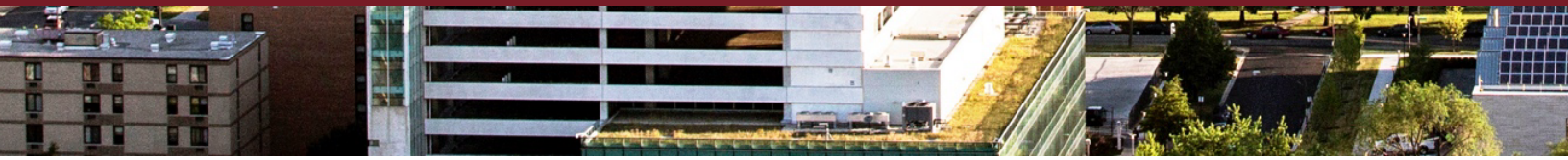
AT THE FOREFRONT

UChicago Medicine

The University of Chicago Section of Hematology/Oncology



Welcome to the Section of Hematology/Oncology at the University of Chicago. Our Section boasts a long-standing tradition of excellence in research-based patient care, clinical and scientific discovery, and outstanding education of residents and fellows. Consistently ranked as one of the top cancer programs in the country, our Section includes nationally and internationally recognized faculty with expertise in all major types of malignancies, blood disorders, and experimental therapeutics.

The Section of Hematology/Oncology is among the largest subspecialty sections in the University of Chicago's Department of Medicine. We are composed of more than 60 faculty members, 27+ network physicians, 21 fellows, and a professional staff of over 200 employees, all of whom are devoted to growing our tripartite mission of excellence in research, patient care, and education. Our faculty are experts in their fields, and frequently publish and present prominently about their areas of research and clinical care. We take tremendous pride in training the next generation of leaders in Hematology/Oncology. Our fellowship has 7 positions per year, with an opportunity for fellows to develop research and clinical skills in a variety of fields. We hold two T32 Training Grants (Medical Oncology and Clinical Pharmacology), as well as a K12 Paul Calabresi grant.

Our Section maintains an active research agenda, reflected in numerous clinical trials of all phases and a strong grant portfolio. We take pride in focusing on both basic

science and translational research, ensuring that clinical trials are available to our patients. We have many "bench to bedside and back to bench" trials leading to new treatments. This enables our clinicians to provide care that is truly at the forefront of hematological and oncological knowledge. These trials are available to patients with blood malignancies, such as leukemias and lymphomas, as well as those with solid tumors in the lung, head and neck, breast, gastrointestinal tract, and genitourinary tract, among others.

Our research is supported by an extensive portfolio of both federally and privately funded grants. While the positive impacts of our research initiatives are too numerous to list, several key initiatives stand out. These include: our use of artificial intelligence to enhance precision medicine; advances in immunotherapies and cellular therapies, including CAR-T and TIL therapy; computational oncology; and precision-based identification of patient populations that may benefit from these and other novel therapies. Our laboratory-based faculty have developed programs of excellence in cancer metabolism, genetics of cancer risk in both solid tumor and hematologic settings, understanding and exploiting the tumor microenvironment, and mechanisms of drug resistance.

Our institution has a long tradition of excellence in cancer research, clinical care, and the interdisciplinary training of the next generation of oncology leaders. This tradition includes significant accomplishments such as:

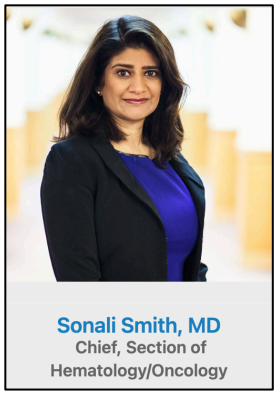
- the 1941 discovery of the remarkable effects of hormone therapy on prostate and breast cancer culminating in the 1966 Nobel Prize to Dr. Charles Huggins;
- the 1942 discovery of the effectiveness of nitrogen mustard as treatment for Hodgkin Disease by Dr. Leon Jacobson, former Dean of the Biological Science Division;
- Dr. Janet Rowley's 1971 discovery of the *t(9;22)* translocation in CML, culminating in the awarding of a National Medal of Science, the Lasker Award, and the National Medal of Freedom;
- the 2004 Lasker Award for Basic Medical Research presented to Dr. Elwood V. Jensen, for discovery of the estrogen receptor which had a rapid, direct, and lasting impact on treatment and prevention of breast cancer;
- and Dr. John Ultmann's practice-changing contributions to the precise staging of Hodgkin Lymphoma.

Select other important contributions by our Section faculty and leaders include the following

- the development of organ-sparing combined modality therapy for cancers of the head and neck by Dr. Everett Vokes;
- the first observation that the gut microbiome informs response to immunotherapy, by Dr. Tom Gajewski;
- a robust clinical trials program leading to multiple new treatments for patients with acute and chronic myeloid neoplasms, led by Dr. Richard Larson;
- the creation of a holistic Adolescent and Young Adult program by Dr. Wendy Stock;
- the deep investigation of genetics of breast cancer amongst the African diaspora by Dr. Funmi Olopade;
- global expertise in the field of mesothelioma by Dr. Hedy Kindler;
- the discovery of numerous cytogenetic abnormalities in treatment-related leukemias by Dr. Michelle Le Beau;
- leadership of CALGB/Alliance for 15 years and service as the first CMO of ASCO by Dr. Richard Schilsky;
- and advocacy and research in the space of pharmacogenetics, pharmacoeconomics, and rational drug development by Dr. Mark Ratain.

Our dedication to both basic and translational research continues, with our Section faculty frequently publishing their work in the highest-impact journals in our field. By collaborating with cooperative research groups, like the Alliance for Clinical Trials in Oncology, our cancer program provides patients with access to leading research teams across the U.S. and the world. We have had 4 ASCO Presidents come from our Section: Drs. John Ultmann, Harvey Golomb, Richard Schilsky, and Everett Vokes.

The innovations from our Section have made significant, practice-changing impacts on the diagnosis and treatment of many types of cancer, benefiting the patients who come through our doors and those receiving care globally.



Sonali Smith, MD
Chief, Section of Hematology/Oncology

Fellowship Program & Training

The Section of Hematology/Oncology is dedicated to educating the next generation of cancer experts and takes pride in its comprehensive educational efforts. Our initiatives include training and providing support for medical students, interns, residents, and fellows. For decades, our Fellowship Program has nurtured some of the brightest and most innovative physicians in the country, many of whom have achieved national and international recognition. The University of Chicago Medicine's state-of-the-art inpatient and outpatient facilities offer a broad and deep clinical experience, while the University's extensive research facilities promote the development and pursuit of foundational science skills.

The Hematology and Medical Oncology training program at the University of Chicago aims to prepare exceptional postdoctoral trainees for research-intensive careers in academia, government, industry, or private health systems. Since the program's inception in 1987, the integration of training in basic research and clinical oncology has continued to evolve and improve. We have training in cancer genomics, immunology, bioinformatics, and population health/health services research. Additionally, we offer a range of training grants that accommodate various levels of trainees, including the R25 SOAR grant (PI: Funmi Olopade), T32 in Basic Medical Oncology (PI: Funmi Olopade), T32 in Clinical Pharmacology (PI: O'Donnell), and the K12 Paul Calabresi Award (PI: Olopade).

For more information on all of our training programs, please review the information on our Hematology/Oncology Fellowship website and our Hematology/Oncology Fellowship Training Program Brochure.

Hematology and Medical Oncology Fellowship Program (ACGME-accredited)

Our ACGME-accredited Hematology/Oncology Fellowship Training Program, directed by Dr. Kenneth Cohen, is a vital part of the Section of Hematology/Oncology. This Section is the largest subspecialty within the Department of Medicine and is an integral component of the University of Chicago Comprehensive Cancer Center (UCCCC). Both the Section and the UCCCC provide the foundation for the training program's robust research environment and our faculty provide mentorship across a wide range of research topics. Fellows are offered

numerous continuing education opportunities, from seminars to workshops and retreats.

To foster new interdisciplinary research programs, the University of Chicago has expanded its infrastructure to support "team science" and translational research. A key example of this vision for collaborative research is the construction of several new buildings:

- The innovatively organized Gordon Center for Integrative Science (GCIS), which houses the Ben May Cancer Research Institute;
- The Knapp Center for Biomedical Discovery (KCBD), which is home to physician scientists in Hematology/Oncology;
- The Pritzker School of Engineering, which integrates science and engineering at a molecular level up to an organismal level

Additionally, the University has made significant investments in genomics, bioinformatics, and computational biology with the establishment of the NCI's Genomic Data Commons on our campus, led by Dr. Sam Volchenbaum.

In addition to enhanced training in genomics, immunology, public health sciences, health services research, two new Master's degree programs have been started: the MSc in Public Health Sciences for Clinical Professionals (MSCP) and the MSc in Biomedical Informatics within the ITM. These programs are designed to prepare postdoctoral trainees for careers as independent and collaborative researchers, with a focus on clinical research and medical informatics. Such training opportunities are critical for building a strong and enduring pipeline for the next generation of leaders in clinical and translational research. Our joint training program in Clinical Therapeutics in Oncology offers a unique fellowship that combines comprehensive training in oncology with clinical pharmacology and pharmacogenomics.

For more information, please visit our Fellowship website or contact us directly with any additional inquiries:

Kenneth Cohen, MD
Associate Professor of Medicine
Director, Fellowship Training Program
Section of Hematology/Oncology

Jennifer Coopperrider, MD
Assistant Professor of Medicine
Associate Program Director of the
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Post-doctoral Research Training Program

The postdoctoral training program in Hematology/Oncology at The University of Chicago offers advanced, multidisciplinary training for qualified applicants in the expansive field of cancer research. Funded primarily by an NIH Institutional Research Service Award, the program equips postdoctoral fellows with the skills necessary for successful academic research careers. This is done by emphasizing both foundational and cutting-edge approaches to cancer biology, including training in emerging areas such as artificial intelligence (AI) and computational oncology. Weekly lectures and seminars, delivered by leading national and international experts, keep researchers informed of the latest advances in the field.

Trainees benefit from close collaboration with faculty in the Section of Hematology/Oncology, as well as investigators across the broader University of Chicago research community. This integrated environment provides comprehensive, laboratory-based experience in state-of-the-art molecular and cellular techniques. Additionally, trainees have access to the Polsky Center for Entrepreneurship and Innovation, offering resources and mentorship for those interested in translating their discoveries into biotech startups.

Mentorship is a cornerstone of the postdoctoral training program, with individualized guidance provided by experienced faculty who support the development of each trainee's trajectory and career goals. In addition to lab-based training, trainees are encouraged to present their work at national conferences and participate in on-campus seminars and research talks. These opportunities foster professional development, academic networking, and deeper engagement with the broader scientific community.

You can learn more through our Committee on Cancer Biology website.

Hematology/Oncology Clinical Programs

The Section of Hematology/Oncology at The University of Chicago is dedicated to providing comprehensive, multidisciplinary care and advanced research in the treatment of adult hematologic and oncologic diseases. Each year, our experts care for approximately 5,000 new patients who seek our help for various blood disorders and cancers.

Our dedicated faculty manage four inpatient services and a general consultation service, working alongside an exceptional team of nurses, advanced practice providers (APPs), medical assistants (MAs), technicians, mental health professionals, and colleagues from other Sections and Departments. The Section consistently receives national recognition as one of the top cancer programs in the country, with many of our physicians earning accolades for their outstanding patient care year after year. This includes having more physicians consistently recognized as top doctors in the Chicagoland area than any other institution.

The hallmark of our Section is the compassionate, high-quality and expert clinical care our physicians deliver to patients. Many of our programs seamlessly incorporate clinical trials into their treatment offerings, ensuring that our patients have access to cutting-edge therapies. Led by our highly focused faculty, clinical trials research efforts are supported by a dedicated team of research nurses, data analysts, research coordinators, technicians, and regulatory specialists. Currently, we offer over 200 investigator-initiated and industry-sponsored clinical trials for patients with:

- Leukemia, lymphoma, myeloma, and other hematologic malignancies
- Lung cancer
- Head and neck cancer
- Breast cancer
- Gastrointestinal cancer
- Genitourinary cancer
- Mesothelioma
- Melanoma/sarcoma
- Other solid tumors

For more information about the clinical services we offer, please visit The University of Chicago Medicine website.

Adolescent & Young Adult (AYA) Program

Focus: comprehensive and holistic approach to the care of the adolescent/young adult with cancer, continuum of cancer care, supportive oncology services for young adults

Section Faculty: Adam DuVall, MD, MPH (Co-lead), Wendy Stock, MD (Co-lead)

When facing cancer, adolescents and young adults (AYA) often confront different personal, psychosocial, and medical challenges than younger children and older adults with the same diagnosis. That's why the University of Chicago Medicine created the Adolescent and Young Adult (AYA) Oncology Program — a collaborative program offering coordinated cancer care for young adults ages 15-39 through a large multidisciplinary team. Our program aims to deliver state-of-the-art, clinical science-driven care with a holistic approach to the many issues that are unique to cancer care for young adults, including fertility support, psychological care that spans the inpatient and outpatient continuum, physical therapy, social work, pharmacy support, nursing, and a comprehensive community health worker program. We've created a community of care to foster trust, adherence, and a sense of well-being throughout the continuum of cancer care. Our holistic care encompasses a wide range of supportive oncology services, geared specifically towards the needs of our AYA patient population and delivered at the bedside during infusion and other clinical appointments.

Major Accomplishments:

- Nationally unique joint pediatric-adult clinic that focuses exclusively on AYA cancer care. This integrated clinic ensures that all care needs are met within the program, reducing the need for referrals across the system and avoiding fragmented care.
- Pioneered the current standard of care for young adults with acute lymphoblastic leukemia (ALL), published in *Blood* and *Blood Advances*, which are the basis for the current AYA ALL guidelines under development by the American Society of Hematology.
- Leadership in NCTN cooperative groups, fostering the development of interventional clinical trials and evaluation of patient outcomes, including current national leadership of a joint pediatric/adult trial for patients with Hodgkin Lymphoma.
- Embedded survivorship clinic is a fundamental part of the continuum of care for our patients, to ensure that any long-term side effects of treatment are addressed and managed, published in a variety of high impact publications such as the *Journal of Clinical Oncology*, *Lancet Oncology*, and *Nature Medicine*. This includes a partnership with the Childhood Cancer Survivor's Center to ensure continuity of care for our youngest patients and those who had a previous cancer diagnosis in childhood.
- Advocacy and public education, including on topics like increasing rates of certain cancers in young and middle-aged adults.
- Lead psychosocial interventional trials designed to improve the quality of life of patients.

What's next?

- Providing consultation for supportive care services for young adults receiving treatment outside of the AYA clinic who are within the UCMC system or at other sites.
- Expansion of supportive care services, including: in-house support groups; in-house activities like yoga and massage therapy; and coordination/integration with national AYA advocacy groups.

Classical Hematology Program

Focus: thrombotic & bleeding disorders, microangiopathies, Hereditary Hemorrhagic Telangiectasia (HHT), cytopenia, pancytopenia, non-malignant disorders of elevated blood counts, ITP, autoimmune hemolytic anemia, hemochromatosis, PNH, M-GUS, CHiP, genetic diseases like bone marrow failure states and WHIM syndrome, Sickle Cell Disease, a full diversity of hematologic disorders

Section Faculty: Kenneth Cohen, MD (Lead), Michael Drazer, MD, PhD, Chris Daugherty, MD, Michael Thirman, MD

Our team— composed of our four faculty physicians, an APN, and 3 nurses—sees a large panel of patients who come to us with a wide variety of hematologic conditions and diseases. Our expertise is both broad and deep, with the majority our work falling into the following disease groups:

- Thrombotic and hemostatic disorders
- Microangiopathies
- Sickle Cell Disease
- Hereditary Hemorrhagic Telangiectasia (HHT)
- Cytopenia and non-malignant disorders of elevated blood counts
- Genetic diseases, such as bone marrow failure states and WHIM

We work closely with our colleagues in interventional radiology, cardiology/pulmonary hypertension, and vascular surgery to meet the holistic healthcare needs of those in our care for thrombotic disorders. For our patients diagnosed with Sickle Cell Disease, we partner with collaborating providers in emergency medicine, pediatrics, internal medicine, and transfusion medicine. Our patients with HHT are cared for by a large multidisciplinary group of adult and pediatric physicians. We are proud of our ability to see patients across the spectrum of hematologic disorders and throughout a patient's disease experience.

Major accomplishments:

- The team has incorporated the HHT Center of Excellence (the only such center in Chicago) into the Classical Hematology Program, consisting of a multidisciplinary team that provides multifaceted longitudinal care
- We approach the care of sickle cell disease patients through standardizing comprehensive pain management, incorporating the newest therapeutics, and working with transplant colleagues to bring cell-based therapy to patients.

What's next?

- Expansion of the adult sickle cell program.
- Build out the clinical research infrastructure to support future clinical investigation and translational research in classical hematology.

Cutaneous Oncology Program

Focus: melanoma and non-melanoma skin cancers, TIL-therapy, neoadjuvant immunotherapies, biobank to study mechanisms of resistance, refractory melanomas, uveal melanoma

Section Faculty: Dan Olson, MD (Co-Lead), Thomas Gajewski, MD, PhD (Co-Lead)

Our Cutaneous Oncology Program focuses on the treatment melanoma and all other skin cancers, with a particular focus on immunotherapy-based approaches. Our program, both through translational and clinical investigation, seeks to improve the treatment of patients with resistance to standard immunotherapy. We do this through a robust portfolio of novel early-phase immunotherapy studies targeting mechanisms of resistance to standard immunotherapy. We also have a large biobank that helps us to study mechanisms of resistance, as well as running quite a few early-phase trials focused on patients with refractory melanomas. In coordination with the Cell Therapy program, our Cutaneous Oncology program is poised to be a national leader in the field of Tumor Infiltrating Lymphocyte Therapy (TIL-therapy), with new treatment options being approved by early 2024.

Major accomplishments:

- Led a clinical trial of PD1+CTLA4 antibodies and after PD1 antibody failure showing improved clinical outcomes over standard treatment, leading to NCCN-endorsement in clinical practice guidelines. These results originally appeared in the *Journal of Clinical Oncology* in 2021.
- Multiple fundamental discoveries in cancer immunotherapy including the definition of the T cell-inflamed/non-T cell inflamed tumor microenvironment and germline polymorphisms and composition of the gut microbiome on immunotherapy efficacy. This translational discovery and others have contributed to the testing of novel immunotherapy approaches such as IDO inhibitors, STING agonists, DGK-zeta inhibitors and others.
- Reported on our Phase II trial findings and tumor mutational spectrum analysis from Cabozantinib versus chemotherapy in metastatic uveal melanoma in *Clinical Cancer Research*.

What's next?

- Expansion of TIL and TCR-based cell therapy approaches to advanced melanoma.
- Adoption of neoadjuvant immunotherapies as a new paradigm for high-risk, resectable melanoma.
- Launch of investigator-initiated trials targeting specific mechanisms of resistance to standard immunotherapy based in foundational translational discoveries.
- Early adoption of emerging novel immunotherapies with the expectation to quickly offer RP1 + nivolumab, pending approval in July 2025.

Developmental Therapeutics Program

Focus: development of new therapeutics, development and testing of new drug and radiotherapy combinations, research trials, CAR T-cell therapy, tumor-infiltrating lymphocyte (TIL) therapies

Section Faculty: Gini Fleming, MD (Co-lead), Russell Szmulewitz, MD (Co-lead), Dan Olson, MD (Co-lead), Mark Ratain, MD, Randy Sweis MD (GU), Christina Bestvina MD (lung) Manik Amin , MD (GI), Ari Rosenberg, MD (Head and Neck)

Our Developmental Therapeutics Clinic focuses on offering treatments to patients with all tumor types for whom standard of care therapy is no longer effective and who are interested in participating in clinical research. We are exceedingly multidisciplinary work closely with our tumor type programs, and have lead investigators from the multiple tumor types (see above) with a particular interest in developmentl therapeutics. Our research trials encompass a wide variety of agents, including those which are injected, those which are given with radiotherapy, targeted agents, theranostics, and immunotherapy. We also work very closely with the cell therapy program to offer novel adoptive cell therapies, such as CAR and TCR T-cell and tumor-infiltrating lymphocyte (TIL) therapies for solid tumors. Through this work, we are able to offer treatment options that are cutting edge and often unavailable elsewhere. Our work with TIL, for example, has made us one of the first in the country to offer this treatment option for advanced melanoma.

Major accomplishments:

- Trials combining immunotherapy with radiotherapy have been published in a variety journals, including *Journal of Clinical Investigation*, *Journal of Clinical Oncology*, and *Clinical Cancer Research*
- Major participant in a trial of tumor infiltrating lymphocytes (TILS) for the treatment of cervical cancer.
- Ongoing collaboration on major grant projects to address disparities in research by increasing recruitment of minority patients to early phase clinical trials.
- Yearly developmental therapeutics symposium which highlights the expertise of the team while also inviting in colleague clinicians to advance learning in the developmental therapeutics space.
- Quarterly newsletter highlighting selected new trials

What's next?

- A continuing pipeline of trials testing antibody drug conjugates, bispecific T-cell engagers, theranostic agents and additional novel immunotherapies

Gastrointestinal Program

Focus: multidisciplinary team approach to treatment of GI cancers (neuroendocrine tumor program, liver tumor program, regional therapies program), innovative clinical trials (targeted therapies, immunotherapies, cellular therapies), team science (translational research collaborations)

Section Faculty: Chih-Yi (Andy) Liao, MD (Lead), Joseph Franses, MD, PhD (Director of Translational GI Cancer Research), Blase Polite, MD, Ardaman Shergill, MD, Manik Amin, MD, Janet Chin, MD, Anu Neerukonda, MD

The Gastrointestinal Oncology Program's unique approach includes a multidisciplinary-team based approach to treatment of these cancers, wherein patients may see a variety of specialists within the same clinic visit (for example, in our Liver Tumor Clinic, patients will see an oncologist, transplant hepatologist, surgeon and interventional radiologist in the same visit). This multidisciplinary approach streamlines patient care and improves outcomes. Our program has a rich clinical trial portfolio, including investigator-initiated trials, multidisciplinary disease team trials, and high-impact trials that change the clinical practice. This includes potentially paradigm-shifting clinical trials investigating laparoscopic HIPEC for metastatic gastric cancer with peritoneal disease, and ct-DNA guided treatment strategies for colorectal cancers. We also emphasize translational research collaborations, with exciting work in progress to better understand the tumor microenvironment in hepatocellular carcinoma.

Major accomplishments:

- The development of multidisciplinary neuroendocrine tumor program, liver tumor program, and regional therapies program. Our neuroendocrine program is ranked #1 in the Chicagoland area.
- Published research in *Cancer Discovery* about the incorporation of personalized targeted therapies for metastatic gastric cancer.
- Publication of our team's liver cancer trial data in the *International Journal of Radiation Oncology, Biology, and Physics* examining the safety and efficacy of combining SBRT and immunotherapy in patients with advanced hepatocellular carcinoma.
- Publication in *Endocrine-Related Cancer* of our translational research regarding MEN1 mutations in pancreatic neuroendocrine tumors, potentially leading to development of novel combination treatments.

What's next?

- Development of new multidisciplinary programs, including the Theranostics Program (capitalizing on our cyclotron facility and collaborating with Argonne National Laboratory), and a Comprehensive Colorectal Cancer Program to capture all facets of care for these patients
- Developing and bringing in clinical trials of new treatment modalities, including theranostics and cellular therapies
- Bolstering translational research in liver cancer, neuroendocrine tumors, and pancreatic cancer, funded by a SPORE Grant.

Genitourinary Multidisciplinary Disease Team

Focus: New GU therapies, biomarkers in: Prostate Cancer, Urothelial Cancer, Renal Cancer, Testicular Cancer

Section Faculty: Russell Szmulewitz, MD (MDT leader), Peter O'Donnell, MD, Akash Patnaik, MD, PhD, Randy Sweis, MD, Jonathan Trujillo, MD, Mohammad Atiq, MD

Multidisciplinary Team leaders: Scott Eggener, MD (Urology), Piyush Agarwal, MD (Urology), Stan Liauw, MD (Radiation Oncology), Sean Pitroda, MD (Urology), Glad Paner, MD (Pathology)

The Genitourinary Multidisciplinary Disease Team (GU MDT) is a multidisciplinary team dedicated to the treatment and prevention of a variety of GU cancers, with a special focus on prostate, urothelial, renal, and testicular cancers. Our unique approach to the clinical management of these malignancies includes a multi-modal team approach with physicians specializing in medical oncology, urology, radiation oncology, and pathology collaborating on the care of every patient regardless of the stage of their cancer diagnosis. Our goal is to provide every patient with the best options to manage their cancer, whether that means minimally invasive and/or nerve-sparing surgical procedures, cutting edge focal therapy for early state prostate cancer, high resolution imaging for diagnostics, or chemotherapies and immunotherapies. In addition we focus on anti-cancer treatment options to prevent the occurrence of malignancies before they begin.

Major Accomplishments:

- Co-leadership of the development of the first tyrosine kinase inhibitor for metastatic renal cell carcinoma, as shared in the *New England Journal of Medicine*.
- The team demonstrated, in an article in the *Journal of Clinical Oncology* the noninferiority of reduced dose abiraterone acetate with low-fat diet for metastatic prostate cancer, leading to a change in NCCN guidelines.
- The team co-led clinical trials in urothelial cancer, the results of which led to the FDA approval of enfortumab vedotin as the first line treatment for cisplatin-ineligible patients, as was shared in the *Journal of Clinical Oncology*.
- The team has led or been a key participant in many practice-changing clinical trials in prostate, urothelial, and renal cancers.

What's next?

- Investigator-initiated clinical trial of afatinib in genomically altered urothelial cancer.
- Investigator-initiated clinical trial of neoadjuvant dual AR and GR antagonism with enzalutamide/relacorilant in high risk localized prostate cancer.
- Co-leading a translational clinical trial of cabozantinib-nivolumab in metastatic prostate cancer.
- Incorporation of wearable biomarkers in new hormone-based clinical trials in medically vulnerable, geriatric patients with metastatic prostate cancer.
- Collection of patient-derived tumor material for translational research in prostate and urothelial cancers.

Leukemia Program

Focus: Leukemia, high-risk myeloid malignancies, adolescent and young adult population, hematologic malignancies cancer risk and prevention, clonal hematopoiesis

Section Faculty: Olatoyosi Odenike, MD (Program Director), Anand Patel, MD (Medical Director, Inpatient Leukemia Service), Christopher Daugherty, MD, Michael Drazer, MD, PhD, Adam Duvall, MD, MPH, Satyajit Kosuri, MD, Richard Larson, MD, Mariam Nawas, MD, Caner Saygin, MD, Wendy Stock, MD, Michael Thirman, MD

The Leukemia Program is at the forefront of the development of novel clinical and molecularly oriented trials for individuals with leukemia, myeloid malignancies, and other bone marrow disorders. These range from early-phase studies to large Phase III studies that have changed the standard of care. There is close collaboration and interdigitation with the transplant and cellular therapy program. Our team is also focused on the characterization hereditary genetic features that may predispose patients to developing leukemia and myelodysplasia. The leukemia program works very closely with our expert hematopathologists collaborating in the refinement of diagnostic and risk stratification criteria for these diseases.

Major accomplishments:

- An early-phase study of the menin inhibitor revumenib in patients with NPM1-mutated or KMT2A-re-arranged relapsed/refractory acute leukemia published in *Nature* that demonstrated very promising response rates in a population where standard therapies are not very effective.
- Investigated a novel approach to treating T-cell acute lymphoblastic leukemia (T-ALL) demonstrating that the combination of a BCL2/BCLxL inhibitor with the tyrosine kinase inhibitor dasatinib was effective at treating T-ALL in pre-clinical models, published in *Clinical Cancer Research*.
- A multidisciplinary study has identified a potential predictor marker of response to the drug azacitidine in acute myeloid leukemia (AML). Using patient samples from an investigator-initiated study, we investigated azacitidine combined with chemotherapy, changes in 5-hydroxymethylcytosine signature were associated with overall survival, published in *Advanced Science*.
- A multidisciplinary study investigated the dietary nutrient trans-vaccenic acid and demonstrated its role in promoting T-cell functioning. This finding has potential applications to the use of leukemia treatments such as CAR-T cells and bi-specific antibodies; the findings were published in *Nature*.
- Participation in the 2022 European LeukemiaNet (ELN) expert panel which develops consensus recommendations for the diagnosis, risk stratification, and management of AML and 2022 International Consensus Criteria (ICC) to update and refine the diagnosis of acute leukemia and myeloid malignancies.

What's next?

- An ongoing Phase II clinical trial focused on the use of a chemotherapy-free induction regimen incorporating dasatinib and inotuzumab in Philadelphia-Chromosome Positive acute lymphoblastic leukemia.
- An ongoing, early-phase study investigating the use of the MEK inhibitor selumetinib in combination with azacitidine for a variety of myeloid malignancies including advanced myelofibrosis, myelodysplastic syndrome, and myelodysplastic syndrome/myeloproliferative neoplasm overlap diseases.
- An investigator-initiated clinical trial focused a novel combination of targeted therapy in T-cell acute lymphoblastic leukemia funded by the Leukemia Lymphoma Society.
- An investigator-initiated clinical trial focused on a combination of JAK inhibition and IDH inhibition in IDH-mutated advanced-phase myeloproliferative neoplasms based on previous work demonstrating the effectiveness of IDH inhibition.

Lymphoma Program

Focus: Lymphoma, high-risk lymphoma, adolescent and young adult population

Section Faculty: Justin Kline, MD (Program Director), Michael Bishop, MD, Adam Duvall, MD, MPH, Peter Riedell, MD, Sonali Smith, MD, Ken Cohen, MD

The Lymphoma Program is at the forefront offering breakthrough care as the first medical center in IL to offer CAR-T cell therapy and providing care for a variety of fast-grown lymphoma subtypes through the High-Risk Lymphoma Clinic. Additionally, our team is focusing on prevention, diagnosing and treating lymphoma through the collection and storing donated biospecimens at the Hoogland Lymphoma Biobank. By examining these specimens, the lymphoma team is evaluating how lifestyle, occupation, environment and genes affect lymphoma. The clinical lymphoma program also works very closely with our expert hematopathologists in identifying lymphoma and pinpointing its different subtypes which are difficult to diagnose. Our hematopathologists also review pathology on complex lymphoma cases and other blood disorders to ensure a proper diagnosis is confirmed and refined.

Major accomplishments:

- We published in *Journal of Clinical Oncology* about our work creating a gene signature that predicted response among diffuse large B cell lymphoma patients to Bruton's tyrosine kinase inhibitors.
- Our faculty have been involved in numerous CAR-T cell therapy clinical trials in lymphoma with practice changing implications. This includes institutional efforts on a phase II study of tisagenlecleucel for the treatment of follicular lymphoma which led to FDA approval of this agent. Our work in this study has been published in *Nature Medicine*.
- We have led the University of Chicago's efforts evaluating lisocabtagene maraleucel in the treatment of diffuse large B-cell lymphoma in patients ineligible for stem cell transplant due to co-moribidites or advanced age. Based on the results of this trial, lisocabtagene maraleucel was granted second-line FDA approval in diffuse large B-cell lymphoma. The results of this work were published in *Lancet Oncology.*
- An international, randomized, phase III study of tisagenlecleucel versus standard of care in relapsed/refractory diffuse large B cell lymphoma, with results published in *NEJM*.
- Dr. Smith continues to play a major role in national lymphoma societies and cooperative groups. She is immediate past chair of the Lymphoma Research Foundation Scientific Advisory Committee and is co-chair of the Southwestern Oncology Group (SWOG) lymphoma committee

What's next?

- ZUMA-23 which is a trial comparing standard of care chemoimmunotherapy to axicabtagene ciloleucel CAR T-cell therapy in the front-line setting for diffuse large B-cell lymphoma

Mesothelioma Program

Focus: Multidisciplinary care of pleural, peritoneal, tunica vaginalis and pericardial mesothelioma, innovative clinical trials, cancer genetics

Section faculty: Hedy Lee Kindler, MD (Program Director), Michael Drazer, MD, PhD (Cancer Genetics)

Collaborating faculty: Darren Bryan, MD (Associate Director, Thoracic Surgery), Mecker Möller, MD (Peritoneal Surgery), Scott Eggner, MD (Genitourinary Surgery), Aditya Juloori, MD (Radiation), Aliya Husain, MD (Pathology), Monica Malec, MD (Supportive Oncology), Samuel Armato, PhD (Medical Physica), Christopher Straus, MD (Radiology)

Our Mesothelioma Program is internationally recognized as a center for clinical excellence in this rare and heterogenous disease, attracting patients from across the country and around the globe for our expert multidisciplinary care and innovative clinical trials. We are international leaders in defining standards in treatment, staging, tumor measurement, germline testing, and pathologic diagnosis. Our highly collaborative multidisciplinary team includes experts from medical, surgical, and radiation oncology, radiology, pathology, supportive care and cancer genetics who focus on patients with pleural, peritoneal, tunica vaginalis and pericardial mesothelioma. Our significant expertise in this rare disease enables us to tailor our treatments to the unique characteristics of the individual patient. Our robust biobank includes clinical, imaging, and genomic data which informs our clincal and translational research.

Major accomplishments:

- This program is the international leader in defining diagnostic and treatment standards, including leading the ASCO guideline on the treatment of pleural mesothelioma, and developing the modified RECIST 1.1 criteria for the precise measurement of this irreguluarly shaped tumor.
- This program has built an innovative clinical trials program that is one of the largest in the world for this disease. This ensures that the mesothelioma program has been a leader in the evaluation of now standard agents such as pemetrexed and immunotherapies, and are now at the cutting edge of evaluating novel targeted therapies for this disease.
- The identification that 12% of mesothelioma patients have a germline mutation that increases the risk of mesothelioma in patients with asbestos exposure. This was published in the *Journal of Clinical Oncology*.

What's next?

- Leading the update of the ASCO guidelines on pleural mesothelioma, focusing on immunotherapy, surgery, and germline genetics.
- Innovative clinical trials, including:
    - Precision medicine trials against targets such as BAP1, NF2 and MTAP.
    - Cellular therapy trials for mesothelioma.
    - Multimodality surgical trials for peritoneal mesothelioma, incorporating normothermic intraperitoneal chemotherapy (NIPEC) and pressurized intraperitoneal aerosolized chemotherapy (PIPAC).

Multidisciplinary Breast Cancer Program

Focus: multidisciplinary and holistic cancer care, personalized medicine, health disparities & reducing inequities, collaboration with local partners, AI & machine learning

Section Faculty: Rita Nanda, MD (Director of Breast Oncology), Nan Chen MD, Gini Fleming MD, Olwen Hahn MD, Frederick Howard MD, Sudha Yarlagadda MD

Collaborating Faculty: Breast Surgical Oncology: Cristina O'Donoghue (Surgical Director, Breast Center), Betty Fan, DO, Nora Jaskowiak, MD, Sarah Shubeck, MD; Radiation Oncology: Steven Chmura, MD, PhD, Yasmin Hasan MD; Reconstructive Surgery: David Chang, MD (Chief of Plastic and Reconstructive Surgery), Maureen Beederman, MD, Summer Hanson, MD, PhD, Mark Tan, MD

The University of Chicago Multidisciplinary Breast Cancer Program is a nationally recognized team of physicians dedicated to breast cancer care and research. This program brings together experts from medical oncology, surgical oncology, radiation oncology, radiology, plastic and reconstructive surgery, supportive oncology, and pathology to provide comprehensive and personalized care from diagnosis to survivorship. The program's approach is rooted in leading-edge research and innovative treatments, ensuring that patients receive the most advanced and tailored interventions available. With a focus on clinical excellence, the University of Chicago Multidisciplinary Breast Cancer Program is at the forefront of advancing our understanding of breast cancer and improving outcomes for those affected by this challenging disease. This program focuses on a holistic and collaborative approach to breast cancer care, where every aspect of a patient's journey is considered and addressed with the utmost expertise and compassion.

Major Accomplishments:

- Led one of the first randomized studies demonstrating the effectiveness of immunotherapy for early-stage, high-risk breast cancer, published in *JAMA Oncology*.
- Led that first study demonstrating the effectiveness of immunotherapy for metastatic triple-negative breast cancer, published in *Journal of Clinical Oncology*.
- Co-led the randomized phase III trials that demonstrated the effectiveness of ovarian suppression in premenopausal women with aggressive, hormone receptor-positive breast cancer, published in the *New England Journal of Medicine*.
- Conducted one of the largest scale analyses of the prognostic implications and chemotherapy sensitivity in HER2-low breast cancer, published in *JAMA Oncology*.

What's next?

- A trial comparing androgen receptor blockade with enzalutamide or enzalutamide plus mifepristone to chemotherapy in metastatic androgen receptor-positive, triple-negative breast cancer.
- Evaluation of the most promising novel therapies for early-stage breast cancer through the I-SPY2 clinical trial.
- Novel immunotherapies for early and metastatic breast cancer, including:
    - ALX148, an anti-CD47 myeloid checkpoint inhibitor, in combination with trastuzumab deruxtecan for HER2-low and HER2-positive breast cancer (PRE-I-SPY)
    - A vaccine therapy adagloxad simolenin in GloboH positive triple-negative breast cancer with residual disease after neoadjuvant therapy (GLORIA)
    - Novel combinations of the immunotherapy drug avelumab in metastatic, triple-negative breast cancer (InCITe)
- A study evaluating blood-based methylation biomarkers to better predict response to therapy in both early stage and metastatic breast cancer.
- Spearheading the Chicago Breast Cancer Research Consortium, a network focused on eradicating breast cancer disparities in the Chicagoland area.

Multidisciplinary Head and Neck Program

Focus: personalized medicine, treatment optimization, artificial intelligence applications, novel therapeutics, tissue- & blood-based biomarkers

Section Faculty: Alexander Pearson, MD (Program Director), Ari Rosenberg, MD (Clinical Trials Lead), Everett Vokes, MD, Noura Choudhury, MD

The Multidisciplinary Head & Neck Program is unique in its comprehensive approach to cancer care, with a team that includes experts in medical oncology, radiation oncology, and head/neck surgery. Our medical and surgical care is complemented by an experienced team of supportive oncology professionals who provide state-of-the-art care to patients in our high-volume clinic. In addition to clinical care, our program has a substantial national impact in the development of improved treatment strategies for head and neck cancer. This includes multiple trials evaluating response-adapted treatment, in which an individual patient's response to systemic therapies drives personalized care planning, including the incorporation of novel and biomarker-driven therapeutic approaches. Our program continues to investigate innovative multidisciplinary treatments, such as organ-preservation "non-surgical" treatment for advanced tongue cancer. We are continually investigating novel drugs in the treatment of recurrent and metastatic head and neck cancer, in addition to advanced salivary, thyroid, and non-melanoma cutaneous malignancies; our treatment options include novel immunotherapies, targeted treatments, antibody-drug conjugates, and novel radiosensitizers, among others. Our portfolio of high-impact prospective clinical trials is paired with robust translational research collaboration with many Section-led lab groups, focusing on projects such as cancer genomics, tissue- and blood-based biomarkers, machine learning applications, and radiomics.

Major Accomplishments:

- A paper about the "Optima" trial, focused on response-adaptive de-escalation in HPV+ oropharynx cancer published in *Annals of Oncology*.
- An ASCO 2022 publication under review about neoadjuvant nivolumab/chemotherapy and response-adaption in HPV-associated disease.
- An oral presentation at *ASCO 2023* about on our "DEPEND" trial which examines induction nivolumab/chemotherapy with adapted chemo-radiation in locally advanced HPV negative head and neck cancer.
- A paper about curative intent reirradiation in locally recurrent head and neck cancer, published in the *British Journal of Cancer*.
- A paper in *Annals of Oncology* about novel immunomodulatory combination therapy in advanced thyroid cancer.

What's next?

Ongoing, investigator-initiated clinical trials, including:

- A novel de-escalation clinical trial, "TARGET HPV," for HPV+ oropharyngeal cancer, in which patients receive neoadjuvant treatment with a novel HPV-specific viral immunotherapy and chemotherapy followed by response-adaptive de-escalated minimally-invasive surgery or de-escalated radiation.
- The "SYNERGY" trial for patients with recurrent and/or metastatic head and neck cancer in which circulating tumor DNA is used to guide the best and personalized treatment for a given patient.
- The "PaRTTi" study, an innovative multi-modal reirradiation for recurrent head and neck cancer and incorporating immunotherapy and PARP inhibition.
- A trial for patients who are cisplatin-ineligible/vulnerable, evaluating xevinapant with carboplatin, paclitaxel, and radiotherapy.

Myeloma Program

Focus: improving treatment outcomes in newly diagnosed myeloma, incorporating immunotherapies (i.e.: CAR-T, cellular therapy, bi-specific antibodies), measurable residual disease, high-risk multiple myeloma

Section Faculty: Andrzej Jakubowiak, MD, PhD (Lead), Benjamin Derman, MD, Jennifer Cooperrider, MD, Michael Bishop, MD

Our Myeloma Program focuses on improving the treatment outcomes of patients with newly diagnosed myeloma, in particular those with high-risk multiple myeloma. We have a strong portfolio of investigator-initiated trial for patients at every stage of the disease process. These trials include: the development of novel quadruplet treatment combinations; the utilization of innovative strategies for the measurement of measurable residual disease (MRD) using bone marrow-based measurement of MRD by next generation sequencing; and blood-based liquid biopsies using mass spectrometry and next generation sequencing. We have been and remain actively involved in the development of several cellular therapies, both in advanced and refractory multiple myeloma and, more recently, in newly diagnosed myeloma. Our research efforts have yielded important changes in clinical practice, including early access to all approved CAR-Ts and bi-specific antibody treatments.

Major accomplishments:

- A paper published in *JAMA Oncology* which highlights our work on a Phase II study examining the impact of a treatment regimen of Elotuzumab with Carfilzomib, Lenalidomide, and Dexamethasone on MRD in those who were newly diagnosed with multiple myeloma.
- The publication of our interim analysis of our Phase III ATLAS trial in *Lancet Oncology*.
- A paper published in *Blood Advances* showcasing our Phase I and II study of Dara-KPd in the treatment of relapsed multiple myeloma.
- Publication of our CARTITUDE-1 study in *Lancet* demonstrating the safety and clinical efficacy of cilta-cel in patients diagnosed with refractory or or relapsed multiple myeloma.

What's next?

- Investigating the incorporation of cellular CAR-T therapy (using Johnson & Johnson Cilta-Cel therapy) in those with newly diagnosed multiple myeloma, including CARTITUDE-6 (CAR-T therapy v autologous stem cell transplant) and Phase I trial with Novartis PHE885
- Further development of measurement of MRD, including blood-based MRD and their potential use in guiding decision-making.
- Developing new treatment strategies for patients who have relapsed after CAR-T therapy including an investigator-initiated trial of Belantamab mafodotin and KPd, as well as new CAR-T constructs for alternate targets.
- Identifying markers that may predict risk of secondary hematologic malignancies.

Neuroendocrine Tumor (NETs) Program

Focus: NETs of the GI tract, pancreas, lung and thymus, pituitary gland; medullary thyroid cancer; pheochromocytomas and paragangliomas; some rare genetic disorders such as Von Hippel-Lindau and Multiple Neoplasia Type 1 and 2

Section Faculty: Chih-Yi Liao, MD; Blase Polite, MD

Collaborating Faculty: Xavier M. Keutgen, MD, FACS; Daniel Appelbaum, MD; Yonglin Pu, MD, PhD; Osmanuddin Ahmed, MD; Thuong Van Ha, MD; Carla Harmath, MD; Aytekin Oto, MD, MBA; Nicole Cipriani, MD; Namrata Setia, MD

The fully integrated Neuroendocrine Tumor (NETs) Program is a leader in NET patient care with dedicated specialists across surgery, oncology, interventional radiology, nuclear medicine, and pathology. Our program offers the only multidisciplinary NET clinic (surgery/oncology) and the only NET-specific tumor board in the Chicagoland region. We offer advanced surgical techniques and use leading-edge technology to successfully treat these tumors. As a leader in Peptide Receptor Radionuclide Therapy (PRRT), we have the only medical cyclotron in the region for creating novel radiotracers for NETs, with the aim of developing a program that will help create next-generation PRRT treatments in-house. We utilize molecular profiling of NETs to allow for a personalized approach using therapies that work best on each specific patient's tumor. We have researchers conducting the latest studies on NETs both in the laboratory and clinic. Recently, we were one of few institutions were selected to collaborate on an important NETs alpha particle therapy trial that will be open for accrual soon. The goal of this study is to evaluate the safety, tolerability, pharmacokinetics, and preliminary efficacy of [212Pb]VMT-α-NET in subjects with SSTR2 expressing advanced unresectable or metastatic neuroendocrine tumors. This study will further the development of treatment options for patients with positive neuroendocrine tumors.

Major accomplishments:

- First to offer neoadjuvant PRRT for pancreatic NETs and first to study DNA repair in tumors undergoing PRRT.
- Due to the strong relationship with patient advocacy groups, UChicago is the only hospital in the region to host the annual Neuroendocrine Tumor Research Foundation (NETRF) patient symposium and the North American Neuroendocrine Tumor Society (NANETS) regional conference.

What's next?

- NETs alpha particle therapy study to open soon.
- Collaborating with Novartis to discuss areas of joint research plans.

Preventive Oncology Program

Focus: personalized medicine, imaging/ screening, shared-decision making

Section Faculty: Olufunmilayo Olopade, MD, FACP (Program Director)

Collaborating Faculty: Lorraine Canham, MD, Sonia Kupfer, MD, Hiroyuke Abe, MD, PhD, Kirti Kulkarni, MD

The Preventive Oncology Program is forward-thinking in its approach to patient care, centering on a paradigm shift from the one-size-fits-all method of screening to personalized care. Our clinic emphasizes the importance of shared-decision making, focusing on medical decisions that best suit our patients' lifestyle and needs. We offer a clinical trial highlighting intensive radiologic screening for early detection of breast cancer for patients who are at high hereditary risk, as an alternative to prophylactic mastectomy. We seek to investigate the clinical effectiveness of a biannual abbreviated MRI protocol with ultrafast DCE technique and establish a patient database of serial images to develop image markers integrated with biomarkers for breast cancer risk for future studies. Likewise, as we aim to improve risk-stratified recommendations for breast cancer prevention and early detection, we are a proud study partner of the national trial Women Informed to Screen Depending on Measures of Risk (WISDOM) study. As part of our efforts in global oncology, we are partnering with oncologists in Nigeria to support research of the efficacy and safety of optimal neoadjuvant to adjuvant anti-HER2-based therapy in Nigerian women with HER2 positive breast cancer and the potential of using -omic markers as a surrogate of chemotherapy resistance in triple negative breast cancer among Nigerian women.

Major Accomplishments:

- Publication of an article in *Radiology: Artificial Intelligence* about the external evaluation of a mammography-based deep learning tool for breast cancer prediction in a dataset from a high-risk population.
- Cohort study of patients with breast cancer, published in *JAMA*, that showed racial disparities in response to NACT were associated with disparities in survival and varied across different breast cancer subtypes.
- Several papers have been published in *Human Molecular Genetics*. One paper talked about the results of a study that suggests that TNFSF10 plays an important role in the regulation of antiviral immune responses in TNBC, and the expression is in part regulated by a genetic variant associated with breast cancer in Black women. A second paper talked about the use of polygenic risk scores for the prediction of breast cancer risk in women of African ancestry.
- Work on the relationship between physical activity during adolescence and early-adulthood and ovarian cancer among women with a BRCA1 or BRCA2 mutation was published in *Breast Cancer Research and Treatment*.

What's next?

- Expand MRI study (CAPS) nationally to test whether it is clinically effective, adaptable, and can scale to optimize intensive surveillance for high-risk women.
- Partner with primary care to use liquid biopsy to better understand markers for risk and early detection.
- Join an Alliance study offering Denosumab to *BRCA1* carriers as a form of chemoprevention.

Sarcoma Program

Focus: management and treatment of patients with a wide range of advanced sarcomas, pain management, bone cancers, soft tissue sarcomas

Section Faculty: Dan Olson, MD (Lead), Janet Chin, MD

Collaborating Faculty: Rex Haydon, MD (Ortho Surgery Co-Lead), Tessa Balach, MD (Ortho Surgery Co-lead), Mecker Moller, MD (Surgical Oncology), Phil Connell, MD (Radiation Oncology), Peter Pytel, MD (Pathology), Nicole Cipriani, MD (Pathology)

Our Sarcoma Program is a multidisciplinary program, focused on the treatment of patients with advanced musculoskeletal, bone, and other sarcomas. We focus on the multidisciplinary management of patients with these diagnoses, based on the unique need for multi-specialty healthcare for our diverse patient panel. Our team includes medical oncology, orthopedic surgery, surgical oncology, interventional radiology, and radiation oncology, all working together to ensure the best outcomes for those with this often-aggressive form of cancer. In our labs, our scientists are examining new approaches to bone regeneration and in honing in on the genetic bases for these cancers, while in our clinic our team's robust portfolio of treatment options are often used in tandem to ensure the best clinical results for our patients; these include limb-sparing and computer-assisted surgical procedures, chemotherapy, radiation, bone implants for reconstruction, and innovations through clinical trials, including Phase I trials. We also specialize in pain management and quality of life during treatment.

Major accomplishments:

- Integration of patients into our large panel of early-phase trials within the Developmental Therapeutics program.
- Participation in multiple cooperative group, sarcoma-focused clinical trials, including Phase I trials.
- A publication in the *Journal of Bone and Joint Surgery* about the use of multidisciplinary care to treat pathologic fractures.

What's next?

- Offering afami-cel, a novel TCR T-cell based cell therapy treatment, to be approved this coming year for the treatment of synovial sarcoma and myxoid round cell liposarcomas.
- Providing treatment for desmoid tumors through a newly FDA-approved systemic treatment option. This work is part of a cancer risk clinic for patients who have a diagnosis of heritable cancer syndrome FAP, which has resulted in many referrals for patients with desmoid tumors.

Stem Cell Transplant & Cellular Therapy Program

Focus: Hematopoietic stem cell transplant & cellular therapy, hematologic malignancies, MDS/MPN, aplastic anemia, CAR-T, TIL therapy, TCR engineered therapy, solid tumor cellular therapy, gene therapy, Transplant Optimization Program (TOP), geriatric oncology, graft-versus-host-disease (GVHD)

Section Faculty: Michael Bishop, MD (Lead), Satyajit Kosuri, MD, Benjamin Derman, MD, Adam DuVall, MD, MPH, Andrzej Jakubowiak, MD, PhD, Justin Kline, MD, Richard Larson, MD, Mariam Nawas, MD, Daniel Olson, MD, Peter Riedell, MD, Sonali Smith, MD, Wendy Stock, MD, Greg Roloff, MD

Collaborating Faculty: James LaBelle, MD, Saara Kaviany, DO, John Cunningham, MD

The Adult and Pediatric Stem Cell Transplant and Cellular Therapy Program is at the forefront of hematopoietic stem cell transplant, cell therapy clinical trials, and new and emerging therapies. These treatments range from new conditioning regimens, GVHD prevention and treatment, novel donors, solid tumor cell therapy, gene therapies, and cell-based therapies for non-oncologic indications such as autoimmune diseases. We utilize autologous and allogeneic stem cell transplant, CAR-T, CAR NK, TCR, TIL, and gene therapies, as well as alternative donors, including haplo-identical and mismatched unrelated donors. Other trials have included: new conditioning regimens such as total marrow irradiation, or novel GVHD prophylaxis such as abatacept, post-transplant cyclophosphamide, and clinical trials utilizing T-regs and other novel agents. We also have a vareity of clinics that work in with specific populations, including: our GVHD clinic for adult allogeneic stem cell transplant; the TOP Program for geriatric and high-risk patients following transplant; and our Solid Tumor Cell Therapy Program which uses many innovative cell therapy products, including NK cells, TILs, and TCRs. Because of our program's heavy involvement with many cell therapy clinical trials, we are often chosen as one of the earliest sites for newly FDA-approved cell and gene therapies.

Major accomplishments:

- Several pieces published in *Blood Advances*, including: one piece about work on total marrow irradiation in patients with hematologic malignancies undergoing a second allogeneic stem cell transplant; a second piece on a multicenter trial about patients who did not achieve remission from CAR-T therapy; and a third piece about treatment for patients who relapsed following allogeneic stem cell transplant.
- A publication in *Transplantation and Cellular Therapy* about the multi-site ADMIRAL trial that determined patients with FLT-3 mutated AML could successfully be treated with gilteritinib following an allogeneic stem cell transplant.

What's next?

- A tri-car protocol that uses anti-CD19/CD20/CD22 CAR T-cells that are manufactured with duvelisib for the treatment of relapsed/refractory mature B-cell lymphoma after prior CD19 CAR T-cell failure
- Retrospective research using our internal Cell Therapy Biobank.
- Collaborative projects with physical therapy on the impact of frailty assessed using physical therapy assessment tools on post CAR-T outcomes and cardiology to delineate the outcomes of CAR-T recipients with impaired left ventricular ejection fraction
- Continuing leadership of the Cell Therapy Consortium.

Thoracic Oncology Program

Focus: non-small cell lung cancer, small cell lung cancer, immunotherapy, targeted agents, thymic epithelial tumors, digital pathology

Section Faculty: Marina Chiara Garassino, MD (Lead), Christine Bestvina, MD, Everett Vokes, MD, Noura Choudhury, MD

Lung cancer, a leading cause of cancer deaths, has seen treatment progress. Specific gene changes, called "driver" alterations in non-small cell lung cancer (NSCLC), are targeted with therapies, and immunotherapy enhances the immune system's tumor-fighting capabilities. Predicting immunotherapy success is aided by assessing PD-L1 expression. Patients with intact target genes and PD-L1 >50% respond well to initial immunotherapy, possibly combined with chemotherapy. Artificial Intelligence (AI) and Machine Learning (ML) are harnessed to personalize treatment by analyzing diverse data sources for response prediction. The I3LUNG project utilizes AI/ML models to create a medical tool predicting immunotherapy outcomes in NSCLC, aiming to refine tailored treatment decisions and potentially revolutionize lung cancer therapy.

Major accomplishments:

- A paper in *Clinical Lung Cancer* describing a study to promote individualized treatment in aNSCLC, with the goals of improving survival and quality of life, minimizing or preventing undue toxicity, and promoting efficient resource allocation. The final objective of the project is the construction of a novel, integrated, AI-assisted data storage and elaboration platform to guide IO administration in aNSCLC, ensuring easy access and cost-effective use by healthcare providers and patients.
- A collaborative paper in *Frontier Oncology* showing the development of a ML algorithm based on real-world data, explained by SHAP techniques, and able to accurately predict the efficacy of immunotherapy in sets of NSCLC patients.
- A collaborative paper in *NPJ Precision Oncology* demonstrating the use of synthetic histology for augmenting pathologist-in-training education, showing that these intuitive visualizations can reinforce and improve understanding of histologic manifestations of tumor biology.

What's next?

- Using homegrown models to build and validate a deep learning algorithm to assist with accurate identification and histopathologic characterization of Thymic Epithelial Tumors (TETs). The long-term goal is to validate an artificial intelligence (AI) diagnostic tool to help improve diagnostic accuracy and consistency for these challenging tumors.
- Collaborating with colleagues in Istituto Nazionale dei Tumori (Milan, Italy) to deep-characterize the Tertial Lymphoid Structures (TLS) microenvironment by single cell, spatial transcriptomic analysis, and digital pathology with artificial intelligence algorithms in NSCLC patient after neoadjuvant chemo-ICI treatment.
- Collaborating with colleagues in the Pathology department in developing and characterize organoids model to study metabolism in LKB1-mutant tumors in NSCLC patients.

Basic & Translational Research Programs

Our Section prides itself on a longstanding tradition of excellence in cancer research, spanning the spectrum of basic research to translational research and clinical trials. We take a "team science" approach, where collaboration amongst and between teams is encouraged and facilitated. Led by our expert faculty, research efforts are supported by a dedicated team of staff scientists, graduate students, post-doctoral scholars, fellows, data analysts, research laboratory managers, and technicians.

Building on this strong foundation, our faculty possesses deep expertise across a broad range of research areas, including cancer metabolomics, tumor immunology, and cellular therapy. This wealth of expertise is fundamental to the collaborative spirit of our team science model, fostering innovative and diverse partnerships. Our partnerships extend across several leading basic and translational research entities, including the Ben May Department for Cancer Research, the University of Chicago Comprehensive Cancer Center (UCCCC), the National Cancer Institute (NCI), and the Pritzker School of Molecular Engineering (PME).

Our basic and translational research spans a variety of fields, including:

- Developmental biology and genetics
- Cellular biology (focusing on intracellular pathways and signal transduction)
- Drug resistance and the development of new therapeutics
- Cell Therapy
- Tumor Immunology
- Genetics
- Metabolomics
- Transplant biology
- Protein targeting
- Artificial intelligence
- Computational Oncology

Much of our basic research carries over into translational research and clinical studies. With our patient-facing research, the Section believes in a multimodal, multidisciplinary approach that follows a bench-to-bedside model, integrating both laboratory and clinical research in pursuit of the best treatment and care options available.

Our robust research activities receive support from several prestigious sources, including the National Institutes of Health (NIH) and various non-federal granting agencies like the American Cancer Society. Research training is bolstered by an NCI-sponsored training grant, which supports both MD and MD/PhD post-doctoral investigators. Currently, the Section manages nearly $25 million in federally-funded grants, non-federally funded research projects, philanthropic donations, and clinical trials.

Chen Lab

Focus: cancer metabolism, metabolomics, immunology, signal transduction, chemical biology, therapy development

PI: Jing Chen, PhD

Our lab has a long-term interest in elucidating the signaling links between metabolism and cancer for a better understanding of cancer metabolism and improved clinical outcomes. Two major research foci of this lab include (1) to determine both metabolic and signaling functions of intracellular metabolites and circulating "blood chemicals", which influence tumorigenesis and tumor progression, and responses to anti-cancer therapies including chemotherapy and immunotherapy; and (2) to decipher mechanistic basis underlying the pathogenic links between diets and particular oncogenic mutations by exploring the pro- and anti-tumor effects of diet-derived substances on tumors with specific genetic backgrounds. Our hypothesis is that the circulating "blood chemicals" including diet-derived nutrients have a vital, and specific, influence on anti-tumor immunity; uncovering the relevant blood chemicals and underlying mechanisms will provide the foundation for new clinical treatments to control tumor growth and eliminate tumor invasion and metastasis.

Major accomplishments:

- Publication of a paper in *Nature* about a blood nutrient compound library-based screening approach to demonstrate that dietary trans-vaccenic acid (TVA) directly promotes effector CD8+ T cell function and anti-tumor immunity in vivo. These findings reveal that diet-derived TVA represents a mechanism for host-extrinsic reprogramming of CD8+ T cells as opposed to the intrahost gut microbiota-derived short-chain fatty acids. TVA thus has translational potential for the treatment of tumors.
- Two papers have been published in *Molecular Cell*. One paper demonstrates that intracellular PLA2G7 is selectively important for cell proliferation and tumor growth potential of melanoma cells expressing mutant NRAS, but not cells expressing BRAF V600E and shows that PLA2G7 and Lyso-PAF exhibit intracellular signaling functions as key elements of RAS-RAF1 signaling. The second paper shows that mutant isocitrate dehydrogenase (IDH) 1 and 2 play a pathogenic role in cancers, including acute myeloid leukemia (AML), by producing oncometabolite 2-hydroxyglutarate (2-HG).
- A paper that elucidates the signaling basis underlying reductive carboxylation in cancer cells and was published in *Cell Chemical Biology*.

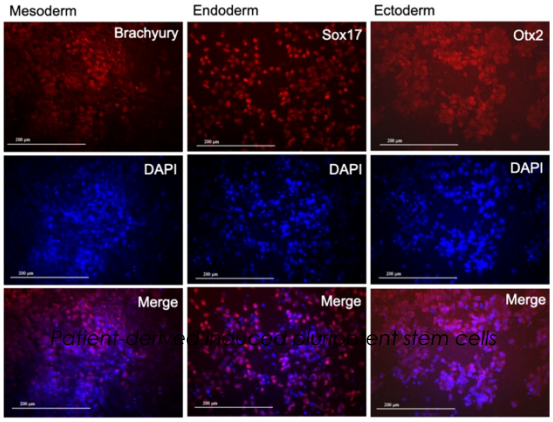
What's next?

- Recent research focuses on how diet/nutrients affect anti-tumor immunity, i.e., the immune system's responses against tumorigenesis, tumor growth, and metastasis. The hypothesis is that the circulating "blood chemicals" including diet-derived nutrients have a vital, and specific, influence on anti-tumor immunity; uncovering the relevant blood chemicals and underlying mechanisms will provide the foundation for new clinical treatments to control tumor growth and eliminate tumor invasion and metastasis.

Drazer Lab

Focus: Human genetics, stem cell biology, hereditary blood cancers, hereditary cancer syndromes

PI: Michael Drazer, MD, PhD



Patient-derived induced pluripotent stem cells

We are focused on discovering the mechanisms of hereditary blood and cancer syndromes, with the understanding that these mechanisms may inform the treatment of both hereditary syndromes and cancers more broadly. Our team uses novel gene editing techniques (BE4max base editing, ABEmax base editing, Cas9 editing) to engineer stem cell models of these syndromes – which we refer to as patient "avatars" since they are genetically identical to the patients we care for in the clinic. We are a bioinformatics-heavy group that uses a variety of genomic and transcriptomic techniques to better understand these disorders, with a particular emphasis on optimizing bioinformatics pipelines to improve the diagnosis of these syndromes. We are one of the only groups in the world with this research focus that is also linked to a clinic dedicated to the care of people with hereditary blood and cancer syndromes, which increases the translational impact of our work.

Major accomplishments:

- A paper in *JAMA Network Open* about how research-based bioinformatics pipelines were "reverse engineered" to better detect mesothelioma patients with hereditary cancer syndromes. This paper will help to build the case for universal germline testing in meso (which will be included in the upcoming ASCO Clinical Guidelines).
- A collaborative paper in *Blood* showing that hereditary blood cancer syndromes are much more common than previously recognized in stem cell transplant patients - this has important implications for the way donor evaluations are performed in the clinic.
- Collaboration with an Australian group and the NIH to publish a paper in *Blood Advances* that was the first paper to demonstrate that clonal hematopoiesis is common in *GATA2* and *RUNX1* germline mutation carriers (two hereditary blood cancer syndromes).

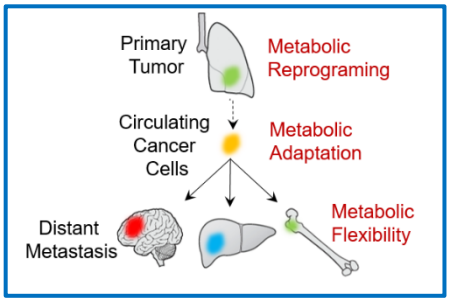
What's next?

- Using homegrown models to develop treatments to prevent leukemia formation in people with hereditary blood cancer syndromes – previously developed stem cell models form the backbone of this effort.
- Developing machine learning models that incorporate genomics data, improving our ability to predict prognosis in patients with blood cancers.
- Collaborating with colleagues in the Department of Radiology to use artificial intelligence-informed radiomics (their work) with contemporary circulating tumor DNA genomics (our work) to develop non-invasive methods of determining tissue histology in patients with mesothelioma.

Faubert Lab

Focus: Cancer Metabolism, Metastasis, Lung Cancer, Tumor Microenvironment

PI: Brandon Faubert, PhD



Our lab is driven to understand how altered metabolism shapes the trajectory of cancer. By dissecting the metabolic programs that drive cancer cell metastasis, we aim to uncover critical nodes that can be targeted to improve patient outcomes. Our efforts are centered on identifying tumor metabolic phenotypes directly in patients, before interrogating the underlying biological mechanisms in preclinical mouse and tumor models. We use a robust toolkit to investigate these metabolic networks, including patient-derived tumor models, isotope-labeled metabolic tracers, high-resolution mass spectrometry, and flux analysis. Primary research directions of the lab include a) understanding how metastatic cancer cells adapt metabolic programs to survive in different organ environments, and b) developing metabolism-based strategies to sensitize cancer cells to chemotherapy.

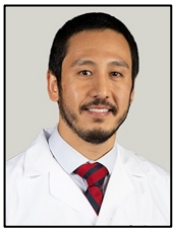
Major accomplishments:

- A paper in *Cancer Discovery* where we studied tumor metabolism directly in patients to discover how altered cancer metabolism predicts poor outcomes. Blocking this pathway suppresses the metastasis of human NSCLC cells in mice.
- A pair of reviews, first in *Nature Reviews Cancer* describing methods of studying tumor metabolism directly in patients through a technique called 'stable isotope tracing' and in *Metabolic Health and Disease*, explaining how to bridge the gap between clinical and lab-based models for studying metabolism.
- Collaborative papers in *Nature Metabolism* and *Cell Metabolism* that examine how altered metabolism in cancer can be harnessed to improve responses to chemotherapy in preclinical models.
- A collaborative paper in *Nature Metabolism* investigating how the tumor microenvironment can support the metastasis of cancer cells through metabolic reprogramming.
- A collaborative study in *Cell Metabolism* that shows how physiological nutrients alter cellular biology, and how this can be harnessed to improve immune cell function

What's next?

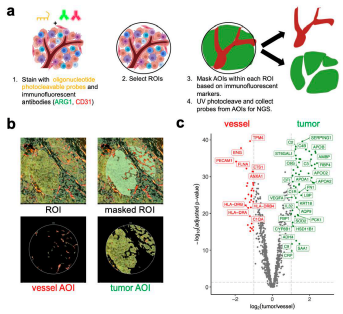
- We have an IRB-approved study to perform stable isotope tracing in patients with advanced or treatment-resistant lung cancer. We aim to understand how tumor metabolism adapts in these conditions to better understand disease progression.
- We are collaborating with colleagues in the Department of Neurosurgery to study how lung cancer metabolically adapts to survive in the brain.

Franses Lab

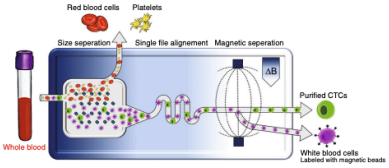


Focus: tumor environment and metastasis in liver cancer, circulating tumor cell purification devices, circulating tumor DNA assays, special transcriptomic platforms

PI: Joseph W. Franses, MD, PhD



Spatial transcriptomic characterization of the hepatocellular carcinoma tumor microenvironment.



CTC purification and downstream sequencing and additional assays

Our lab is focused on the tumor microenvironment (surrounding cells and extracellular matrix) and metastasis (distant spread of solid tumors) in primary liver cancers. We utilize state-of-the-art biospecimen profiling technologies – including circulating tumor cell (CTC) purification devices, circulating tumor DNA (ctDNA) assays, and spatial transcriptomic platforms – to develop biomarkers and motivate the evaluation of novel drug targets. We also utilize these data to develop mechanistic hypotheses to evaluate using cell and animal model systems. This methodology has been applied to identify the LIN28B RNA-binding protein as a targetable cancer driver. We aim to increase the translatability of our results by leveraging the clinical trial and biospecimen infrastructure and the University of Chicago Comprehensive Cancer Center. We collaborate with molecular and computational experts within the University of Chicago and across the country.

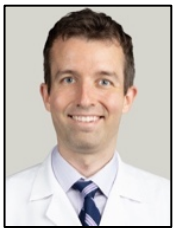
Major accomplishments:

- Established that the RNA-binding protein LIN28B is a potential drug target to inhibit metastasis in pancreatic cancer, published in *Nature Communications*.
- Published papers about work in refining circulating tumor DNA subtyping for immune therapy response prediction in *Oncologist* and about lenvatinib resistance in *Gastroenterology*.
- Established that aggressive bulk transcriptomic subtypes of hepatocellular carcinoma are driven by vascular endothelial cell gene expression in *Hepatology Communications.*

What's next:

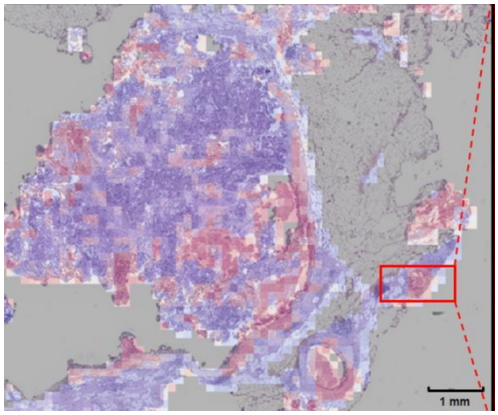
- Utilizing next-generation spatial transcriptomics characterization of pre/post-treatment liver cancer tissue specimens to develop predictive biomarkers.
- Single-cell transcriptomic and additional characterization of liver and biliary CTCs
- Developing targeting and co-targeting therapeutic strategies in LIN28B-driven GI cancers for pre-clinical and clinical evaluation.

Howard Lab



Focus: applying novel computational tools and artificial intelligence to improve the treatment of breast cancer

PI: Fredrick Howard, MD



There is a wealth of readily available data on cancer patients which is incompletely utilized. Our work focuses on integrating multiple dimensions of data – including digital histology, radiographic imaging, clinicopathologic parameters, and genomic data – to improve characterization of breast cancer, allowing for better personalization of treatment and prognostication. The main questions our lab is here to answer are: 1) Can artificial intelligence be used to improve prediction of response to therapy in breast cancer, and thus lead to better personalization of therapies? 2) Can deep learning use readily available pathologic and imaging data to improve upon or supplement existing genomic biomarkers in breast cancer in order to reduce cost, prevent unnecessary treatment delays, and improve access to biomarkers? & 3) Given the rapid growth of big data / artificial intelligence tools in oncology, what safeguards need to be in place to ensure these tools do not recapitulate healthcare disparities that are currently prevalent in cancer care?

Major accomplishments:

- Conducted one of the largest studies of epidemiology of HER2-Low breast cancer and impact on response to therapy/long term outcomes in *JAMA Oncology*.
- Developed a deep learning model predictive of OncotypeDX signature using digital histology in *npj Breast Cancer*.
- Characterized batch effect / site specific signatures in digital histology and the impact on training deep learning models in multi-site repositories, published in *Nature Communications* with an example of impact on model accuracy described in *Cancer Cell*.

What's next?

- Ongoing collaborations with several external cooperative groups and organizations that will yield ~10,000 pathology slides for validation and further refinement of deep learning models for recurrence risk / OncotypeDX and response to therapy, to bring these tools closer to clinical practice.
- Building novel architectures to better integrate histologic and radiographic imaging data (predominantly breast MRI), so that predictions can be made from informative features on both the microscopic and macroscopic scale, and to better understand how histology is reflected in imaging and vice versa.

Izumchenko Lab

Focus: Human genetics, translational cancer research, molecular biomarkers for early detection, mechanisms of the progression from premalignant to invasive disease, head and neck cancer

PI: Evgeny Izumchenko, PhD

Our research focuses on understanding the interplay between the genomic alterations in carcinogenesis and disease progression, and on exploiting this understanding for developing novel biomarkers for diagnosis and risk stratification as well as identifying targets for therapeutic intervention. Specifically, we are interested in defining the drivers underlying the premalignant progression and early immune evasion of head and neck cancers. Our studies forge an inter-disciplinary collaboration between investigators with complementary and integrated expertise, including (clinicians/oncologists, translational researchers, health disparity experts, computational scientists, and biostatisticians). We are actively engaged in partnering with pharmaceutical industry worldwide, to advance our ability to detect and treat head and neck cancer.

Major accomplishments:

- A publication in *Nature Communications* about a nanoengineered topical transmucosal cisplatin delivery system which induces an anti-tumor response in animal models and patients with oral cancer.
- A study, published in *Cancer*, about a low-cost, rapid, and accurate sequencing-based test with high clinical utility aimed at detecting mutations in an oral rinse for the early diagnosis and potential screening of oral cancer. Based on this study and the patented technology, the lab has founded OrisDX, a salivary diagnostic company focusing on non-invasive molecular-based detection of cancers of the oral cavity.
- An article published in *Cell Death & Disease* describing the antitumor activity of AL101 (NOTCH signaling inhibitor) using Adenoid cystic carcinoma (ACC) cell lines, organoids, and patient-derived xenograft models, showing that AL101 has potent effects in models with activating NOTCH1 mutations and constitutively upregulated NOTCH signaling pathway.
- A comprehensive computational analysis in *Frontiers in Oncology* found that DCLK1 expression positively correlates with NOTCH signaling pathway activation.
- An article in *Cancer Letters* about our work designing designed an ultra-deep amplicon-based sequencing library preparation approach that covers the entire mitochondrial genome. These findings provide the foundation for using mitochondrial sequencing for risk assessment, early detection, and tumor surveillance.
- We published in *Aging Cell* about a new study in which we applied a comprehensive AI-driven analysis of large-scale omic datasets using PandaOmics, an innovative target discovery engine, with a goal to identify dual-purpose target candidates for the treatment of cancer and aging.

What's next?

- Deciphering the role of PDCD10 in HNSCC evolution and developing a non-invasive, saliva-based assay for early detection of oral cancer.
- Immunogenetic map of OCSCC progression using whole-exome sequencing, RNA-seq, and TCR-seq, coupled with the comprehensive high-throughput computational analyses, to map specific mutational patterns & corresponding immune landscape.
- Identifying HPV16-specific immunotherapy for high-risk HPV16 strains).
- Collaborating across the university on multi-omics predictors of combination systemic therapy response/resistance in HNSCC.

Jakubowiak Lab

Focus: multiple myeloma: clinical trials, prognostic factors, minimal residual disease, genetics and immunology

PI: Andrzej Jakubowiak, MD, PhD

We conduct translational research in multiple myeloma using samples from our investigator-initiated studies to improve treatment outcome. We take advantage of many clinical trials led by our group and the ability to correlate clinical characteristics and disease outcomes with the investigated parameters. In recent years, we have emerged as a leading group in evaluation of minimal residual disease (MRD) by utilizing mass spectrometry in peripheral blood, as complementary methodology to evaluating MRD using next-generation sequencing in bone marrow and/or peripheral blood. Currently, we are broadening our research scope by investigating the genetics of myeloma biology, the impact of different treatment modalities on the incidence of secondary malignancies, and the role of the immunological microenvironment. The ultimate goal of all our efforts is to generate a rationale for developing clinical trials that pursue the concept of personalized therapy.

Major accomplishments:

- Published a paper in *Blood* with the results of our investigator-initiated phase 2 trial of extended carfilzomib, lenalidomide, and dexamethasone treatment with autologous hematopoietic stem cell transplantation in newly-diagnosed multiple myeloma.
- Published a pioneering paper in *Blood Cancer Journal* showing abilities of mass spectrometry for ultrasensitive disease activity assessment in myeloma patients.
- Published a paper in *JAMA Oncology* with the results of our investigator-initiated phase 2 trial of MRD-directed elotuzumab, carfilzomib, lenalidomide, and dexamethasone treatment in newly-diagnosed multiple myeloma.
- Interim results of the phase 3 ATLAS trial conducted in collaboration with Polish Myeloma Consortium were published in the *Lancet Oncology*. The study evaluates MRD-directed, risk-adapted maintenance with carfilzomib, lenalidomide, and dexamethasone as compared to lenalidomide alone.
- Published a paper in *Blood Advances* with the results of our investigator-initiated phase 1/2 trial of carfilzomib, pomalidomide, dexamethasone plus/minus daratumumab in refractory/relapsed multiple myeloma.
- Published in *British Journal of Haematology* an analysis of humoral immunity reconstitution among patients treated in different arms of the ATLAS trial.

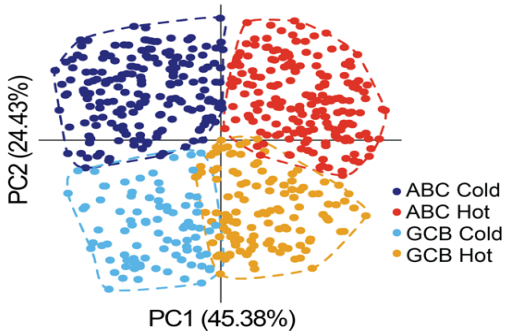
What's next?

- Continue running clinical trials with landmark collection of blood and bone marrow samples and expect new results in the near future andrefine our understanding of myeloma disease assessment in peripheral blood by more advanced mass spectrometry and cell-based analyses.
- Investigate the prevalence of clonal hematopoiesis of indeterminate potential in the large cohort of patients treated with different maintenance therapies.
- Conduct advanced genomic research focused on the genetic determinants of myeloma among specific patients' populations.
- Pursue studies of immune microenvironment, particularly in the context of immunotherapies.

Kline Lab

Focus: lymphoma, tumor immunology, immunotherapy, cellular therapy

PI: Justin Kline, MD



Using RNA-seq samples from 600 DLBCL patients, we identified clusters with distinct oncogenic pathways and immune microenvironments.

The Kline Lab is focused on overcoming immune evasion pathways activated in blood cancers and on improving the effectiveness of immune-based treatments for people with lymphoma. Our main disease of interest is diffuse large B cell lymphoma (DLBCL), the most common type of non-Hodgkin lymphoma.
We utilize in vivo mouse models and techniques, including CRISPR gene-editing and in vitro co-culture systems, to answer a range of basic and translational questions. We employ computational tools to analyze RNA-sequencing and whole exome sequencing data from tumor biopsies. We also investigate strategies to improve immune therapies for DLBCL with a focus on manipulating CAR T cells to enhance their persistence and function in vivo.

Major Accomplishments:

- Characterized a subset of DLBCL patients with *PD-L1* gene alterations, which harbor a T-cell-inflamed tumor microenvironment, published in *Blood*. These patients likely stand to benefit from anti-PD-1 checkpoint blockade therapy, a trial that initiated by this lab in collaboration with Merck.
- Established the requirement for dendritic cells (DCs) to be MHC-dressed for effective anti-tumor immune responses, published in *Immunity*. MHC-dressing is a phenomenon wherein tumor-cell-derived peptide:MHC is transferred to DCs for priming of anti-tumor $CD8^+$ T cells.
- In collaboration with Janssen, this we developed a gene expression signature that identifies DLBCL patients sensitive to the addition of a Bruton's tyrosine kinase inhibitor (BTKi) to standard chemoimmunotherapy. This work is published in *Journal of Clinical Oncology*.
- Using computational approaches and a large dataset, identified 4 DLBCL immune environments (so-called immune quadrants (IQs)), each enriched for particular recurring genomic alterations. We associated DLBCL IQs with response to bispecific antibody and CAR T cell therapies. This work is published in *Blood*.

What's next?

- Using novel computational methods to characterize and predict recurrent features of immune-inflamed DLBCL using multi-omic data and exploring how lymphoma cell-intrinsic alterations regulate the tumor microenvironment and responses to immunotherapy.
- Chimeric antigen receptor (CAR) T cell therapy has brought significant benefits to patients with relapsed/refractory DLBCL, but the reality remains that a majority of patients will progress. We are interested in exploring methods to improve CAR T cell persistence and function through genetic and pharmacologic manipulations.

Olopade Lab

Focus: Cancer Genomics and BRCA-associated Breast Cancer

PI: Olufunmilayo I. Olopade, M.B.B.S., F.A.C.P.

We are engaged in understanding the etiology and molecular mechanisms of tumor progression in high-risk individuals. We employ novel techniques including artificial intelligence in imaging, sequencing technologies and bioinformatics to develop innovative interventions to eradicate breast cancer as a cause of premature deaths, and thereby promote health equity. Our team has been the first and only laboratory in the world that has invested in sequencing the genomes of Black women in the US as well as Nigerian breast cancer patients from Africa to describe the spectrum of mutations found in these understudied populations. The lab members work in teams: Cancer Genomics, Computational Biology, Data Science and Preclinical Models.

Major accomplishments:

- Published on work in *Nature Communications* that highlighted a comprehensive spectrum of mutations observed in breast cancer patients from Africa for the first time, and discovery of distinct mutational processes and previously unreported significantly mutated genes unique to Nigerians. Further publication in *Clinical Cancer Research* on this work is forthcoming.
- Published about the regulation of viral mimicry and antiviral immunity by *BRCA1* pseudogene transcripts, which serve as immunoregulatory RNAs in breast cancer in *Cancer Research* and on the investigation of the functional significance of a SNP found to be associated with ER-negative breast cancer revealed that it regulates *TNFSF10* (*TRAIL*) expression in *Human Molecular Genetics*. Results from experiments using a syngeneic mouse model of breast cancer and CRISPR-Cas9 genome-editing tools to change *TNFSF10* expression in triple-negative breast cancer cells suggest that *TNFSF10* plays an important role in the regulation of antiviral immune responses in triple-negative breast cancer.
- An internal collaboration to externally evaluate a mammography deep learning tool, MIRAI, for breast cancer prediction in a high-risk population enriched for *BRCA* mutation carriers, benign breast disease and African Americans was published in *Radiology Artificial Intelligence*.

What's next?

- Using genomics to optimize treatment of high-risk early breast cancer before surgery, saving lives, and reducing disparity in outcomes. This lab is continuing comprehensive and expanded DNA/RNA sequencing studies, examining the prognostic value of immune signatures and comparing these between Black and White patients.
- Examining associations among "Omic" signatures, molecular subtypes and environmental risk factors which contribute to the etiology of breast cancer.
- With collaborators, this lab will employ emerging artificial intelligence algorithms to quantitatively analyze imaging data such as scanned H&E-stained slides from tumor blocks from our large patient cohort.
- Developing PDOs in such a way that the endogenous immune and non-immune stromal elements are preserved to allow human *in vitro* immunotherapy modeling.

Park Lab

Focus: Tumor microenvironment, immunotherapy outcomes, gut microbiome, metabolomics

PI: Joon Seok Park, PhD

The tumor microenvironment (TME) is the ecosystem surrounding cancer cells. It consists of various innate and adaptive immune cells, cancer-associated fibroblasts, vascular cells, and nerves. Notably, the outcome of cancer immunotherapy is strongly associated with many immune-specific markers in the TME, including macrophage polarization, dendritic cell subsets, CD8+ T cell to regulatory T cell ratio, and expression of co-stimulatory/co-inhibitory molecules, and T cell exhaustion. Previously published reports and our preliminary data suggest that gut commensal microbes shape the immune landscape in the TME. However, how gut microbes regulate these cellular processes is not well-defined. We aim to dissect the signaling mechanisms by which specific gut microbes regulate immune cells in the TME. We will determine signaling receptors and mediators, such as PD-L2/RGMb and innate sensing pathways, that link gut microbial signals to changes in tumor-infiltrating immune cells. Additionally, we focus on gut microbial metabolites and immunomodulatory ligands that can impact the metabolism and exhaustion of T cells in the TME. Our ultimate goal is to engineer bacteria to produce desirable molecules that enhance anti-tumor immunity and to develop methods for delivering these molecules to the TME. Beyond our mechanistic studies, we aim to define how the microbiome interacts with & influences responses to cancer therapy and are actively establishing institutional collaborations to do so. Our hope is to ultimately aid in the development of innovative therapeutic interventions.

Major Accomplishments:

- An article in published in *Nature* that first determined the causal immune mechanism by which gut commensal microbes regulate anti-tumor immunity and identified a novel role of PD-L2/RGMb pathway in T cell-mediated immunity.
- The publication of a review paper in *Experimental & Molecular Medicine* that proposed a conceptual framework describing how gut microbial molecules can regulate co-stimulatory and co-inhibitory pathways.
- A research article published in in *Molecular Cell* that showed that the glycerol-3-phosphate shuttle plays a critical role in balancing redox homeostasis and lipid synthesis in certain cancer, providing the foundation for our current manuscript in submission, which describes the function of Gpd2 in regulating T cell exhaustion and cytotoxicity.

What's next?

- Identify the bacterial molecules that promote anti-tumor immunity and determine the innate signaling receptor that mediate the effect of our bacterial isolates and its immunomodulatory molecules.
- Elucidate the molecular mechanisms by which RGMb regulates T cell activation and to identify the signaling factors associated with the RGMb complex. This will be done by analyzing the clinical samples to investigate the association between the microbiome features and the expression of PD-L2 and RGMb.
- Publishing a current manuscript that revealed the role of Gpd2 in T cell differentiation and aiming to modulate glycerol metabolism in the TME through diet interventions and engineered bacteria, thereby developing an innovative strategy to harness commensal microbes for regulating immunometabolism.

Patnaik Lab

Focus: Prostate Cancer, Innate Immunity, Immunotherapy, Myeloid Immunosuppression, Combination Therapies, Clinical Trials

PI: Akash Patnaik, MD, PhD, MMSc

Immunotherapy has demonstrated limited anti-tumor efficacy in metastatic, castrate-resistant prostate cancer (mCRPC). Our immune profiling studies of the tumor microenvironment (TME) in mCRPC patients revealed an enrichment of innate immunosuppressive myeloid cells, such as tumor-associated macrophages (TAM) and myeloid derived suppressor cells (MDSC). However, evaluation and targeting of the myeloid TME has been under-investigated in mCRPC, despite emerging data that it is a highly relevant component for immune escape and immunotherapy resistance. Using genetically defined murine models of AVPC, we have discovered and developed several therapeutic strategies to activate myeloid innate immunity in the TME driven by neutrophils (a paradigm shift in cancer immunotherapy research) and macrophages. Our lab has successfully translated these discoveries into innovative clinical trials, which we lead nationally and for which we organize tumor and blood-based specimens for multi-omic profiling. These efforts are being supported by NCI R01 and SPORE grants, V Foundation Translational Cancer Research Award, two Prostate Cancer Foundation (PCF) Challenge Awards and industry funding.

Major accomplishments:

- A publication in *Cancer Discovery* demonstrating how a tyrosine kinase inhibitor (cabozantinib) eradicates advanced murine prostate cancer by activating anti-tumor innate immunity.
- A publication in *Journal of Clinical Oncology* which led to the FDA approval of rucaparib in men with metastatic castration-resistant prostate cancer harboring a BRCA1 or BRCA2 gene alteration.
- A publication in *Molecular Cancer Therapeutics* demonstrating how BET inhibition sensitizes immunologically-cold Rb-deficient prostate cancer to immune checkpoint blockades; and a second on how cabozantinib unlocks efficient in vivo targeted delivery of neutrophil-loaded nanoparticles into murine prostate tumors.
- Two publications in *Clinical Cancer Research*: one about suppression of tumor cell lactate-generating signaling pathways eradicates murine PTEN/p53-deficient aggressive-variant prostate cancer via macrophage phagocytosis; and a second about the reversal of lactate and PD-1-mediated macrophage immunosuppression controls growth of PTEN/p53-deficient prostate cancer.
- A paper in *Molecular Cancer Research* highlighting significant TAM heterogeneity within the TME of prostate cancers, and a therapeutic strategy to target the most immunosuppressive TAM populations that drive progression and metastasis.

What's next?

- Several novel mechanistically-driven strategies are being developed to enhance immunotherapy efficacy in PC. These include:
    - Activating the cGAS/STING Pathway and NOD-like receptor (NLR) family pyrin domain containing 3 (NLRP3) inflammasome
    - Targeting immunometabolic cross-talk between tumor cells and TAM using targeted therapies and/or dietary interventions.
    - Targeting novel immunologic checkpoints to enhance immunotherapy efficacy.
    - Elucidating the role of circadian dysregulation/molecular clocks on immunotherapy efficacy in prostate and other immune-refractory cancers

Pearson Lab

Focus: Computational oncology, medical artificial intelligence, deep learning, digital biomarkers, mathematical modeling, head/neck cancer, salivary gland cancer

PI: Alexander Pearson, MD, PhD

The Pearson Lab integrates clinical expertise, mathematical modeling, high dimensional statistics, and tumor biology to improve cancer care using data. We believe that cross-contextualizing multiple types of cancer data can improve the lives of patients. The Pearson Lab has been at the forefront of research leveraging AI, especially deep learning, to transform cancer care and outcomes. Our work has focused on developing robust deep learning models to analyze complex cancer data, including digital pathology slides, radiology images, and multimodal data, to guide clinical decision-making. Key innovations have included novel techniques to improve model performance, such as synthetic cancer histology generation, uncertainty quantification, and the application of deep learning to pathology for predicting cancer recurrence. We have worked on developing and validating clinical machine learning models to guide decision-making and improve outcomes across cancer types. A core focus has been building prognostic models using features from clinical data, genomics, digital pathology, radiology data, and combinations of these data types. The work provides a framework for developing machine learning models that clinicians can trust and reliably act upon to benefit patient care. Overall, Pearson Lab is at the leading edge of demonstrating how many different data types can be thoughtfully and transparently translated to improve clinical decision-making and outcomes for cancer patients. We have developed integrated laboratory and computational platforms to better understand the complexities of human cancers, along with a live-cell imaging platform to observe and collect information about interactions between tumor cells, immune cells, and treatments. This information is passed into a custom-built multi-scale agent-based mathematical model of the tumor, which can be used for detailed simulations to optimize treatment combinations. The Pearson Lab conducts interventional clinical and translational research. Our lab leads multiple clinical trials to evaluate new treatment strategies, and organizes and analyzes samples derived from these studies. We interface closely with the University of Chicago Head and Neck Cancer Program, which is an internationally-recognized leader in treatment innovation.

Major Accomplishments:

- Developed a deep learning platform for automated digital pathology-based prediction of cancer molecular subtypes directly from diagnostic samples.
- Described and reversed sources of model bias capable of reducing AI biomarker accuracy, particularly in underrepresented groups.
- Showed how generative AI can be used to teach human physicians with synthetic images.
- Described human susceptibility to being tricked by generative AI content.

What's next?

- A unique portfolio of internally-maintained custom-built software pipelines to analyze cancer data.
- An expert team of data scientists to curate data, build servers, facilitate regulatory compliance, and enable collaborations both within our institution and with partners such as the Argonne National Laboratory.
- A series of custom-built GPU servers for AI research, from learning to high-performance computing needs.
- HIPAA and FISMA compliant data storage solutions to facilitate computational research on human health data.

Rahbani Lab

Focus: leukemia, adipose tissue, bone marrow adipocytes, metabolomics

PI: Janane Rahbani, PhD

Our research focuses on uncovering how adipose tissue—especially bone marrow adipocytes—drives leukemia progression and influences treatment outcomes through metabolic communication. We investigate how these specialized fat cells provide key nutrients and signaling molecules that leukemia cells exploit for growth, survival, and resistance to therapy. By combining in vivo models with dietary interventions like calorie restriction and time-restricted feeding, we aim to map how shifts in adipocyte metabolism reshape the tumor microenvironment. The big vision behind our work is to reimagine leukemia therapy by targeting the body's metabolic ecosystem—rather than cancer cells alone—as a novel and powerful axis of intervention. Our long-term goal is to translate these discoveries into metabolism-based therapies that weaken leukemia from its metabolic roots, offering more effective, less toxic, and personalized treatment strategies for patients.

Major accomplishments:

- Two *Nature* publications (one, two) revealed a novel mitochondrial mechanism in brown fat that fuels energy expenditure via creatine-dependent thermogenesis. The works identified creatine kinase B (CKB) as a key driver of this futile creatine cycle, demonstrating that its disruption impairs thermogenic function, lowers energy output, and accelerates obesity—uncovering a promising metabolic pathway for therapeutic targeting in obesity and related disorders.
- A paper published in *Nature Metabolism* demonstrated that $G\alpha_q$ signaling amplifies $G\alpha_s$ pathway activity in adipocytes, leading to a sustained and synergistic increase in whole-body energy expenditure. This finding uncovers a powerful mechanism to boost thermogenesis and highlights a promising therapeutic strategy for tackling obesity and metabolic disease.
- A paper published in *Cell Metabolism* challenged the long-standing belief that UCP1 is the sole driver of adaptive thermogenesis, unveiling alternative heat-generating mechanisms and reshaping our understanding of how the body maintains energy balance.

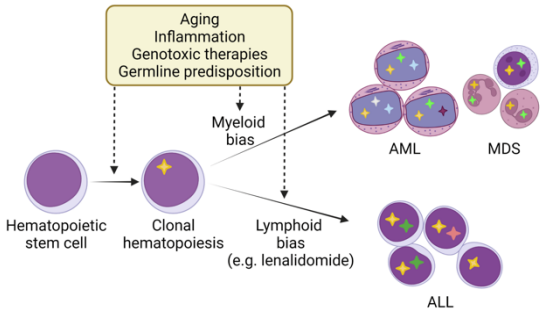
What's next?

- Reprogramming obesity-altered bone marrow adipocytes to investigate how changes in adipose metabolism reshape the leukemia microenvironment and drive disease progression, with the goal of uncovering new therapeutic strategies to improve outcomes in obese cancer patients.
- Refining protocols to isolate the bone marrow adipocyte secretome, allowing comprehensive lipid and protein profiling to uncover diet-regulated adipokines and cytokines that modulate immune responses, inflammation, and leukemia progression.
- Leveraging adipocyte-specific preclinical models to uncover how distinct fat depots (e.g. brown adipose tissue, subcutaneous adipose tissue, epididymal adipose tissue and bone marrow adipose tissue) shape cancer progression by deconvoluting their unique signaling pathways and their impact on energy homeostasis.

Saygin Lab

Focus: Leukemia biology, clonal hematopoiesis, experimental therapeutics

PI: Caner Saygin, MD



Saygin Lab studies leukemia biology by using *in vitro* and *in vivo* models of acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL), as well as human samples obtained from patients treated at the University of Chicago. We are particularly interested in drivers of CHIP (clonal hematopoiesis of indeterminate potential) progression to leukemias of myeloid vs lymphoid lineage in *de novo* and therapy-related leukemogenesis. Our translational research lab aims to identify mechanisms driving these fatal diseases and leverage them for new experimental therapeutics. Our drug development efforts focusing on high-risk subsets of AML and ALL have led to "home-grown" phase I/II investigator-initiated clinical trials.

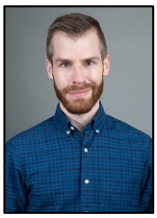
Major accomplishments:

- A recent manuscript in *Clinical Cancer Research* identified mechanisms driving BH3 mimetic resistance in T-ALL. We showed that LCK and ACK1 signaling pathways confer resistance to BCL-2 and BCL-xL inhibition, respectively. Dual targeting of BCL-2/BCL-xL and LCK/ACK1 signaling pathways with the combination of NWP-0476 plus dasatinib or ponatinib was more effective than single agent therapy in murine models of T-ALL. These preclinical data laid the foundation for our investigator-initiated phase 1b/2 clinical trial, funded by the Leukemia Lymphoma Society.
- A manuscript published in *Leukemia* deciphered the evolution of AML from pre-existing CHIP at the leukemia stem cell level.
- A paper published in *Blood Cancer Discovery* showed the discovery that clonal hematopoiesis can be a precursor for acute lymphoblastic leukemia (ALL), and ALL with myeloid mutations is a high-risk disease with inferior survival outcomes.
- Another manuscript published in *Blood Advances* defined molecular and clinical characteristics of therapy-related ALL. This study represents the largest cohort ever studied for this rare entity, and offers new mechanistic insights to understand and prevent the evolution of lymphoid malignancies from pre-existing CH.

What's next?

- Mouse models of *TP53*-mutated acute leukemias to study the mechanisms of de novo and therapy-related leukemogenesis. *TP53*-mutant AML and ALL have the worst prognosis, thus represent areas of unmet therapeutic need. We aim to further validate our preclinical data by performing comprehensive multi-omic bulk and single cell analyses of patient samples. Collectively, these studies will identify new opportunities for drug development.
- Investigating new pathways to target for treatment of AML and ALL. These preclinical efforts in experimental therapeutics will be leveraged for future phase 1b/2 clinical trials.

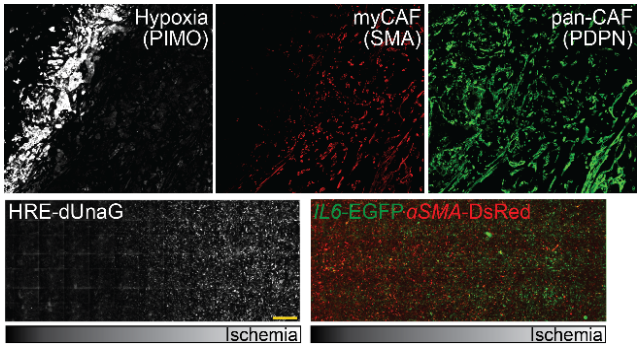
Schwörer Lab



Focus: Cancer metabolism, cancer-associated fibroblasts (CAFs), pulmonary fibrosis, pancreatic cancer, breast cancer

PI: Simon Schwörer, PhD

We are interested in understanding the role that fibroblasts play in tumor progression and fibrotic disease. We are specifically interested in how metabolism controls fibroblast activation as well as the plasticity and function of fibroblasts, how metabolic rewiring in fibroblasts contributes to pro-tumor and pro-fibrosis function, and how alterations in nutrient availability impact fibroblast fate and function and can lead to therapeutic vulnerabilities. Ultimately, we aim to identify fibrosis- or tumor-specific metabolic vulnerabilities in fibroblasts that could be targeted in combination with other therapeutic approaches to improve patient outcomes.



In tumors, a subtype of CAF is excluded from hypoxic areas (top). We can recapitulate this in a dish using a novel culture method that generated oxygen gradients (bottom).

Major accomplishments:

- The metabolic conditions in tumor contribute to the heterogeneity of cancer-associated fibroblasts in pancreatic tumors. The role of hypoxia in generating a pro-tumor fibroblast subset is published in *Cancer Research*.
- Metabolic rewiring contributes to fibrotic disease. Fibroblast synthesis of the amino acid proline is required for the production of collagen, which accumulates in fibrosis, published in the *EMBO Journal*. Another paper published in *Science* shows that mitochondrial NADPH generation is selectively required for proline synthesis, and its deletion impairs collagen production, which suggests that targeting metabolism could be a way for alleviating fibrotic disease.
- A paper published in *Nature Metabolism* shows that fibroblasts undergo metabolic rewiring in tumors to maintain collagen synthesis despite depletion of the nutrients normally required for this process. This offers a potential therapeutic avenue to impair collagen buildup in tumors selectively.

What's next?

- Using a novel fibroblast reporter (FIRE) in pharmacological and genetic screening approaches to define novel regulators of fibroblast heterogeneity.
- Using a novel mouse model to define the metabolic programs that support fibroblast state decisions in vivo.
- Testing the role of metabolic pathways for their relevance for alleviating fibrotic disease and tumor progression.
- Working to understand how fibroblast metabolism affects immune cells to define novel mechanisms of fibroblast immune cell crosstalk.
- Establishing matched pairs of CAFs and organoids isolated form pancreatic tumors from the same patient to generate co-culture models that can be used to understand how CAFs influence cancer cell growth and therapy resistance.

Stock Lab

Focus: NCI National Clinical Trials Network (NCTN) referral center for evaluation minimal residual disease, translational research in acute leukemias including pre-clinical modeling and clinical validation, myelodysplastic syndromes and myeloproliferative neoplasms, hematopoietic cell therapies.

PI: Wendy Stock, MD

The Stock Lab focuses on translational research in the field of acute leukemias. We are the referral center for the NCI National Clinical Trials Network (NCTN) for work related to the evaluation of minimal residual disease in acute lymphoblastic leukemia (ALL) and its correlation with clinical trial outcomes. This is based on work our lab has produced, focused on identifying new biological prognostic factors in specific subsets of leukemia that lead to novel clinical trial design and has focused particularly on the clinical significance of molecular detection and monitoring of subclinical disease (or minimal residual disease) using quantitative molecular methods. We are also involved in pre-clinical modeling of novel strategies to overcome treatment resistance in ALL to inform the design of innovative early phase trials. Another area of focus for our lab is on the identification of biomarkers of response and resistance. Additionally, we have designed biologically risk-adapted clinical trials for patients with acute leukemias, leading national trials for treatment of acute lymphoblastic leukemia (ALL) that have helped to change the standard of care for young adults with this disease.

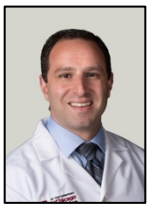
Major accomplishments:

- Leadership in the NCI's NCTN related to in correlative sciences in leukemia.
- Collaboration with national groups to identify new genomic subsets of ALL and to evaluate new methods of treatment sensitivity and resistance.
- Leukemia and Lymphoma Society Clinical Trials Award for innovative approach to relapsed T-ALL.
- A paper published in *Clinical Cancer Research* about work done to develop rational combination strategies for the treatment of T-ALL.
- A publication in *Haematologica* focused on measurable residual disease in ALL.
- Work, published on in *Blood*, using integrated whole-genome (WGS) and -transcriptome sequencing (RNA-seq), enhancer mapping, and chromatin topology analysis to identify previously unrecognized genomic drivers in B-ALL.
- Publication in *Blood Advances* of our work to better understand the genomic and epigenetic mechanisms of drug resistance in pediatric ALL.
- An article in *Blood Cancer Journal* about FLT3 mutant AML and potential treatment options in murine models.
- The publication of our work in *Cancer Discovery* combining venetoclax and navitoclax with chemotherapy for patients with relapsed or refractory ALL or lymphoblastic lymphoma.

What's next?

- Continued innovation evaluating and validating novel agents and identification of mechanisms of resistance to inform the next generation of clinical trials.

Sweis Lab



Focus: Immunotherapy resistance in solid tumors, translational science, microbiome, bladder cancer, Immunotherapeutic development, phase 1 trials

PI: Randy Sweis, MD

Our lab investigates mechanisms of resistance to cancer immunotherapies in solid tumors, with a goal of translating findings into clinical trials for patients. We use state-of-the-art technology to mechanistically investigate immune responses to cancer using preclinical laboratory modeling and translational studies of human cancer. We also leverage mathematical modeling and artificial intelligence to advance our understanding of tumor-immune interactions. Our goal is to translate findings into clinical trials to improve the efficacy of cancer immunotherapy for patients. Dr. Sweis is an active phase I investigator in out developmental therapeutics program thus findings from our lab can be rapidly translated into trials.

Major accomplishments:

- This lab was the first to link FGFR3 mutations with non-T cell-inflamed bladder cancer and published this work in *Cancer Immunology Research*. This finding led to a number of clinical trials combining FGFR inhibition and anti-PD-1 therapy including a combination trial with rogaratinib plus atezolizumab.
- Published an international collaborative perspective paper in *Cancer Cell* on future directions with microbiome research in cancer.
- Published twice in *Scientific Reports*. The first paper was about the development of a mathematical model to determine the critical factors affecting responses to immune checkpoint blockade. The second paper was about using a machine learning pipeline to select neoantigens based on patterns of nucleotide sequences, which can identify those most likely to induce a productive anti-tumor immune response.
- European Urology Oncology: Clinical trial investigating macrophage reprogramming with sitravatinib combined with anti-PD1 immune checkpoint blockade in bladder cancer. Responses observed in patients with prior resistance to checkpoint blockade.
- Published in *Clinical Cancer Research* about our work on the first Phase 1 study evaluating intratumoral STING agonist combined with anti-PD-1 therapy.

What's next?

- Developing novel, genetically engineered preclinical murine models for mechanistically investigating the impact of FGFR3 on the immune microenvironment and resistance to immune checkpoint inhibitors.
- Studying the relationship of the immune microenvironment in bladder cancer specimens (including spatial transcriptomics) with clinical outcomes and responsiveness to immune checkpoint blockade
- A mathematical modeling collaboration with Dr. Trachette Jackson at the University of Michigan continues with future studies including the immunological effect of the antibody drug conjugate enfortumab-vedotin on bladder cancer in vitro and in vivo.
- Evaluation of the relationship between the urine microbiome, urine metabolomics, and responsiveness to BCG immunotherapy in early stage bladder cancer.
- Finalizing our manuscript with clinical trial data combining FGFR3 inhibition and anti-PD-L1 therapy in bladder cancer patients.

Szmulewitz Lab

Focus: Prostate Cancer therapeutics, biomarkers

PI: Russell Szmulewitz, MD

The Szmulewitz lab is a translational research group focused on identifying novel therapeutic targets and accelerating the discovery and implementation of new treatment strategies for terminal prostate cancer. One of our primary goals is to understand and target resistance to standard hormonal-based therapies in order to ultimately improve patient outcomes. To this end, the Szmulewitz lab utilizes preclinical models of human prostate cancer and collected biospecimens from patients for analysis and further model development. We also collaborate with investigators across the University of Chicago to test emerging treatments, imaging strategies, and drug-delivery systems. In addition to working on prostate cancer therapeutics, a key mission is to combine those therapies with biomarkers to enhance precision medicine in the prostate cancer space.

Major accomplishments:

- Discovery that subsequent to treatment with potent standard androgen receptor (AR) targeted therapies, prostate cancer compensates by expressing an alternative receptor called the glucocorticoid receptor (GR) as described in *Hormones and Cancer.* This was followed by publications in *Molecular Cancer Therapeutics* and showing that novel GR antagonists can be effective to ameliorate resistance to therapy. Clinical trials led by Dr. Szmulewitz targeting GR and AR concurrently have stemmed from this work.
- Development of novel circulating tumor cell (CTC) biomarkers for multiplex protein analysis that have been incorporated into clinical trials, as shared in the *Journal of Translational Medicine* and *Clinical Cancer Research*.
- Demonstrated that a subset of resistant prostate cancer driven by the overexpression of the protein SOX2 could be targeted by co-targeting the AR and WEE1 cell-cycle regulator, shown in *Cancer Letters*.

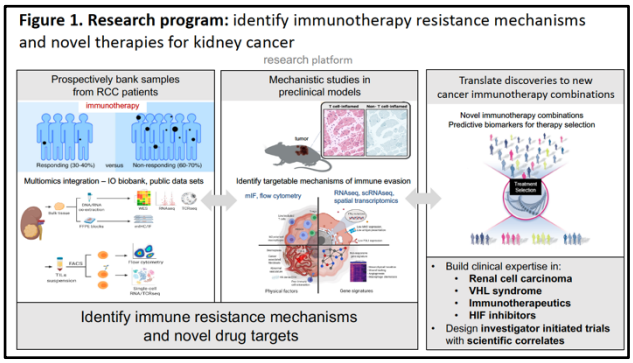
What's next?

- Examining the cooperative effects of GR and AR splice variants in therapy resistant prostate cancer.
- Understanding the potential role for targeting WEE1 in prostate cancer independent of SOX2 expression.
- Development of novel prostate cancer imaging agents and radiotherapeutics, in collaboration with our institution's Department of Radiology faculty.
- Interrogation of novel drug delivery mechanisms in collaboration with faculty in the Ben May Department.
- Developing new patient-derived prostate cancer organoids from patients of diverse racial/ethnic backgrounds.
- Understanding and targeting the biology driving prostate cancer disparities in men of African ancestry.

Trujillo Lab

Focus: Immunotherapy resistance mechanisms, immunobiology of renal cell carcinoma and melanoma, hypoxia inducible pathway biology, immunology and immunopathology of COVID-19

PI: Jonathan Trujillo, MD, PhD



We focus on identifying determinants of resistance to cancer immunotherapies, with a goal of translating findings to new therapeutic strategies for patients diagnosed with kidney cancer. Our team employs a multidimensional approach, integrating basic mechanistic studies in preclinical models, translational studies on patient tumor specimens, and bioinformatic methods to identify factors that impact on anti-tumor immunity. Projects include the elucidation of mechanism by which tumor cell-intrinsic oncogenic pathways, such as hypoxia inducible factors (HIFs), disrupt the anti-tumor immune response and immunotherapeutic responses. Our research also extends to discovering immunological mechanisms of coronavirus disease severity. We completed a large human COVID-19 biobank study that, through comprehensive immune profiling during infection, integrated multidimensional immunologic and clinical data to uncover drivers of severe COVID-19. This effort resulted in several multidisciplinary collaborations at the University of Chicago, establishing an institution wide mechanism to bank clinical trial samples to provide scientific correlative data for various investigator-initiated, IRB-approved COVID-19 studies.

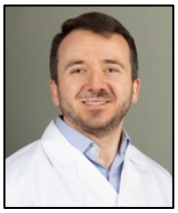
Major accomplishments:

- A retrospective study published in *Blood* on CD19-directed CAR T-cell therapy response in T-cell/histiocyte-rich large B cell lymphoma (T/HRLBCL), an aggressive subtype of large B cell lymphoma. This finding has spurred the exploration of alternative treatments, including anti-PD-1 immune checkpoint blockade, for these patients.
- Two papers published in *Journal for ImmunoTherapy of Cancer*, one describing novel cases of acquired immunotherapy resistance in melanoma patients, associated with either active β-catenin signaling or PTEN gene deletion, and a second demonstrating the safety and immunogenicity of COVID-19 vaccination in patients undergoing anticancer therapies for solid tumors.
- A collaborative study published in *Blood Advances*, demonstrating lymphatic vessels in lungs and lung-draining lymph nodes in fatal COVID-19 cases exhibit fibrin clotting which correlated with intralymphatic neutrophil extracellular traps (NETs). Higher levels of NETosis were observed in severe cases of COVID-19 with low antiviral antibody titers.

What's next?

- Utilizing innovative tumor models to determine whether activation of cancer cell-intrinsic HIF-1α or HIF-2α functions by impairing naïve T cell priming and/or constraining effector T cell infiltration and function within the tumor.
- Employing preclinical models to evaluate the effects of HIF-2α inhibitor treatment on response to immune checkpoint blockade.
- Development of human and murine kidney cancer models to elucidate the impact of BAP-1 loss on anti-tumor immunity and immune checkpoint inhibitor efficacy in renal cell carcinoma.

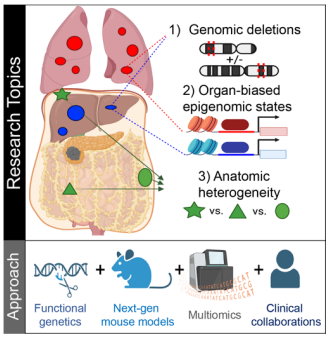
Tsanov Lab



Focus: metastasis, genetics, epigenetics, tumor microenvironment, pancreatic cancer, gastric cancer

PI: Kaloyan (Kal) Tsanov, PhD

Our laboratory investigates metastatic disease – the major cause of cancer-related deaths. The overall goal of our research is to elucidate mechanisms that sustain metastatic tumors and to identify related vulnerabilities that can be therapeutically targeted. We focus on pancreatic and gastric cancers, and the three most common sites (liver, peritoneum, and lungs) of distant metastasis across gastrointestinal malignancies. Our work integrates innovative mouse models, functional genetics tools and multiomic approaches to dissect and target the interplay of genetic, epigenetic and microenvironmental factors in metastatic tumors. Our vision is that understanding natural barriers to metastasis and tumor–microenvironment crosstalk at different metastatic sites will reveal a set of governing principles that can be leveraged for novel therapies that are better tailored to metastatic tumors.



Major accomplishments:

- Co-developed an experimental framework for functional analysis of chromosomal deletions and used it to discover that frequent co-deletion of the type I interferon gene cluster at chr9p21 promotes immune evasion, metastasis, and immunotherapy resistance (published in *Nature Cancer* and *JTO*).
- Developed a new mouse model of pancreatic cancer and used it to discover that metastatic site can influence the functional output of driver gene lesions (in revision, preprint at *bioRxiv*).
- Co-developed a suite of novel mouse models – termed EPO-GEMMs – that feature hallmark properties of all three non-viral subtypes of metastatic gastric cancer and provide unique genotype and host flexibility. By leveraging this flexibility, we discovered genotype-specific patterns of metastatic spread and modes of immune surveillance of metastatic tumors (published in *Nature Cancer*).

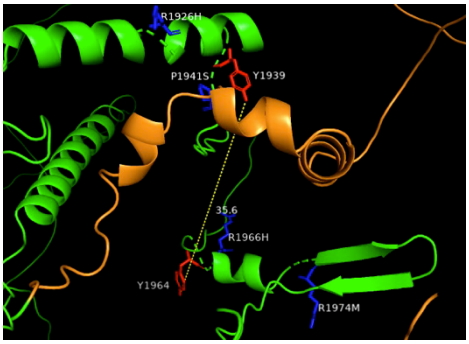
What's next?

- Systematic functional interrogation of recurrent genomic deletions, with the goal of identifying new anti-metastatic genes. Functional restoration of such natural barriers to metastasis, or targeting of liabilities created by their loss, can provide novel therapeutic opportunities for metastatic tumors.
- Investigating microenvironmental factors that induce and/or select for organ-biased epigenomic states and identifying targetable vulnerabilities presented by them. Such knowledge can inform new therapies that target tumor-microenvironment crosstalk.
- Leveraging next-generation mouse models to understand the molecular basis of anatomical heterogeneity in metastatic tumors, and test at scale new therapeutic strategies that take into account this heterogeneity.
- Establishing cross-departmental collaborations to generate patient-derived resources for integrative functional oncogenomic studies of metastatic tumors.

Wickrema Lab

Focus: Epigenetic regulation focused on mechanism of action of TET2 during blood cell development; Erythropoiesis, Anemia and Sickle Cell Disease; Development of novel cell therapies

PI: Amittha Wickrema, PhD



*Predicted Interaction between **JAK2 Kinase** domain (orange) and **TET2** C-terminal (green) region along with sites of tyrosine phosphorylation (Red) and patient mutations (blue).*

Our work is focused on elucidating the mechanism of action of epigenetic control of gene transcription by TET2. TET2 is a hydroxylase enzyme responsible for modifying methyl cytosines in DNA. With ageing TET2 acquires numerous mutations but only some mutations lead to leukemia and/or MDS. Our work is focused on understanding structural functional relationships in normal and mutant TET2 proteins with the hope of designing novel therapies to treat malignant conditions arising due to TET2 mutations. The second area of investigation consist of understanding molecular basis of erythropoiesis with the goal of treating anemic conditions. A very well characterized human cellular model developed by our group is used in these studies to uncover molecular pathways responsible for red blood cell production. Additionally, we also focused on developing new agents to treat sickle cell anemia using both human and mouse models of sickle cell disease. A third area of investigation is pre-clinical and clinical in nature, where novel cellular therapies are being developed including more potent and effective Chimeric Antigen Receptor (CAR-T)- based cellular therapy product manufacturing. This work is being performed in a state-of-the-art facility that was designed and operated by our group at the University of Chicago Medical Center (MCMC).

Major Accomplishments:

- Publication of a paper in *Cancer Discovery* identifying how TET2 enzyme is activated in developing blood stem cells and during development of red blood cells
- Two papers (in *PNAS* and *Clinical Cancer Research*) about the mechanisms underlying myelodysplastic syndromes and a potential molecular target to treat the condition.
- International partnerships resulting in a paper in *Elife* entitled "Activation of targetable inflammatory immune signaling is seen in myelodysplastic syndromes with SF3B1mutations".
- A paper in *Cytotherapy* about the validation of novel tools for efficient manufacturing of immune-based cellular therapies for the treatment of cancer and autoimmune diseases.
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What's next?

- Using Artificial Intelligence (AI) – based highly accurate computer modeling of mutant TET2 proteins to predict functional outcomes during ageing and cancer by correlating computer-generated models with experimentally derived data.
- Development and validation of novel epigenetic-based small molecule drugs to treat sickle cell disease.
- Development of low-cost, high-value CAR T-cells and other cellular therapies for phase I and II clinical trials.