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:

This year marks the 25th anniversary of the Harold E. Eisenberg Foundation's extraordinary partnership with the Robert H. Lurie Comprehensive Cancer Center of Northwestern University. We are deeply thankful for your longstanding commitment to advance breakthrough gastrointestinal (GI) research and increase survivorship. As we celebrate this special milestone, we remember and honor Harold (Hal) Eisenberg and his inspiring legacy.

Lurie Cancer Center is one of just 57 Comprehensive Cancer Centers in the country, and the only one in Illinois to earn an "exceptional" rating from the National Cancer Institute. Our cancer program at Northwestern Memorial Hospital is once again ranked among the nation's best. Our more than 300 members conduct groundbreaking laboratory, clinical, prevention, behavior and population-based investigations to spur innovative clinical trials and provide cutting-edge treatment options that are often not available anywhere else. The Harold E. Eisenberg Foundation's generosity over the years has helped fuel our work forward, contributing to these accomplishments and much more.

With appreciation, we share this annual report on our Gastrointestinal Oncology Program and Harold E. Eisenberg Foundation GI Cancer OncoSET Program, as well as updates on the research of current and past recipients who have received Harold E. Eisenberg Research Scholar Awards.

Thank you again for your vital support and continued commitment to accelerate life-changing research.

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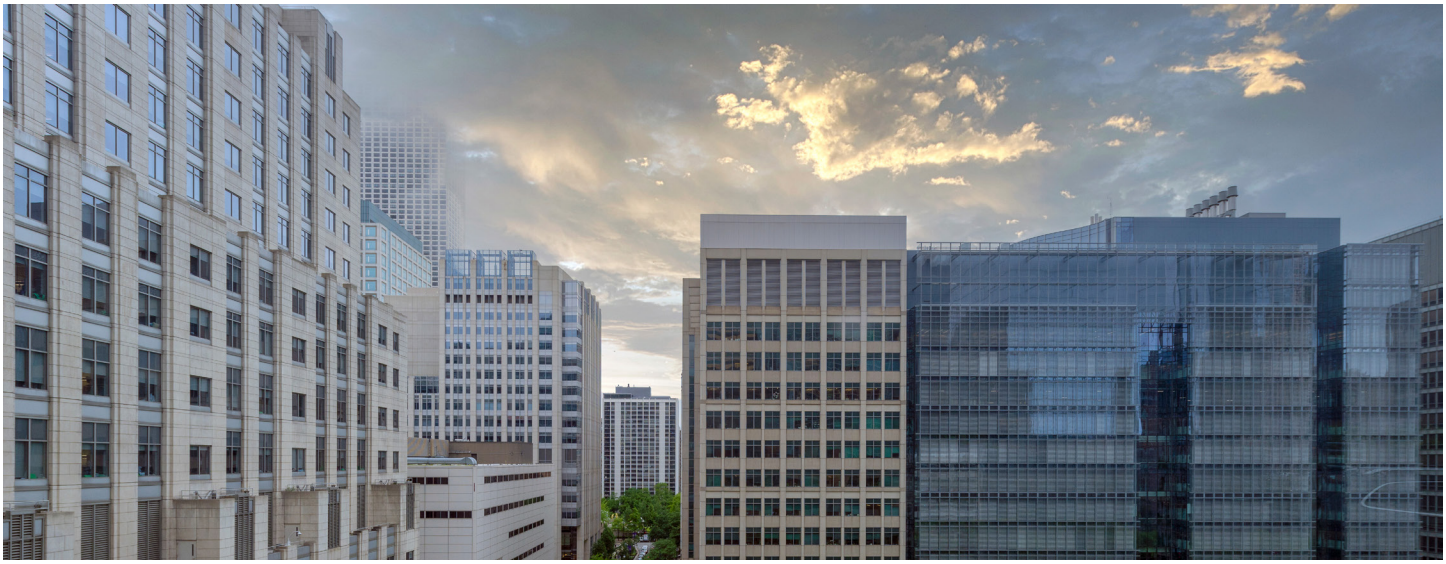

Harold E. Eisenberg Foundation GI Cancer OncoSET Program

OncoSET

OncoSET harnesses the power of precision medicine to identify tailored therapies for patients based on the abnormal genes specific to their tumor. Following three vital steps—Sequence, Evaluate, and Treat—this breakthrough program targets tumors from any type of cancer that is not responsive to standard forms of treatment.

The Harold E. Eisenberg Foundation GI Cancer OncoSET registry continues to enroll patients with GI cancers. A total of 619 patients with GI cancers have contributed to our understanding of the molecular genetics of GI cancers by enrolling in the research study associated with the OncoSET program. We continue to improve patients' ability to enroll in our registry study electronically and outside of clinic, rather than having to wait for their next appointment. We hold Molecular Tumor Board meetings to discuss how best to evaluate sequencing results and treat based on those results. We are pleased that this past year, Northwestern Memorial Hospital started offering a test evaluating methylation patterns of DNA, and not just the DNA sequence. This novel methylation assay helps to characterize cancers that have an unknown origin, which is often the case with GI cancers, especially pancreatobiliary cancers.

Clinical Trials Update

In the past year, there have been 354 GI patients accrued to prevention, diagnostic, supportive care, and treatment trials at Lurie Cancer Center. In addition to this, there are an additional 302 patients enrolled in Observational trials for a total of 656 GI patients enrolling in clinical trials across our network locations. The types of interventional trials patients enroll in include Phase I, II, III, and pilot studies. A total of 78 trials have been open to accrual for this population in the last year. The impact of the addition of network locations that bring trials closer to home can be seen by the large increase in accrual compared to the previous year. Current locations include: Lake Forest, Glenview, Grayslake, McHenry, Huntley, Central DuPage, Warrenville, Kishwaukee, Orland Park, and Palos. Additional locations will be added in the coming year.

Spotlight on GI Oncology Research Nurses

Heidi Ray RN, BSN, OCN, serves as the clinical operations coordinator in the Infusion Suite at Lurie Cancer Center. Having worked in oncology her entire career of 43 years, oncology is truly her passion. Heidi and her colleagues are making a significant difference in the future of so many people, patients, and families.

"I know that I make a difference daily with my patients and my team. Nursing is a true calling. The Eisenberg Foundation with their generous Care Packages have allowed me to bring a smile to a patient who is overwhelmed and frightened at the thought of beginning therapy. The care packages are made with items from the heart, items that patients don't think to bring to infusions. Thank you." - Heidi Ray RN, BSN, OCN

Northwestern University Feinberg School of Medicine has again been recognized as one of the best medical schools in the nation, ranking 13th among research-oriented institutions, according to the latest *U.S. News & World Report* rankings.

Focus on Precision Medicine

Over the past few years, Lurie Cancer Center has partnered with technology companies in the area of GI cancers, specifically colon cancer. Utilizing the Harold E. Eisenberg GI Cancer Tissue Bank, these partners have helped complete next-generation sequencing of 500+ of our colon cancer cases and organoid development. Organoids provide a detailed view of how organs form and grow, which can also provide new insights on human development, disease, and treatment options. Drug interaction with these "mini-organs," can potentially revolutionize the field of drug discovery and open new approaches to personalized medicine.

Additionally, colon cancer Tissue Microarrays (TMA), which contain small representative tissue samples from multiple patients within the same paraffin embedded tissue block, were created and paired with next generation sequencing data, various clinical data, and patient outcomes. Tissue MicroArrays allow diagnostic, prognostic, and new treatment predictive biomarkers analysis of multiple patient tissue samples at the same time.

Over the past year, we have continued our digital pathology efforts to convert physical glass slides to digital images using a whole slide scanner to enable AI-assisted analysis of histological tissue images in the future. Digital pathology offers various benefits that can enhance patient care and diagnostic accuracy via pathologist collaboration and AI-assisted analysis of data. 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.

27,339

specimens in Tissue Bank

1,549

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.

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

Colorectal carcinoma is the third most commonly diagnosed malignancy worldwide. The rising incidence of early onset colorectal carcinoma and a patient's five-year survival rate being less than 15 percent are consistent with colorectal carcinoma being a major and growing health challenge. Chemotherapeutic drugs most often used for treating colorectal carcinoma drive stable Topoisomerase I (TOP1)-DNA cleavable complexes that induce genomic instability. However, chemotherapeutic drug resistance and limited treatment options remain a major challenge. Thus, there is an imminent need to identify molecular vulnerabilities that can be therapeutically targeted to drive efficient elimination of colon cancer cells to enhance the survival of patients with colorectal carcinoma.

Through transcriptomic analyses of matched tumors and non-neoplastic tissues and cancer cell lines, Dr. Lauberth and colleagues reveal a comprehensive catalog of downstream-of-gene (DoG) RNA signatures. Through separate lines of evidence, we support the biological importance of DoG RNAs in carcinogenesis. First, Dr. Lauberth and team show tissue-specific and stage-specific differential expression of DoG RNAs in tumors versus paired normal tissues with their respective host genes involved in tumor promoting versus tumor suppressor pathways. Second, they identify that differential DoG RNA expression is associated with poor patient survival. Third, they identify DoG RNA induction is a consequence of treating colon cancer cells with the TOP1 poison CPT and following TOP1 depletion.

The group's results underlie the significance of DoG RNAs and TOP1-dependent regulation of DoG RNAs in diversifying and modulating the cancer transcriptome. This work is currently in the revision stage at *Science Advances* and is expected to be published soon. It also has been shared at numerous scientific conferences including the recent Fusion Genome Regulation. In addition, the data that was obtained based on this Harold E. Eisenberg Foundation-supported study was used to prepare a R01 grant application that was submitted to 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. 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.

They have submitted a revised manuscript related to this work and anticipate publication soon in one of the *American Association for Cancer Research* journals.

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 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.

Dr. Munshi currently has a paper in revision describing this work, and a grant to continue this avenue of research is currently under review.

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 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. 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 in patients with inflammatory bowel disease.

This study is currently in revision at *Proceedings of the National Academy of Sciences* after receiving positive reviews. Dr. Prindle has received other pilot funding for related work from the American Society for Gastrointestinal Endoscopy, and he and colleagues are currently preparing a National Institutes of Health (NIH) R01 application based on this Eisenberg-supported pilot study.

Devalingam Mahalingam, MBBChBAO, PhD; 2021 Scholar
Area of focus: Metastatic colorectal cancer therapy

B-Raf mutated colon cancer constitutes eight to ten 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 induction may lead to resistance to this therapy. Dr. 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/ 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 addition of hydroxychloroquine to B-Raf inhibitors, observed in B-Raf mutated melanoma patients, we wanted 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 and has enrolled two patients. Given this rare mutation, we anticipate one patient enrolled every two months. To date, both patients are tolerating therapy and remain on study.

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. 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. 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 accomplished 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. 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 in that way 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) released by neutrophils to mediate their pro-angiogenic activity, and targeting it therapeutically is the current and future focus in the lab.

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

Through a large patient cohort study, Dr. Yang and his colleagues identified the unique profile of genetic alteration in young colorectal cancer patients. Specifically, the Braf mutation and Lynch syndrome are among the common genetic alterations in this group of patients. Dr. Yang's group published their work last year in the journal *Human Pathology*. Dr. Yang also worked with Shannon M. Lauberth, PhD, associate professor of Biochemistry and Molecular Genetics, on a National Institutes of Health program grant proposal focusing on colorectal cancer, and with Bin Zhang, MD, PhD, professor of Medicine (Hematology and Oncology) and Microbiology-Immunology, on a proposal on immunity and colon cancer (focusing on Braf mutation/ Lynch syndrome and h-mutant burden colon cancer).

Our Deepest Gratitude

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 down 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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