Dr. Egeblad's team has revealed new opportunities to interrupt the cycle of inflammation, clotting, and metastasis.

Cell Surface Chemistry Affects Cancer Progression

Study: Plasma Membrane Cholesterol Influences Breast Cancer Metastatic Potential

Investigators: Peter Espenshade, Andrew Ewald

Obesity and hypercholesterolemia have been implicated as two major independent risk factors for postmenopausal breast cancer. Using aggregated, deindividualized data from the Johns Hopkins electronic medical record, the group observed that patients with hypercholesterolemia had an 8-fold increased risk of breast cancer, and this risk was independent of obesity. Notably, while a BMI < 18.5 was associated with a 5-fold reduction in breast cancer risk compared to patients with BMI > 18.5, this protective effect was abolished in the presence of hypercholesterolemia, suggesting that hypercholesterolemia may underlie a much larger component of breast cancer risk than previously acknowledged. These findings also support the notion that dysregulation of cholesterol metabolism at the systemic level plays a major role in breast cancer pathophysiology. However, the regulatory points of cancer progression at which cholesterol exerts its effects remain poorly understood, leading to conflicting evidence about the efficacy of cholesterol-reducing treatment such as statin therapy on breast cancer outcomes.

To address this knowledge gap, researchers have begun to characterize two points at which cholesterol regulates breast cancer progression. First, they found that inhibition of the sterol regulatory element-binding protein (SREBP) pathway that controls cholesterol homeostasis led to a marked growth defect in both MCF-7 and MDA-MB-231 breast cancer cell lines grown in lipoprotein-deficient serum conditions. This growth defect was rescued by the addition of cholesterol, but not by the cholesterol precursor mevalonate, suggesting that suppression of cholesterol biosynthetic flux by SREBP inhibition was chiefly responsible for this phenotype. Second, they extracted epithelial cell clusters from mouse MMTV-PyMT mammary tumors and modulated their plasma membrane cholesterol (PMC) levels ex vivo. The group found that decreasing PMC with low dose MBCD decreased colony formation, while increasing PMC with cholesterol-loaded MBCD increased colony growth, suggesting a role of plasma membrane cholesterol as a limiting metabolite for metastatic outgrowth. These findings warrant further investigation into the biology of cholesterol as it pertains to cancer progression. Giovanis Institute funding will determine the molecular mechanisms underlying this requirement for cholesterol. In addition, the team will test whether a high cholesterol diet impacts breast cancer PMC and metastatic potential.

Finding Function in 'Exhausted' Immune Cells

Study: Multimodal delineation of a layer of effector function among exhausted CD8 T cells in tumors

Investigator: Arja Ray

This groundbreaking study challenges the understanding of how the immune system fights cancer by discovering that not all "exhausted" immune cells are equally dysfunctional. Using an innovative fluorescent protein reporter system to track T cell activation in real-time, Dr. Ray's lab identified four distinct groups of exhausted CD8 T cells in tumors. The most significant finding was a subset called Q2 cells that, despite showing signs of exhaustion, maintained robust cancer-killing abilities through enhanced production of granzyme B and immune-signaling molecules.

These Q2 cells were strategically located at tumor edges near other immune cells, expressed high levels of activation-associated AP-1 transcription factors, and retained superior tumor-killing capacity compared to fully exhausted cells. Most importantly, analysis of human cancer patients across multiple tumor types revealed that those with higher ratios of functional Q2 cells to deeply exhausted Q4 cells had significantly better survival outcomes.

This research provides a new biomarker (the Q2/Q4 ratio) that could predict patient outcomes and guide treatment decisions. It also identifies molecular targets for new therapies - treatments could be designed to increase Q2 cells, enhance their function through AP-1 pathway modulation, or prevent their progression to full exhaustion. Finally, understanding that Q2 cells cluster near antigen-presenting cells suggests new approaches for optimizing immunotherapy delivery.

These findings offer hope for patients whose immune systems appear overwhelmed by cancer. By revealing that some exhausted T cells retain potent anti-tumor capabilities, this research paves the way for more personalized and effective immunotherapy strategies. Rather than viewing T cell exhaustion as a uniform state of dysfunction, we now understand it as a spectrum where certain cells maintain the ability to fight cancer - knowledge that could transform treatment approaches for patients who don't respond to current therapies.

A Multidisciplinary Metastasis Brain Trust

The Cancer Invasion and Metastasis (CIM) Program at the Sidney Kimmel Comprehensive Cancer Center

Co-Leaders: Andrew Ewald and Mikala Egeblad

The Cancer Invasion and Metastasis Program is a new research program that was founded by Dr. Ewald to unite a diverse group of scientists, engineers, and physicians to uncover and target the processes that enable cancer to spread. Together, the 40 faculty members of CIM represent 13 departments across the Johns Hopkins University School of Medicine, the Bloomberg School of Public Health and Whiting School of Engineering.

The program is organized around three common research aims:

- **Understanding how cancer cells migrate:** Through the use of innovative experimental models, working to uncover and target the processes that enable cancer cells—whether individually or collectively—to invade new organs.

- **Demystifying the tumor microenvironment:** Revealing how the "neighborhood" around a tumor shapes cancer behavior, and identifying ways to disrupt the harmful interactions that enable its spread.

- **Overcoming recurrent disease:** Understanding why some cancers resist treatment or return after therapy, CIM scientists are examining the cellular and molecular drivers of therapy resistance, tumor dormancy, and recurrence to identify new strategies for lasting cures.

Collectively, the CIM's highly accomplished scientists have published 768 studies, a significant portion of which (20%) have appeared in top-tier scientific journals. CIM investigators raise $13 million in grants per year, including more than $7 million awarded by the National Cancer Institute. The CIM stands as a model of the bold, cross-disciplinary collaboration needed to conquer metastasis.

Grant Spotlight

Metastasis Research Network (MetNet) Grants

Metastasis Research Network (MetNet) Grants from the National Cancer Institute are highly sought-after funding opportunities awarded to scientists focused on advancing the understanding of metastasis as a whole body, systems-level problem. MetNet's goal is to support the development of a comprehensive and cohesive picture of the emergent processes involved in cancer's spread. With fewer than 12 awards in total disbursed throughout the country, it is highly significant that two funded projects are being led by the Giovanis Institute's own Dr. Andrew Ewald and Dr. Mikala Egeblad, respectively.

Mapping the Single Cell State Basis of Metastasis in Space and Time

Primary Investigator:
Andrew Ewald, PhD
Collaborator:
Genevieve Stein-O'Brien, MHS, PhD

Cancer is the second leading cause of death in the United States and 90% of deaths occur at metastatic stages. Metastasis requires the cancer cell to accomplish many distinct tasks as it moves through the body to form new tumors in distant organs. This study seeks to identify systematically how a cancer cell's molecular toolkit changes during metastasis with the goal of identifying new therapeutic targets to prevent metastasis and for treating patients with metastatic disease.

Defining Brain-Body Feedback Loops Mediating Stress-Induced Metastasis

Primary Investigator:
Mikala Egeblad, PhD

Chronic stress is significantly linked to an elevated risk of metastasis and cancer recurrence, yet there remains a substantial knowledge gap regarding the underlying mechanisms driving this process. We discovered that stress induces the formation of metastasis promoting neutrophil extracellular traps and local activation of the sympathetic nervous system at the metastatic site, while reciprocally metastasis alters the activity of stress-regulating neurons in the brain, thus establishing a stress metastasis feedforward loop. In this study, we are elucidating the mechanisms driving this feedforward loop, with implications for preventing metastasis from disseminated cancer cells and treating stage IV cancer.

In Gratitude

Reflections from Faculty and Leaders

A Message from Dean DeWeese

Dear Ted,

Reflecting on the initial years of the Giovanis Institute for Translational and Cell Biology, it is impossible to separate the progress being achieved from your vision that started it all. From the very beginning, you challenged us to transcend traditional research silos in order to pursue bolder investigations into cancer's fundamental biology. Today, guided by those founding principles, our exceptional Giovanis Institute faculty are transforming your vision into reality, advancing each day toward defeating metastasis.

Ending the threat of metastatic cancer demands excellence across disciplines and beyond traditional oncology research. By establishing the institute, you have created an intellectual environment where innovation can flourish and unexpected collaborations can emerge. The momentum we are building on is rooted in the aspirational and pioneering course you set for us in bringing the institute to life.

Today, despite significant challenges faced by our research community, you ensure that we can keep discovery moving forward. Your partnership helps us remain true to our mission while building resilience that will carry us into the future. I am confident that we will not only persevere but emerge better prepared to withstand future challenges and continue our work to advance discoveries that change lives. Thank you for the dedication you have shown by ensuring that the Giovanis Institute for Translational Cell Biology is positioned to become a global leader in metastasis research. I join you in anticipation of all that comes next.

With gratitude,

Theodore L. DeWeese, MD
Dean of the Medical Faculty and CEO, Johns Hopkins Medicine

"Ted has been a literally ideal partner in our battle against metastasis. We have both lost people dear to us to metastatic cancer and understand that there is no time to waste—delay is lives lost. Ted reinforces my urgency to take risks and to work on the really big, hard problems. No matter the obstacles we face, he sees the potential for us to thrive in every environment, to focus forward, and succeed anyway. It has been a privilege to work closely with him and learn from him for the past decade and I equally look forward to continuing our collaboration in the decade ahead."

Andrew Ewald, PhD

"Creation of the Giovanis Institute enabled the colocation of our lab with the Ewald and Egeblad labs, which will lead to natural collaborations and catalyze discovery. Institute funding has been essential to our cancer research efforts, allowing us to take risks that NIH would not traditionally support. Data generated with these funds will be leveraged to secure multi-year federal grants to advance our understanding of cancer biology and future therapy."

Peter Espenshade, PhD

"Metastasis is one of the greatest challenges in cancer research. My lab has shown that inflammation and the body's stress responses are key determinants of whether cancer spreads. Joining the Giovanis Institute has enabled me to build new collaborations to tackle the problem of metastasis through the lens of how the nervous system responds to and influences cancer. With my colleagues at the Giovanis Institute, I think we are redefining what's possible in metastasis research—bringing us closer to the day when it is no longer something patients have to fear."

Mikala Egeblad, PhD

"I am thrilled to have recently started my own group under the auspices of the Giovanis Institute for Translational Cell Biology and the Department of Cell Biology at Johns Hopkins. In the coming year, I'm most excited to sculpt my initial ideas and hypotheses to best answer critical questions that will affect the treatment of cancer. I am equally looking forward to recruiting and nurturing a team of young scientists who will be carrying the science forward with me. With the support of the Giovanis Institute, I am confident that the effort and commitment in the next year will be instrumental in setting the course of my lab and future work for years to come."

Arja Ray, PhD

"As scientists, we strive to tease apart the mechanisms of diseases like cancer in as much detail as possible, reducing the "noise" that can obscure discovery. Conquering metastasis, however, demands more than precision alone; it requires excellence across disciplines and the courage to explore new and bigger questions using methods that transcend research bottlenecks. The Giovanis Institute, centered on promoting and facilitating cross-disciplinary collaboration, sets a common table where ideas are welcome. Here, the brightest minds are coming together to tackle one of the most challenging frontiers in cancer research."

William G. Nelson V, MD, PhD, DSc

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