IMPACT

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Gastrointestinal Oncology Program

Prepared for:

The Harold E. Eisenberg Foundation

Northwestern Medicine®
Feinberg School of Medicine

Grateful for Your Support

Dear Friends, Board Members, and Supporters of the Harold E. Eisenberg Foundation:

The Robert H. Lurie Comprehensive Cancer Center of Northwestern University is tremendously grateful for the Harold E. Eisenberg's partnership over more than 25 years to advance gastrointestinal (GI) cancer research. Through our Gastrointestinal Oncology Program and Harold E. Eisenberg Foundation GI Cancer OncoSET Program, our team of world-class physicians and scientists is making great strides to provide effective, targeted cancer treatments to patients who currently have limited options.

Our most recent recipient of the Harold E. Eisenberg Research Scholar Award is Weiguo Cui, PhD. We are pleased to offer this prestigious award each year to our scientists who are exploring new ideas aimed at discovering cures for GI cancers.

As a National Cancer Institute-designated Comprehensive Cancer Center, our physicians and scientists are translating discoveries into new possibilities—offering the newest, most effective treatments through clinical trials, sharing vital education and services in the larger community, and providing state-of-the-art cancer services and ongoing support to patients and families across Northwestern Medicine.

On behalf of Lurie Cancer Center and the Division of Hematology and Oncology, as well as our patients and their families who benefit from your generosity, we thank you for your impactful support.

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Harold E. Eisenberg Foundation GI Cancer OncoSET Program

OncoSET

OncoSET harnesses the power of precision medicine to identify tailored therapies for patients based on genetic alterations specific to their tumor. Following three vital steps—Sequence, Evaluate, and Treat—this breakthrough program targets tumors from any type of solid tumor.

With the help of the Harold E. Eisenberg Foundation, the OncoSET precision medicine program continues to enhance precision medicine for solid tumors, especially GI cancers. The OncoSET registry study has enrolled 735 patients with GI cancers, collecting data and biospecimens to help facilitate precision medicine research. In the Molecular Tumor Board meetings, we discuss how best to evaluate sequencing results and treat based on those results. We are expanding the reach of our tumor board program and recently have gone international, including a site in Brazil. A big push this year has been to work with our colleagues in Molecular Genetic Pathology, sequencing vendors, and our electronic medical record team to better integrate the results of precision medicine tests into the medical record and into the Electronic Data Warehouse, improving both clinical care and research. An upcoming highlight of the year is the OncoSET Symposium. This year, we are focusing on novel immunotherapy approaches and how precision medicine testing predicts response to immunotherapies. Gastrointestinal cancers are less responsive to immunotherapies than some other solid tumors, thus, novel approaches are greatly needed.

Clinical Trials Update

In the past year, 539 patients with gastrointestinal cancers enrolled in clinical trials across the Lurie Cancer Center network—a testament to our commitment to expanding access to life-changing research. This includes 201 patients participating in interventional trials—ranging from early detection and diagnostic studies to cutting-edge treatments—and 338 patients contributing to vital observational research that helps shape tomorrow's standards of care. A total of 79 trials were open to accrual for patients with GI cancers, offering novel options for patients at every stage of disease. These trials are offered not only at our downtown academic center, but also across 12 regional locations, including Lake Forest, Glenview, Grayslake, McHenry, Huntley, Central DuPage, Delnor, Warrenville, Kishwaukee, Oak Brook, Orland Park, and Palos—with more on the horizon.

We have built one of the most advanced community-integrated clinical trials networks in the country, providing patients with the opportunity to receive advanced care close to home without sacrificing access to innovation. This approach is transforming the cancer research landscape, and philanthropic partnership will be key in driving the next phase of growth: expanding to new communities, launching more studies, and accelerating cures.

Spotlight on GI Oncology Research Nurses

Heidi Ray, RN, BSN, OCN, continues to serve as the clinical operations coordinator in the Infusion Suite at Lurie Cancer Center. Heidi has worked in oncology her entire career of 43 years, and is truly making a difference in the lives of so many patients and their families.

"The Harold E. Eisenberg Foundation has made a difference for so many patients with GI cancer. The funding and the research, along with the gift bag distribution, make such an impact. The bags brighten up a dark and scary first-time chemotherapy visit. The thoughtful items and the caring notes bring a tear and a smile. On behalf of the Oncology Team, thank you for your dedication."
- Heidi Ray, RN, BSN, OCN

Focus on Precision Medicine

Over the past five years, Lurie Cancer Center has collaborated with technology companies to create various resources for the research community with a focus on precision medicine. These initiatives include next-generation sequencing (NGS) of more than 500 of our colon cancer cases and organoid development, which can provide new insights on human development, disease, and treatment options. Additional, high quality tissue microarrays (TMA), paired with next generation sequencing data, various clinical data, and patient outcomes, were developed in collaboration with Feinberg's Department of Pathology. This department facilitates high throughput analysis of multiple patient tissue samples at the same time. These collaborative efforts would not have been possible without the Harold E. Eisenberg Foundation Tissue Bank, which provided many of the tumor samples for these forward-thinking partnerships.

Over the past year, the Harold E. Eisenberg Foundation Tissue Bank had an increased focus on digital pathology. This includes transitioning physical glass slides to high quality digital images to promote ease of collaboration, remote analysis, and integration of artificial intelligence (AI) to assist with classification and quantitative analysis of tissue samples. Digital pathology offers various benefits that can enhance patient care and improve diagnostic accuracy.

27,548

specimens in tissue bank

1,572

patients contributed

Past Research Scholar Updates

Through the prestigious Harold E. Eisenberg Research Scholar Award, our dedicated scientists can continue to explore new ideas aimed at discovering cures for GI cancers.

Weiguo Cui, PhD - 2024 Scholar
Area of focus: Immunotherapy for colorectal cancer

Immunotherapies, such as checkpoint blockade therapy (ICB), had shown great promise in treating various cancers, but they did not always yield positive results for patients with colorectal cancer. A significant factor contributing to this resistance was the presence of specific immune cells known as myeloid-derived suppressor cells. These cells played a crucial role in dampening the immune response, making it harder for the body to fight off cancer effectively.

Recent research from Dr. Weiguo Cui's team had pinpointed a protein called Pim1 as a potential "Achilles heel" in myeloid-derived suppressor cells. This discovery was particularly important because targeting Pim1 could help reduce the suppressive effects of myeloid-derived suppressor cells, thereby enhancing the effectiveness of ICB therapy. The team has been actively exploring the possibility of blocking Pim1 to disrupt the functions of myeloid-derived suppressor cells. They conducted detailed studies to understand how Pim1 influenced myeloid-derived suppressor cells' behavior and how its inhibition could lead to better immune responses against tumors. Ultimately, their efforts proved successful, significantly improving treatment outcomes for patients with colorectal cancer. By reducing the immunosuppressive capabilities of myeloid-derived suppressor cells, they enabled the immune system to regain its strength and respond more robustly to ICB therapy. This research not only enhanced existing cancer treatments in preclinical cancer models but also paved the way for new therapeutic strategies aimed at overcoming resistance mechanisms in colorectal cancer. The results obtained from this study have been instrumental for a grant application to the National Institutes of Health for the upcoming cycle and a manuscript preparation.

Shannon M. Lauberth, PhD - 2023 Scholar
Area of focus: RNA-based therapeutics for treatment of colorectal cancer

The Harold E. Eisenberg Foundation Research Scholar Award has been instrumental in advancing research on RNA-based therapeutics for colorectal cancer. This work has led to the generation of high-quality genomic datasets, peer-reviewed publications, and multiple workshops and training sessions that have deepened our understanding of the molecular mechanisms underlying colorectal cancer progression. The Harold E. Eisenberg Foundation Tissue Bank was a critical resource for advancing these studies as paired colon tumors were used for downstream-of-gene (DoG) identification profiling studies. Dr. Shannon Lauberth published her research in *Science Advances* and *Molecular Cell*. A grant award application was submitted and remains on hold at the National Institutes of Health.

Hidayatullah G. Munshi, MD - 2023 and 2020-2021 Scholar
Area of focus: Immunotherapy for pancreatic cancer

Unlike other cancers, pancreatic cancer remains refractory to immunotherapy. Given the very poor prognosis of pancreatic cancer, there is interest in enhancing response to immunotherapy. In recent studies, Dr. Hidayatullah Munshi and his colleagues have found that standard of care chemotherapy changes the tumor microenvironment in such a way that pancreatic tumors become sensitive to the combination of anti-PD-1 immunotherapy and Trametinib, a drug that was first approved for the treatment of melanoma.

This work was recently published in *Molecular Cancer Therapeutics*.

Progress on most recent award:
Kras, one of the key proteins involved in tumor growth, is mutated in over 90 percent of human pancreatic tumors. Recently, inhibitors targeting the mutant Kras have been developed and are in clinical trials. Dr. Munshi and his colleagues have found that they can enhance the response to Kras inhibitors by combining them with drugs (e.g., Venetoclax) that can facilitate active cell killing. These drugs are currently approved for blood cancer. They also have found that when pancreatic cancer cells develop resistance to Kras inhibitors, they undergo a rewiring of their epigenome ('software') to allow the expression of key survival genes. The group's ongoing studies are focused on targeting these genes so that they can prevent the development of resistance to Kras inhibitors.

The first study combining with Venetoclax was recently published in *Cancer Research*.

The second study related to the rewiring of the epigenome is currently under review. The group also plans to resubmit the grant to continue this research.

Arthur Prindle, PhD - 2022 Scholar
Area of focus: Inflammatory bowel disease therapy

Integration of synthetic biology into clinical practice promises to be a transformative approach to modernizing disease diagnosis and monitoring. In particular, inflammatory bowel disease (IBD) is a spectrum of chronic inflammatory gastrointestinal diseases that is difficult to monitor due to the relapsing and remitting nature of disease flares often resulting in downstream complications. To bridge this gap, Dr. Arthur Prindle's pilot study sets the stage for engineered calprotectin sensing probiotics that can be used as a precise and non-invasive method of disease activity monitoring and treatment in patients with inflammatory bowel disease.

Building on this Eisenberg-supported pilot study, Dr. Prindle's group engineered a probiotic bacterium to detect the clinical gold standard biomarker of IBD, calprotectin, with high sensitivity and specificity in patients with inflammatory bowel disease (Xia,...,Prindle. *PNAS*, 2023). This publication is notable because it translates a biological discovery (specific transcriptional response to calprotectin) all the way to its implementation in human patients via retrospective study of a cohort of individuals at Northwestern Memorial Hospital.

Following its publication, Dr. Prindle was contacted by a gastrointestinal clinician at Northwestern who is interested in validating this technology in human clinical trials. Building on this, Dr. Prindle's group is now engineering calprotectin-responsive delivery of therapeutic nanobodies for inflammatory bowel disease treatment in the human microbiome, an ongoing project that was the basis of a successful proposal to the Chan Zuckerberg Biohub Chicago and several patent applications.

Devalingam Mahalingam, MD, PhD - 2021 Scholar
Area of focus: Metastatic colorectal cancer therapy

B-Raf mutated colon cancer constitutes 8-10 percent of all colon cancer patients. Patients with B-Raf mutated advanced colon cancer have worse overall survival. The Food and Drug Administration has approved the doublet therapy of encorafenib (B-Raf inhibitor) and cetuximab (anti-EGFR therapy) combination (EC) in BRAF V600E–mutated metastatic colorectal cancer, although the efficacy remains modest. Based on previous work in B-Raf inhibitors in melanoma, acquired resistance to therapy results in disease progression. Autophagy (cellular process where the cell cleans itself by removing damaged or dysfunctional parts and recycling them for repair and energy) induction may lead to resistance to this therapy. Dr. Devalingam Mahalingam and his team have worked extensively on autophagy modulation to overcome resistance to novel cancer therapeutics, using the autophagy inhibitor hydroxychloroquine through National Institutes of Health and Cancer Prevention and Research Institute of Texas-funded clinical studies. Hydroxychloroquine is a cost effective anti-malarial and anti-lupus drug. Based on some clinical efficacy of the addition of hydroxychloroquine to B-Raf inhibitors, observed in B-Raf mutated melanoma patients, Dr. Mahalingam and his team wished to evaluate this in colon cancer.

The goal is to show that the addition of hydroxychloroquine may result in better tumor responses and duration of therapy with B-Raf inhibitors in colon cancer.

The study opened at the end of 2022.

Beatriz Sosa-Pineda, PhD - 2020-2021 Scholar
Area of focus: Immunotherapy for pancreatic cancer

Pancreatic ductal adenocarcinoma (PDAC) has one of the worst cancer survival rates worldwide. ONECUT2 controls malignancy in many cancers and is highly expressed in metastatic PDAC of the "classical" subtype. Expression of the gene ONECUT2 correlates with poor clinical outcome in various cancer types. Dr. Beatriz Sosa-Pineda and her colleagues uncovered expression of ONECUT2 in precancerous lesions and tumors in the pancreas of mice and humans. They used genetic methods to delete ONECUT2 in the KPC mouse model of pancreatic cancer to investigate if the lack of ONECUT2 activity affects pancreatic tumor formation. Contrary to their initial hypothesis, they found that the lack of ONECUT2 has no noticeable effect on tumor formation in mice. Due to this disappointing result, the project was not pursued. Dr. Sosa-Pineda's current research focuses on uncovering new pathological mechanisms of pancreatitis.

Zhuoli Zhang, MD, PhD - 2019-2020 Scholar
Area of focus: Pancreatic cancer therapy

Dr. Zhang is currently a faculty member at the University of California, Irvine, and serves as director of the Translational Imaging Lab. While at Northwestern and with support of the Harold E. Eisenberg Foundation's award, Dr. Zhang worked to optimize clinically translatable MRI approaches to amplify immune responses of combination therapy of dendritic cell vaccine and irreversible electroporation treatment. He received research grants from the Society of Interventional Radiology and National Institutes of Health. Dr. Zhang published articles in prestigious journals such as the *American Journal of Cancer Research*, *Cancer Imaging*, *Cytotherapy*, and others.

Sui Huang, MD, PhD - 2018-2019 Scholar
Area of focus: Using a molecule created in her lab to treat liver cancer

Dr. Sui Huang is investigating a molecule her lab created, called MEAN. Dr. Huang hypothesizes that MEAN, which stands for 6-methoxyethylaminonumonafide, may be an effective way to treat liver cancer. Dr. Huang completed the project and is submitting grants to seek additional funding to build upon the results from this research. Additionally, Dr. Huang has now developed a second-generation compound and is in the process of evaluating *in vitro* and *in vivo* efficacy.

Ronen Sumagin, PhD - 2017-2018 Scholar
Area of focus: Investigating the connection between inflammation and cancer

In this study, Dr. Ronen Sumagin and his colleagues demonstrated that neutrophils migrating into developing colon tumors can shape the way cancer cells repair broken DNA. Neutrophils affect progression of colorectal cancer and its response to commonly used treatments known as DNA-repair targeted therapy.

Dr. Sumagin and his collaborators are currently investigating how the tumor niche may impact neutrophil functional specialization. This idea stems from the recent identification of neutrophil plasticity and ability to adopt to and be molded by environmental cues. In another recent high-impact publication (*Journal of Clinical Investigations*, 2024) they found that within the tumor niche, neutrophils can acquire pro-angiogenic phenotype, facilitating formation of vessels in the tumor and promoting tumor growth. These novel observations identify another way by which neutrophil activity in the tumor can promote its development and progression. In this work, Dr. Sumagin and his team also identified a molecular target, matrix metaloproteinase-14 (MMP-14), released by neutrophils to mediate their pro-angiogenic activity, and targeting it therapeutically is the current and future focus in the lab.

In ongoing work, Dr. Sumagin and his team are focused on better understanding the regulation and function of neutrophil-derived MMP-14 in colorectal cancer. They observed a dramatic impact of MMP-14 on promoting cancer development, and in preclinical studies successfully used MMP-14

activity inhibition approach to curb colorectal cancer progression. Thus, Dr. Sumagin currently aims to better understand how MMP-14 expression is regulated in neutrophils and in other cells in the tumor niche and how it functions to promote tumor growth. This goal is to find new therapies to treat colorectal cancer.

Guang-Yu Yang, MD, PhD - 2016-2017 Scholar
Area of focus: Gene mutation profiling of colorectal cancer

Dr. Yang has moved on from Feinberg and was appointed in December 2024 as chair of the Department of Pathology at the Virginia Commonwealth University School of Medicine. He spent 18 years at Northwestern, and, since 2012, had held the endowed Joseph C. Calandra Research Professorship in Pathology and Toxicology. In 2017, he was named vice chair and director of Anatomic and Surgical Pathology at Feinberg, a position overseeing 42 pathologists and a staff of more than 80 people in a clinical laboratory that handles more than 60,000 biopsies and surgically resected specimens, and more than 30,000 cytology specimens and 300 autopsies.

A physician-scientist, Dr. Yang has made significant contributions to clinical research on GI pathology, including inflammatory bowel disease (IBD) and colorectal cancer, mainly focused on the molecular pathogenesis of IBD-induced cancer. He presently holds active NIH grants, including one R01 grant. Over the course of a 30-year career in medicine, Dr. Yang has authored 212 peer-reviewed publications and seven book chapters and is associate editor of the publication *Molecular Carcinogenesis*. He is a current member of the College of American Pathologists, the United States and Canadian Academy of Pathology, and the American Association for Cancer Research.

Making an Impact

The Harold E. Eisenberg Foundation is an invaluable partner in helping us to propel forward our GI oncology program and our efforts to provide patients with personalized medicine. Northwestern University Feinberg School of Medicine and the Robert H. Lurie Comprehensive Cancer Center of Northwestern University are incredibly grateful for your philanthropic support, which enables our physicians and scientists to push boundaries, break barriers, and transform the future of cancer care.

If you would like more information regarding this report or Lurie Cancer Center, please contact:

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