

2019 Annual Report

# CURING CANCER, TOGETHER



CASE  
COMPREHENSIVE  
CANCER CENTER



## FROM THE DIRECTOR

# Curing Cancer, Together

High-priority areas mixed with scientific initiatives and multi-investigator efforts.

The Case Comprehensive Cancer Center is ever-evolving, giving way to new discoveries, innovation and collaboration, all furthering our understanding of cancer and ultimately better helping patients. Every aspect of our cancer center is improved thanks to coordinated advances across institutions and collaboration with our Cleveland community partners.

Last year was an important one, and filled with many achievements to celebrate — our 30th anniversary was capped off with an Exceptional merit rating on our NCI designation, plus renewal of our GI SPORE, BETRNet, K12 Paul Calabresi Career Development grant and several large new grants: a P20 planning grant for Cancer Disparities, a U01 on digital pathology plus two R25 training grants expanding our programs to younger students.

As we move forward, we will increasingly focus on our scientific initiatives, all

interdisciplinary, cross-program efforts to encourage novel research across the following areas: Drug Discovery; Genomics; Cancer Immunology; Women's Cancers; Brain Tumors; AYA Cancers and Community and Disparities; and Computational Diagnostic Informatics. We look forward to each of these initiatives generating new cross-center partnerships and multi-PI grant applications.

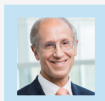
This report only skims the surface of the magnitude of activities conducted at the Case CCC. You will see highlights of scientific advances and descriptions of cutting-edge expertise and technologies, all connected through thoughtful and strategic planning by the dedicated leaders and members of our center. Please read it and share it. I welcome your thoughts and comments. Your feedback helps our leaders plan for the future and ensure we are meeting the needs of the community we serve.



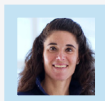
**Stan Gerson, MD**

Director  
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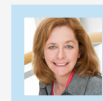
## SENIOR LEADERS



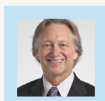
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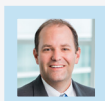
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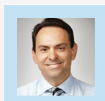
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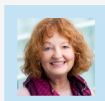
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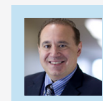
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# 2019 ANNUAL REPORT

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New Multi-PI Grants ■ Inside the Center's New Space ■ Renewed Recognition

## 6 Research in Review

Research programs serve as the backbone of the center. Here, we highlight each program's recent groundbreaking discoveries.

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Shared resources enhance research depth, accessibility and cost-effectiveness.

## 14 Community Engaged Research

We seek to understand and address the cancer-related needs of the community.

## 16 Career Enhancement

We offer comprehensive training and professional development opportunities for middle schoolers through junior faculty.

## 18 Clinical Research

A pioneering team develops a Pap test for the esophagus to help prevent esophageal adenocarcinoma.

## 19 Philanthropy & Pilot Support

Pilot grants jump-start novel projects that advance cancer treatments.

### EXECUTIVE COMMITTEE



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CASE  
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# NEWS OF NOTE

## New Multi-PI Grants

Team science is the undercurrent for many projects at the Case Comprehensive Cancer Center. Through collaboration, researchers with complementary research foci are brought together to tackle complex research problems. Here, we highlight a few examples of these successful partnerships.

**Nathan A. Berger, MD, Monica Webb Hooper, PhD, and Li Li, MD, PhD**, are leading a three-year, \$3.2 million grant from the National Cancer Institute (NCI) to investigate colorectal and breast cancer health disparities. The grant is one of only four Specialized Programs of Research Excellence (SPORE) Planning Grant P20 awards given across the nation to address health disparities. It will provide the infrastructure for a new, comprehensive research program to study cancer health disparities at both molecular and population levels.

**Nima Sharifi, MD**, is leading a multidisciplinary team of investigators from Cleveland Clinic and Dana Farber Cancer Institute developing novel treatments to target androgen and glucocorticoid receptors to prevent castration-resistant prostate cancer. This

research is supported by a \$1 million Mizel Family Foundation PCF VALor Challenge Award. This is the second time in four years that Dr. Sharifi has received the highly competitive grant.



**Keith McCrae, MD, and Alok Khorana, MD**, received a \$4.7 million grant from The National Heart, Lung and Blood Institute (NHLBI) to support a research consortium that will focus on strategies to prevent cancer-associated thrombosis. The team is developing a new assessment tool to



identify which patients will develop blood clots during treatment, and proactively treat those patients with blood thinners, allowing them to be treated for cancer.



**Andrew Janowczyk, PhD, and Anant Madabhushi, PhD**, are leading a three-year, \$1.5 million grant from the NCI Informatics in Technology Cancer Research program and will collaborate with **Hannah Gilmore, MD**, and the University of Pennsylvania to develop AI and deep learning



tools for digital pathology. These "HistoTools" will then be validated for their ability to predict outcome and therapy response for breast and lung cancer tissue images.

**Alex Huang, MD, PhD**, is leading a multidisciplinary and multi-institutional team that received a three-year, \$1.35 million grant from the St. Baldrick's Foundation and the Osteosarcoma Collaborative to develop new ways to treat osteosarcoma by targeting molecules that evade immunity.

**Li Li, MD, PhD, Monica Webb Hooper, PhD, and Nathan A. Berger, MD**





## Exceptional Recognition

The Case Comprehensive Cancer Center has earned an extraordinary endorsement from the National Cancer Institute (NCI): its highest-possible rating and \$31.9 million to continue its lifesaving work. The rating of “exceptional” comes as Case CCC also celebrated its 30th anniversary of improving cancer outcomes through scientific discovery.

The NCI review recognized Stanton Gerson, the cancer center’s director since 2004, for his leadership and for developing initiatives such as implementing a strategic-planning effort and enhanced transdisciplinary collaborations, establishing the Office of Cancer Disparities Research, and recruiting talented new senior leaders and researchers. The review also praised the center for continuing to be a research leader in basic, clinical and population sciences, and for providing exemplary service to the population in Northeast Ohio.



## Inside Case CCC’s New Space

In spring 2018, the Case Comprehensive Cancer Center administrative team moved to new offices on the first floor of the Wolstein Research Building, Case Western Reserve University’s primary biomedical research space. This newly renovated space houses the offices of the director and director-level administration team members. Additional administration staff are on the second and third floors of the building, finally bringing the administrative team under one roof, allowing them a more cohesive flow of interaction and efficient access to center members.

In addition, this new office suite contains a conference room equipped with cutting-edge technology, including a high-definition projector and screen, wireless content sharing and videoconferencing capabilities. The room serves as the primary meeting room for cancer center leadership, program leaders committee, shared resource directors, program mini-retreats and other cancer center gatherings.



# RESEARCH IN REVIEW

**Our seven research programs** serve as the backbone of the Case Comprehensive Cancer Center. These transdisciplinary programs are led by top-notch researchers, bringing together over 380 members from Case Western Reserve University, University Hospitals and Cleveland Clinic to translate basic discoveries into improved methods for cancer prevention, detection and lifesaving treatments.

Intersecting these programs are eight scientific initiatives, all focused on strategically linking discovery, prevention and therapeutics. These themes represent ever-evolving opportunities for research collaboration across our center. Here, we highlight each program's recent groundbreaking discoveries.



## Cancer Prevention, Control and Population Research

Greg Cooper, MD  
Erika Trapl, PhD  
Fredrick Schumacher,  
PhD, MPH

### The **Cancer Prevention, Control and Population Research Program**

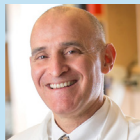
focuses on reducing cancer incidence, elucidating cancer risk factors, and **improving outcomes** after cancer diagnosis within the Case CCC's catchment area and beyond. Primary focus areas include tobacco, obesity, nutrition, genetics, HPV, health policy and poverty.

Cynthia Owusu, MD, led a catchment-based study of racial disparities in the physical function of breast cancer survivors, building on previous work that demonstrated higher prevalence of functional disability among African American breast cancer survivors compared to Caucasian. According to this current study, poor physical performance among older women with newly diagnosed non-metastatic breast cancer disproportionately affects African Americans. This increased disparity may be linked to less engagement in physical activity and subclinical inflammation. (Owusu, *J Geriatr Oncol*, 2017; Owusu, *J Geriatr Oncol*, 2018)

Fredrick Schumacher, PhD, MPH, and colleagues conducted a study on the genetic risk of familial prostate cancer in a multinational cohort. The team identified 62 novel loci associated with prostate cancer as well as one with early onset cancer. This study increased knowledge of prostate cancer genetic risk factors, allowing the team to create genetic risk scores of developing prostate cancer. The work has also led to a clinical trial to assess the utility of the polygenic risk score in a cohort of men at high risk for prostate cancer. These findings improve risk-profiling, an important part of the decision-making process of cancer screening and prognosis. (Schumacher, *Nat Genet*, 2018)

**NEW FOR 2020: Cross-cutting scientific initiatives: drug discovery, genomics, brain tumor,**





## Developmental Therapeutics

John Letterio, MD  
Yogen Saunthararajah, MD

The **Developmental Therapeutics Program** discovers novel mechanism-based therapeutics leading to investigator-initiated clinical trials with a focus on **addressing major diseases** in the Case CCC catchment area. Working groups in drug discovery and resistance, disease-based therapeutic areas and early-phase clinical trials with combinations of novel targets, new agents and cancer immunotherapy.

A team led by Yogen Saunthararajah, MD, conducted a study to better understand nucleophosmin (NPM1), one of the most frequently mutated genes in de novo acute myeloid leukemia (AML). The study's findings support further clinical investigation of the combination of selinexor and decitabine to treat NPM1-mutated AML. Currently, only 50% of patients can expect long-term survival with current treatments, and there are no precision molecular-targeted treatments for this disease. (Gu, *J Clin Invest*, 2018)

A team led by Afshin Dowlati, MD, Daniel Lindner, MD, PhD, and George Stark, PhD, developed a novel therapeutic strategy for small cell lung cancer that targets tumor-initiating cells by combining cisplatin with CBL0137. This combination has shown positive results in preclinical tests, showing promise to combat tumor recurrence. (De, *Cancer Res*, 2018)

## GI Cancer Genetics

Sanford Markowitz, MD, PhD  
Zhenghe John Wang, PhD



Sanford Markowitz, MD, PhD, Amitabh Chak, MD, Joseph Willis, MD, Kishore Guda, DVM, PhD, and Jill Barnholtz-Sloan, PhD, successfully developed a biomarker-based non-endoscopic method for detecting Barrett's esophagus (BE), the only known precursor of esophageal adenocarcinoma. First, the team identified a pair of DNA methylation markers consistent with the presence of BE. Then, they developed a well-tolerated, swallowable, balloon-based esophageal sampling device to capture DNA samples. (Moinova, *Sci Transl Med*, 2018)

Peter Scacheri, PhD, and Brian Rubin, MD, PhD, conducted a preclinical study to better understand the genes and underlying mechanisms that drive metastasis, and successfully identified enhancer elements that drive tumor metastasis. Researchers used innovative epigenetic-centered techniques to block or delete altered enhancers, halting the spread of bone cancer (osteosarcoma) cells to the lungs. These findings may support the development of targeted anti-metastatic therapies for osteosarcoma and other cancers. (Morrow, *Nat Med*, 2018)

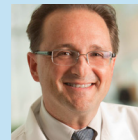
The **Gastrointestinal Cancer Genetics Program** is a team-science oriented program dedicated to discovering genetic and epigenetic causes of GI cancers, translating these discoveries into development of **novel therapeutic approaches** and biomarkers for early detection, prevention, diagnosis, prognosis and prediction of drug responses.

FOR MORE INFORMATION, VISIT  
[case.edu/cancer/research/research-programs](http://case.edu/cancer/research/research-programs)

women's cancer, cancer immunology, adolescent and young adult, community research



## Hematopoietic and Immune Cancer Biology



Jaroslaw Maciejewski, MD, PhD  
Marcos de Lima, MD  
Alex Huang, MD, PhD

**HICB Program** members investigate the hematopoietic process and novel molecular features of hematologic neoplasms, as well as the role of cellular immunity in cancer immune responses and stem cell transplantation, with a goal of developing more **effective treatments** for hematologic malignancies.

The TET2 gene informs cell gene expression by modifying metabolism in pathogens. Mutations of the TET2 gene observed in clonal hematopoiesis of indeterminate prognosis (CHIP) predict increased risk of hematologic malignancy and cardiovascular disease. A team led by Jaroslaw Maciejewski, MD, PhD, studied TET2 clonal evolution patterns and clarified the risk and links between these CHIP mutations and those observed in myelodysplastic syndromes (MDS). These findings strengthen the argument for the diagnostic application of somatic and germ cell line mutations in the diagnosis and prognostication of adult acute myeloid leukemia (AML) and MDS. For the first time, they distinguished a mutation in CHIP from those of AML and MDS. (Hirsch, *Leukemia*, 2018)

A team of researchers led by Sudipto Mukherjee, MD, MPH, conducted a study to understand the risk of hematologic malignancies after treatment with radioiodine (RAI) to treat well-differentiated thyroid cancer (WDTC). Patients with WDTC treated with RAI had an increased early risk of developing AML and chronic myeloid leukemia, but no other hematologic malignancies. Therefore, RAI treatment in patients with WDTC should be limited to high-risk patients, and patients with WDTC treated with adjuvant RAI should be monitored for myeloid malignancies. (Molenaar, *J Clin Oncol*, 2018)



## Molecular Oncology

Justin Lathia, PhD  
Quintin Pan, PhD

Jennifer Yu, MD, PhD, and Shideng Bao, PhD, collaborated to identify vascorin, a growth-factor protein, as a critical link between hypoxia and Notch signaling in glioma stem-like cells (GSCs). Tumor hypoxia is associated with poor patient survival and is a characteristic of glioblastoma. Notch signaling is implicated in maintaining GSCs within the hypoxia niche. This is the first time the molecular mechanisms linking hypoxia and Notch signaling were fully delineated. This research suggests targeting vascorin to deplete the hypoxic GSC population can extend patient survival. (Man, *Cell Stem Cell*, 2018)

Ofer Reizes, PhD, Justin Lathia, PhD, and Paul Fox, PhD, made the startling observation that connexin 26 (Cx26) is necessary for maintenance of self-renewing cancer stem cells (CSCs), drive intratumoral cellular heterogeneity and accounts for persistent tumor growth, therapeutic resistance and metastasis in triple negative breast cancer. Connexins are commonly viewed as tumor suppressors, but not in breast cancer. CSC self-renewal may yield next-generation therapeutic strategies. (Thiagarajan, *Nat Commun*, 2018)

Ge Jin, PhD, and Bingcheng Wang, PhD, uncovered that exosomes released from HIV-infected T cells and those purified from the blood of HIV-positive patients stimulate proliferation, migration and invasion of oral/oropharyngeal and lung cancer cells. They pinpointed the exosome mediator in cancer in HIV-positive patients, providing a mechanism for accelerated metastasis. This non-AIDS-defining cancer remains a major risk for people living with HIV/AIDS on antiretroviral therapy. (Chen, *Nat Commun*, 2018)

**Molecular Oncology** is Case CCC's basic science program. Members work with other Case CCC programs, **sharing expertise** in cancer stem cells, DNA damage repair, tumor-host interactions, non-coding RNA, tumor metabolism and other fundamental areas of cancer biology.

James Babilion, PhD  
Zhenghong Lee, PhD



## Cancer Imaging

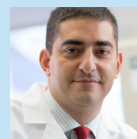
A team led by Mark Griswold, PhD, Vikas Gulani, MD, PhD, and Nicole Seiberlich, PhD, used magnetic resonance fingerprinting (MRF) in breast, prostate and brain to measure multiple tissue properties in a single acquisition as opposed to multiple scans. MRF is a newer technology that is currently being explored, and these studies support the value of pursuing it as an effective clinical tool. (Chen, *Radiology*, 2019; Hamilton, *Magn Reson Imaging*, 2018; Gu, *Magn Reson Med*, 2018)

Anant Madabhushi, PhD, is developing a computerized histologic risk predictor (CHIRP) for early-stage lung cancers that relies on computer-extracted standard tissue images to predict early recurrence in early-stage non-small cell lung cancer (NSCLC). This study hopes to identify which early stage NSCLC patients, following surgery, will receive additional benefit from adjuvant chemotherapy. (Corredor, *Clin Cancer Res*, 2018)

A team led by James Babilion, PhD, and David Wilson, PhD, developed a point-of-care imaging method for non-melanoma skin cancer surgery where excised tissues are imaged with a smart near-infrared, quenched protease probe that fluoresces in the presence of basal cell carcinoma and squamous cell carcinoma to determine if margins are clear of cancer. This study could identify a technique to better detect and locate skin cancer within excised tissue samples, significantly reducing callbacks and potentially reducing unnecessary excision of tissue. (Liu, *J Med Imaging (Bellingham)*, 2019)

The **Cancer Imaging Program** is truly transdisciplinary, linking teams of experts from basic biology, medicine, chemistry, physics and engineering to use novel imaging techniques to conduct cancer biology research and develop new therapeutic techniques, as well as develop computational diagnostic imaging.

## GU Malignancies



Nima Sharifi, MD

Research of the **Genitourinary Program** is focused on better understanding the fundamental biologic pathways of the development and progression of prostate cancer, renal cancer and bladder cancer. Through the collaboration of **multidisciplinary research teams**, program members are actively developing new therapeutic options for patients with GU malignancies.

Nima Sharifi, MD, Jorge Garcia, MD, and Brian Rini, MD, built on their prior research findings related to the metabolism of abiraterone, a prostate cancer drug, and characterized a mechanism of therapeutic resistance in patients with prostate cancer who carry the HSD3B1(1245C) gene variant. This means that patients harboring the HSD3B1(1245C) allele are more likely to experience rapid, androgen-driven tumor progression while taking abiraterone, despite castration, and require consideration of additional therapies. Researchers are using this information to improve current treatments and identify alternative therapies for these patients. (Alyamani, *J Clin Invest*, 2018; Li, *Nature*, 2015)

Drs. Sharifi and Zhenghong Lee developed a PET imaging modality that scans for loss of glucuronidation — a major metabolic reaction that normally limits disease progression — to predict tumors that are more likely to develop castration-resistant prostate cancer. (Zhu, *J Biol Chem*, 2018)

Through transcriptomic analysis, Omar Mian, MD, PhD, Byron Lee, MD, PhD, and Dr. Rini linked the protein coding gene DLL3 with more clinically aggressive and lethal phenotypes of small cell bladder cancer. Their findings indicate DLL3 as a therapeutic target; new biologically oriented mechanisms, such as anti-DLL3 antibodies, are currently being developed and undergoing preclinical tests. (Koshkin, *Clin Cancer Res*, 2018)



**Case Comprehensive Cancer Center** supports 13 shared resources, which utilize state-of-the-art technology and provide expertise across a wide range of scientific disciplines. Our shared resource directors and their staff work directly with investigators to carry out studies aligned with the cancer center's central mission to enhance the quality of basic, clinical and translational research, thereby improving the treatment of cancer. This is achieved by providing investigators access to expertise and technologies that would otherwise be unavailable.

## Athymic Animal & Preclinical Therapeutics

**DIRECTOR:** William Schiemann, PhD

**CO-DIRECTOR:** Daniel Lindner, MD, PhD

Provides expertise and access to mouse modeling, empowering researchers to evaluate cancer therapies and immune contributions in an intact organism.

- Pharmacokinetic evaluation
- Patient-derived xenograft bank: 50 patient-derived models from multiple disease sites (e.g., breast, lung, prostate)
- Immunocompromised mouse models
- Humanized mouse models

## Biostatistics & Bioinformatics

**DIRECTOR:** Ming Li, PhD

**CO-DIRECTORS:** Brian Hobbs, PhD; Ricky Chan, PhD

Aids investigators in basic and clinical cancer research by providing expertise in study design and in the analysis and interpretation of complex data.

- Biostatistics, bioinformatics and clinical informatics expertise
- Study design and protocol development
- Protocol review and study monitoring
- Data analytics and reporting
- Database development and management

## Cytometry & Microscopy

**DIRECTOR:** Brian Grimberg, PhD

**CO-DIRECTORS:** Judy Drazba, PhD; Howard Meyerson, MD; Scott Sieg, PhD; Philip Woost, PhD

Provides cancer investigators access to instrumentation and expertise in microscopy, cytometry and cell sorting, enabling investigators to interrogate cancer at a cellular and subcellular level.

- Multi-channel cell sorting and flow cytometry
- Microscopy including brightfield, fluorescent and electron
- Sample processing for histological staining
- Immunohistochemical services
- Single cell sequencing support
- Immune monitoring services

# SHARED RESOURCES

## Hematopoietic Biorepository & Cellular Therapy

**DIRECTOR:** David N. Wald, MD, PhD  
**OPERATIONS AND QUALITY DIRECTOR:** Jane Reese, MBA

Enhances cancer investigator research efforts through access to clinical grade cell therapy products and a hematopoietic biorepository.

- Procurement, processing, analysis and distribution of human hematopoietic cells (e.g., blood, bone marrow)
- Hematopoietic biorepository
- Production of clinical grade cellular therapy products (FDA and GMP compliant)

## Imaging Research

**DIRECTOR:** Chris A. Flask, PhD  
**MANAGER:** Michael Kavran

Provides investigators a comprehensive array of established and novel preclinical and clinical imaging platforms to evaluate cancer in the context of a living organism.

- Investigate mechanisms of cancer initiation and progression and monitor therapeutic efficacy
- Develop and validate new imaging technologies to transform clinical cancer imaging
- Cryo-fluorescence imaging of whole animals/tissues
- Magnetic resonance fingerprinting (clinical and preclinical MRI)

## Integrated Genomics

**DIRECTOR:** Martina Veigl, PhD  
**CO-DIRECTOR:** Alexander Miron, PhD

Houses state-of-the-art technology for researchers to identify and better understand genes associated with the development and progression of cancer.

- Experimental design and appropriate technology selection
- Nucleic acid isolation from difficult sources and quality assessment
- Genotyping, copy number assessment, LOH and chromosome aberrations
- Gene expression analysis and assessment of microRNA
- Next generation sequencing (genomic, exon and custom)
- RNA sequencing
- Single cell analysis

## Population Cancer Analytics

**DIRECTOR:** Siran Koroukian, PhD  
**CO-DIRECTOR:** Kurt Stange, MD, PhD

Aids cancer center researchers in population-based studies, through access to relevant data sources and analytical expertise. Investigator designed examination of these data sources allows leaders and hospital partners to better understand the cancer care needs and outcomes of its regional population.

- Northeast Ohio Cancer Risk Assessment and Surveillance Engine (NEOCASE) data
- Linked Ohio Cancer Incidence Surveillance System (OCISS) and Medicare data
- Surveillance, Epidemiology, and End Results (SEER) data
- SEER-Medicare Health Outcomes Survey (SEER-MHOS) data
- Death certificate data from Ohio Department of Health
- Healthcare Cost and Utilization Project (HCUP)



FOR MORE INFORMATION, VISIT  
[case.edu/cancer/research/shared-resources](https://case.edu/cancer/research/shared-resources)

## Proteomics

**DIRECTOR:** Mark Chance, PhD  
**CO-DIRECTORS:** Janna Kiselar, PhD;  
Belinda B. Willard, PhD

Provides basic and clinical investigators access to highly experienced personnel and advanced technologies enabling identification and characterization of proteins and therapeutic compounds.

- Advanced proteomic and metabolomics technologies
- Pharmacokinetic studies (e.g., drug metabolism)
- World-class expertise in structural biology
- Integrative bioinformatic systems biology tools allow for multi 'omics' (genomics, proteomics, metabolomics)

## Radiation Resources

**DIRECTOR:** Mitchell Machtay, MD

Provides cancer researchers instrumentation and consultation in sample irradiation. Ionizing radiation has therapeutic and carcinogenic properties, thus investigators can use this resource to mimic cancer-associated damage, as well as standard-of-care therapies.

- DNA damage induction in cells
- Small animal bone marrow ablation
- Therapeutic dosing of tumor bearing small animals
- Gamma Knife™ (localized irradiation)

## Small Molecule Drug Development

**DIRECTOR:** Drew J. Adams, PhD  
**MANAGER:** Yuriy Fedorov, PhD

Houses technology and chemical libraries that facilitate cancer drug discovery in a high-throughput manner.

- High-throughput screening and assay development
- Bioactives chemical library (3,000 compounds)
- Diversity chemical structure library (100,000 compounds)
- Advice and guidance on design, optimization and expansion

## Tissue Resources

**DIRECTOR:** Marta Couce, MD, PhD  
**CO-DIRECTORS:** Daniel Lindner, MD, PhD; Jennifer Ko, MD, PhD

Provides researchers access to human tissue and histology services, allowing for the analysis of microscopic anatomy.

- Central and disease-oriented biorepositories
- Immunohistochemistry (IHC) and Immunofluorescence (IF)
- Tissue microarrays (TMAs) and in situ hybridization
- Laser capture microdissection

## Transgenic & Targeting

**DIRECTOR:** Ron Conlon, PhD

Leader in mouse model and genetic technologies used to test new cancer therapies; uses gene editing of mouse genes to simulate the changes that cause or prevent human cancer.

- CRISPR/Cas9 gene editing (germ-line and somatic)
- Reporter/Cre knock-ins
- Cryopreservation, in vitro fertilization and rederivation
- Chimeras

## Translational Research

**DIRECTOR:** John Pink, PhD

**CO-DIRECTOR:** Daniel Lindner, MD, PhD

Aids in the translation of scientific findings from bench to bedside, with the goal of improved cancer therapies. Provides access to established infrastructure facilitating clinical trial specimen handling and analysis and supporting preclinical drug discovery efforts.

- Nucleic acid isolation
- Multiplex, fluorescent, chemiluminescent assays (cytokines, ELISAs)
- Preclinical drug testing
- Clinical sample processing, shipping and storage
- Laboratory analyses (e.g., single cell DNA damage, cell cycle analysis, flow cytometry)



## RESEARCH HIGHLIGHTS

### ATHYMIC

Using humanized mouse models, showed the administration of an antibody (Leronlimba) blocked development of graft-versus-host disease (GVHD). GVHD is a very serious side effect (often fatal) that can occur following bone marrow transplantation for treatment of blood cancers. [Burger, *Biol Blood Marrow Transplant*, 2018]

### BIOSTATISTICS

Provided statistical expertise to a study led by Anant Madabhushi, PhD, including survival analysis and machine learning techniques, which discovered tissue architecture of tumor-infiltrating lymphocytes can be used to predict likelihood of non-small cell lung cancer recurrence. [Corredor G, *Clin Cancer Res*, 2019]

### HEMATOPOIETIC

Through efforts led by Paolo Caimi, MD, Marcos de Lima, MD, and Jane Reese, MBA, this facility was the first academic center in the country to extensively use an automated manufacturing device to produce CD19 CAR T-cells. Local production of cells enables fast treatment of high-risk Non-Hodgkin lymphoma patients.

### PROTEOMICS

With Sichun Yang, PhD, employed structural mass spectrometry analysis of the human estrogen receptor complex, directly resulting in a newly chemically engineered chemical screening assay for drug discovery of breast cancer and supporting future investigation of targeting the estrogen receptor for breast cancer drug resistance. [Huang, *Nat Commun*, 2018; R01GM114056]

### TRANSLATIONAL

In collaboration with Paolo Caimi, MD, as a prelude to clinical trials, this facility demonstrated that the combination of the two agents, Venetoclax with ADCT-402, was greater than the additive activity of the individual agents. Results support development of a clinical trial utilizing these two agents for treatment of lymphoma.



The Case Comprehensive Cancer Center is committed to understanding and addressing the cancer-related needs of the community, particularly medically underserved and historically underrepresented populations, as well as diseases more common in our community due to excess risk from various causes.



**Eliseo J. Pérez-Stable, MD, addresses the Cancer Disparities Symposium**

The Office of Cancer Disparities Research (OCDR), led by Monica Webb Hooper, PhD, is the academic cornerstone of our systematic efforts to meet this goal. The OCDR supports investigators in their efforts to formulate and execute cancer disparities research, and to increase engagement with key community stakeholders and residents. While there are many examples of community-inclusive cancer disparities activities initiated and supported by the OCDR, three past-year examples include the Forward Movement Project, the 3rd Annual Cancer Disparities Symposium, and the Cancer Disparities Specialized Program of Research Excellence (SPORE) grant.

#### **Forward Movement Project**

Phase I of the Forward Movement Project, a community-based participatory research effort, began with a topic of importance to the community, led to a systematic investigation,

and regarded academic and community partners as true equals. The OCDR and the Case CCC Community Advisory Board collaborated to conduct a “listening tour” to enhance our understanding of factors related to community distrust among underserved and racial/ethnic minority members of the community. Residents from nine neighborhoods in greater Cleveland engaged in open-ended forums for sharing thoughts, ideas and concerns about cancer prevention and control, healthcare systems and research. Case CCC researchers joined us on the listening tour and much was learned about the unmet healthcare needs of the communities we serve and racial/ethnic differences in the lived experiences of patients. (See sidebar for what we heard during the Forward Movement Listening Tour.)

Phase I findings were disseminated throughout the Case CCC and the wider community (Webb Hooper, *Int J Environ Res Public Health*, 2019). Phase II, testing the effects of a user-generated intervention on healthcare and biomedical research distrust, is underway.

# COMMUNITY ENGAGED RESEARCH





**SAVE THE DATE**  
**4th Annual Cancer  
Disparities Symposium**  
**March 6, 2020**

### 3rd Annual Cancer Disparities Symposium

The Cancer Disparities Symposium is the largest Case CCC annual event organized by the OCCR, and is focused on academic-community engagement, and the dissemination of cancer disparities research and outreach initiatives. This year's meeting convened researchers, clinicians, health professionals, patient advocates, students, community organizations and government representatives from 12 states and 53 organizations to discuss current research and new ideas and form collaborations. Our plenary speaker, Eliseo J. Pérez-Stable, MD, director of the National Institute on Minority

Health and Health Disparities, focused on the roles of race, ethnicity and social class in cancer disparities, and highlighted funding opportunities to support minority health and health disparities science.

### Cancer Disparities SPORE

Nathan A. Berger, MD, Monica Webb Hooper, PhD, and Li Li, MD, PhD, are leading a three-year P20 grant from the National Cancer Institute to investigate colorectal and breast cancer health disparities. It will provide the infrastructure for a new, comprehensive research program to study cancer health disparities at molecular and population levels.

### CANCER DISPARITIES SPORE: RELATED RESEARCH

**Epigenetic Age Acceleration, Neighborhood Disadvantage, and Racial Disparities in Risk of Colon Adenoma**

**LEADERS:** Li Li, MD, PhD; and Claudia Coulton, PhD

**Role of MYC-MIZ1 Signaling and the Inflammatory Immune Micro-environment in Triple-Negative Breast Cancer Racial Disparities**

**LEADERS:** Vinay Varadan, PhD; Cynthia Owusu, MD; William Schieman, PhD

## COMMUNITY VOICES

Here is what we heard  
during the Forward  
Movement Listening Tour.

### 1 TRUST IN THE HEALTHCARE SYSTEM IS LOW

Doctors and nurses don't care about every patient

Healthcare is seen as big business

Patients are treated differently based on their neighborhoods and insurance coverage

Doctors and drug companies work together to push medications

### 2 HEALTHCARE EXPERIENCES ARE NEGATIVE

Doctors don't communicate well, spend time with patients or show empathy

High medical bills arrive months after appointments

Out-of-pocket costs are unknown and insurance policies are unclear

Deaf and hearing-impaired patients feel disrespected

### 3 RESEARCH AND TESTING ARE EXCLUSIVE

The African American community feels excluded from medical research

People have concerns about joining research clinical trials testing new medications

Study results are not shared with communities and therefore not helpful to the public





# CAREER ENHANCEMENT

## The Office of Cancer Training, Education and Research

taps into the strengths of the Case Comprehensive Cancer Center to offer career enhancement, comprehensive training and professional development opportunities for middle schoolers through junior faculty. This year, the center started two new programs to engage individuals at an earlier age, leverage their enthusiasm for science and entice them to pursue cancer-focused careers. Trainees are introduced to the fundamentals of cancer biology through immersion programs, sparking interest in biomedical and clinical cancer research and starting them early on the right career path.

FOR MORE INFORMATION, VISIT  
[case.edu/cancer/training-education](http://case.edu/cancer/training-education)

## YOUTH ENGAGED IN SCIENCE (YES)

DIRECTOR: *Nathan A. Berger, MD*

Youth Engaged in Science (YES) is a program to support educational opportunities for under-represented minority middle and high school students from the Cleveland Metropolitan School District (CMSD), along with their teachers and families. The program is supported by a five-year \$2.5 million grant from the NCI and builds upon the Case CCC's NCI-funded Continuing Umbrella of Research Experience Award and Case Western Reserve University School of Medicine's successful high school-student targeted, Scientific Enrichment and Opportunity (SEO) Program.

The program strives to engage students early on, spark their interest in cancer research, and give them the tools to successfully join the biomedical workforce. With the YES program, students as young as middle school, as well as their families, are introduced to the fundamentals of research. YES actively partners with teachers in the CMSD to help them develop programs, better explain cancer basics, and educate on the future opportunities open to their students. The three-pronged structure of YES, which also includes a summerlong research immersion for teachers and high school students, prepares them for future educational opportunities and successful entrance into jobs in clinical or biomedical settings.

"It's very exciting to help these kids discover a love of science and see them succeed," says Nathan A. Berger, MD, principal investigator and director of the Center for Science, Health and Society at Case Western Reserve School of Medicine. "We've had great success with the SEO program, and with the concentration of exceptional labs and research experts in the Case CCC. We are confident YES will support the education of many future researchers from Cleveland."

## CANCER-FOCUSED SUMMER UNDERGRADUATE RESEARCH PROGRAM (CANSUR)

DIRECTOR: *Mark Jackson, PhD*

CanSUR is a new, fully immersive program dedicated to converting aspiring undergraduates into the nation's next cancer research workforce to meet biomedical, behavioral and clinical research needs. This program is funded by a five-year, \$1.6 million grant from the National Cancer Institute and quickly became highly competitive. Over 288 applicants competed for 32 positions for the inaugural 2019 program.

The goal of the program is similar to YES. Program participants will receive a full cancer research experience over a 10-week period. Students are paired with two faculty mentors, one senior and one more junior, to guide them through their journey. The program's curriculum includes an intensive weeklong immersion workshop, an innovative 3-D cancer education model called HoloLens, and a series of interactive cancer research lectures on the basics of cancer biology, current therapies, research techniques and career paths.

"We saw an opportunity to better connect with highly motivated undergraduates and teach them the basics of cancer research," says program director Mark Jackson, PhD, associate director for training and education

at the Case CCC and associate professor of pathology at Case Western Reserve University. "With CanSUR, we can actively foster their excitement through hands-on activities, hopefully motivating them to pursue a career in cancer research."

### CLINICAL ONCOLOGY RESEARCH CAREER DEVELOPMENT PROGRAM


**DIRECTOR:** Stan Gerson, MD

**CO-DIRECTORS:** Mitchell Machtay, MD;  
Alex Huang, MD, PhD

For the past 21 years, the Case CCC Clinical Oncology Research Program (CORP) has provided top-tier training to clinical oncology junior faculty physicians pursuing careers in

translational patient-oriented research. This program, the second-longest-running one of its kind in the country, is supported by the Paul Calabresi Career Development Award for Clinical Oncology from the National Cancer Institute and was recently renewed for five more years. Overall, CORP has had remarkable success and impact, with a majority of program graduates having emerged as successful academic physicians developing independent clinical research programs, often with external funding and active investigator-initiated clinical trial efforts. The best evidence of success is the transformation of scholars from trainee to expert, who have returned to the program to serve as mentors to new scholars.

## The Rewards of Mentorship



Pediatric cancer researcher Dr. Yamilet Huerta, with the help of her mentor, Dr. Alex Huang, secures two grants to further her leukemia research.

In 2018, as her clinical fellowship was ending, Yamilet Huerta, MD, was determined to continue her research into acute myeloid leukemia (AML). A discussion with her mentor, Alex Huang, MD, PhD, about embarking on an immunotherapy approach, led to the pediatric cancer researcher earning not one but two grants — a \$186,405 fellowship award from St. Baldrick's Foundation and a \$200,000 Young Investigator grant from Hyundai Hope on Wheels.

Dr. Huerta, a trainee within the Case Comprehensive Cancer Center and member of the Huang Lab at Case Western Reserve University School of Medicine and University Hospitals Rainbow Babies & Children's Hospital, credits much of her success to the mentorship offered to her by Dr. Huang — both in the lab and in her quest to further her work.

"Dr. Huang guided and encouraged me through the challenges of the grant application process," she says. "He taught me to never give up."

Dr. Huang, co-leader of the Hematopoietic and Immune Cancer Biology Program of the Case CCC, Case

Western Reserve pediatrics professor, and director of the Pediatric Hematology/Oncology clinical fellowship program, notes that such early career development awards provide a distinct advantage to recipients.

"They allow fellows 'protected time' to focus on research leading to clinical trials of new cancer therapies," he says, adding that, essentially, Dr. Huerta is becoming a leukemia expert.

In addition to receiving this financial support, Dr. Huerta earned a junior faculty position and collaboration with a co-mentor, Challice Bonifant, MD, PhD, assistant professor of pediatric oncology at the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University School of Medicine in Baltimore.

Dr. Huerta's experience using Huang Lab's unique intravital imaging equipment to observe and understand cellular interactions matches well with Dr. Bonifant's work on engineering engager CAR T-cells. Together, the two women make a powerful duo for investigating targeted immunotherapy and other novel treatments for AML.

"It has been a delight to help Yami through the initial stages of planning her fellowship project," says Dr. Bonifant. "We are bringing together two complex technologies to learn about AML and host disease biology. Part of the journey has been in understanding the challenges, and discussing these aspects with Yami has been exciting for both of us."

In Dr. Huang's eyes, mentorship has rewards for mentors, as well.

"It's really a joy to watch the trainees come into the program and train them to the point where they become our colleagues, joining us in the Rainbow family, helping to take care of patients," Dr. Huang says. "We can trust them and trust their training."

Pioneering team develops a Pap test  
for the esophagus to help prevent  
esophageal adenocarcinoma.



1



2



3

1. The tethered balloon, about the size of a capsule, is swallowed.

2. Balloon with structured surface inflates in stomach, then is pulled back to sample distal esophagus.

3. Balloon is deflated for retrieval.

A team of Case Comprehensive Cancer Center faculty and physicians has pioneered an affordable, simple screen to help prevent esophageal adenocarcinoma (EAC), a deadly cancer with a less-than 20% survival rate.

Studied in patients diagnosed with gastroesophageal reflux disease (GERD), the screen consists of an innovative, non-endoscopic cell sampling device and biomarker testing for the EAC precursor, Barrett's Esophagus (BE). The method has proven at least 90% accurate in studies conducted by Amitabh Chak, MD, principal investigator and University Hospitals gastroenterologist.

"It is a Pap smear for the esophagus," says Dr. Chak, who is head of the National Institutes of Health-Case Barrett's Esophagus Translational Research Network (BETRNet) program and discoverer of a BE-related gene mutation.

The sampling device, called EsoCheck™ (eee-so-chek), is a swallowable, textured, silicon balloon about the size of a vitamin pill, which Dr. Chak, Sanford Markowitz, MD, PhD (head of the NIH-Case GI Cancers SPORE Program of Research Excellence), and Pathology Vice-Chair for Clinical Affairs Joseph Willis, MD, began conceptualizing just two years ago.

"Having already brought the first colon cancer biomarker screens to market — ColoSure™ and Cologuard™ — our next challenge was sampling the esophagus without endoscopy and putting people to sleep," Dr. Markowitz says, adding that finding Barrett's early allows monitoring so that abnormal cells can be removed through ablation, freezing, cauterizing or excising.

The new BE-screening method takes less than five minutes and can be performed by a registered nurse in a primary care physician's office. Once cells are collected on the balloon, the tip is sent to the lab for DNA testing. The remainder of the single-use device is disposed as medical waste.

"It was over before I knew it," says patient Robert Eiden, a participant in the current BE clinical trial. "I feel very lucky to have found the right doctors and that they caught the

## NEW THERAPIES, NEW TREATMENTS

The Case Comprehensive Cancer Center was once again selected as a Lead Academic Participating Site for the National Clinical Trials Network. This new, six-year, \$8.9M grant, led by co-PIs Mitchell Machtay, MD and Aaron Gerds, MD, MS, affords cancer patients in the area access to improved therapies through National Cancer Institute-funded trials, closer to home. Machtay said the Center is focused on improving the lives of patients in Northeast Ohio by offering cutting-edge therapies and developing the treatments of the future. "This renewal will not only make available cancer clinical trials being conducted at some of the leading cancer centers across the United States, but also help future patients through the development of new treatment approaches."

Lead Academic Participating Sites offer qualifying patients access to the National Clinical Trials Network's late-phase trials, addressing scientific questions that usually require multi-site investigation. "By sharing information and working together we can speed the pace of research and offer more trials, including those targeting rare cancers," said Gerds. "All these lead to improved outcomes for patients."

Barrett's early. At my last visit, Dr. Chak shook my hand and said he'd see me in three years."

Dr. Markowitz says the project illustrates how translational cancer research is a team effort.

"We had a combination of my lab people doing gene discovery and basic cancer genetics," he says, "GI pathologist Joe Willis, who has a keen appreciation of the clinical biology of the disease, and gastroenterologist Amitabh Chak, who has a keen understanding of patient clinical care and opportunities for introducing new modalities."

"The project," he continues, "would not have been possible without the hard work of Professor Helen Moinova, PhD, who developed the methylated VIM and CCNA1 DNA tests used for detecting colon cancer and now BE."

Moving research from academia into people's lives is every physician's dream.

"No one needs to die of esophageal cancer," says Dr. Markowitz, "if we have good tests like this one."

*Support has been provided by National Institutes of Health, American Cancer Society, Case-Coulter Partnership for Translational Research, and Ohio Third Frontier Technology and Validation Start-Up Fund.*

# CLINICAL RESEARCH



# PHILANTHROPY & PILOT SUPPORT

With a tenfold return on investment, pilot grants jump-start novel projects that advance cancer treatments. Over the past few years, philanthropic support from the Research Innovation Fund and VeloSano Bike to Cure have helped to expand the pilot program. Donations are reinvested into center members as pilot awards, driving collaborative research, developing and translating laboratory discoveries into new treatment and helping people in our catchment area.

## Multi-Investigator Awards

- Sex Differences in Glioma (PIs: Eckhard Jankowsky, Justin Lathia and Jill Barnholtz-Sloan)

## Cancer Disparities

- Functional Immune-Phenotypes underlying Racial Disparities in Endometrial Cancer (PI: Stefanie Avril)
- Innovations to Prevent Relapse among Low-Income African American Smokers (PI: Monica Webb Hooper)

## New Collaborations

- MBD2 as a novel therapeutic target in TET2 deficient cancer (PIs: Omar Mian and Babel Jha)
- Sensitizing ovarian cancer to PARPi through attenuation of DNA repair enzymes (PIs: Ofer Reizes and Stefanie Avril)
- Role of microRNAs in regulation of PD1 signaling in hepatocellular carcinoma (PIs: Hawwa Alao and Donald Anthony)
- Incomplete follow-up after positive FIT or stool DNA testing: multimethod approach (PIs: Greg Cooper and Kurt Stange)

## Innovation

- New paradigm: protein tyrosine nitration in tumorigenesis (PI: Zhenghe John Wang)
- Targeting cross-talk between domains in estrogen receptor (PIs: Sichun Yang and Hung-Ying Kao)
- Developing BAFF-R CAR-T cells to target malignant B cells (PI: Reshmi Parameswaran)

## VeloSano

- A Refillable Drug Delivery Device Capable of Treating Recurrent Brain Tumors (PI: Horst von Recum)
- The Oncogenic Impact of LIN9 in Triple Negative Breast Cancer (PI: Ruth Keri)
- Combating resistance to immune checkpoint inhibition; identifying new targets using in vivo forward genetics screening (PIs: Mark Jackson, Lewis Shi)
- Targeting Hexosamine Biosynthetic Pathway for Acute Myeloid Leukemia therapy (PI: Reshmi Parameswaran)
- Targeting thioredoxin reductase in AML (PI: David Wald)
- Novel molecular signatures in Shh Medulloblastoma defines immune phenotypes and predicts immunotherapeutic response (PI: Alex Huang)
- Identifying the molecular targets of mistletoe lectin I for drug development in hepatocellular carcinoma (PI: Richard Lee)



## VELOSANO BIKE TO CURE

Every July for the past six years, VeloSano Bike to Cure has brought people together to raise money to support Cleveland-based cancer research. The VeloSano movement is powerful and personal.

"It's a community of people touched by cancer," says Dr. Brian Bolwell, chairman of Taussig Cancer Institute and deputy director for Cleveland Clinic, "that want to do something to contribute to research that might lead to scientific and clinical progress — and even cures."

A portion of all proceeds raised is gifted to the Case CCC to distribute as pilot grants. To apply, principal investigators must participate in VeloSano. This drives involvement and awareness and adds to the overall fundraising effort.





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