LUDWIG CENTER | MIT

Ludwig Center at MIT: Updates from Fiscal Year 2022 (July 1, 2021-June 30, 2022)

The ***Ludwig Center at MIT*** is focused on understanding and addressing the processes associated with malignant progression, in particular the mechanisms that allow cancer cells originating in primary tumors to disseminate and ultimately form metastatic colonies. This multi-step process involves a series of cell-biological and biochemical changes in malignant cells, which are being investigated at several levels. Our research includes identifying and characterizing the biological determinants that allow disseminated cancer cells to gain a foothold in foreign tissue microenvironments, and then to succeed in spawning rapidly growing metastatic colonies.

The work of Ludwig Center members, and their laboratories, is greatly enhanced by the shared sense of mission and community fostered by a program of regular engagement and support from Center colleagues, administrators, and research and financial resources. The impact of Ludwig Center support can be seen most notably in the research productivity of Center members. Research and programmatic highlights, along with publications and expenditures, are outlined below.

CENTER FACULTY, TRAINEES & COMMUNITY

This fiscal year (FY2022) brought new changes to the Ludwig Center at MIT. While Drs. Weinberg and Jacks continue to serve as co-directors, four new members joined the group: Drs. Stefani Spranger and Jonathan Weissman joined as a full member at the start of the fiscal year, while Drs. Francisco J. Sánchez-Rivera and Yadira Soto-Feliciano started as pilot members in February of 2022. The other active Center members are Drs. Bhatia, Hemann, Hynes, Lees, Manalis, and Vander Heiden.

Dr. Spranger's lab studies how the body's immune system interacts with growing tumors to harness the immune response to fight cancer. Dr. Weissman investigates how proteins fold into their correct shape and how misfolding impacts disease and normal physiology, while building innovative tools for exploring the organizational principles of biological systems. Francisco J. Sánchez-Rivera aims to understand how genetic variation shapes normal physiology and disease, with a focus on cancer. Yadira Soto-Feliciano studies chromatin and epigenetic regulation in normal development and cancer.

All investigators from the Ludwig Center at MIT have continued to collaborate with each other and with members of Ludwig Centers at other institutions, notably the Harvard Ludwig Center. Intra-Center collaborations are facilitated in part by community events and meetings, including the annual MIT Ludwig Center Retreat, which was held on May 5, 2022 at MIT's Endicott House. Almost 70 participants attended talks and posters presented by each of the labs, and general discussions were lively and highly interactive.

Inter-Center collaborations this year included ongoing joint work by Dr. Jacks with Drs. Sandro Santagata and Peter Sorger at Ludwig Center at Harvard. Dr. Vander Heiden's lab also collaborates with a team from the Ludwig Center at Harvard, under the leadership of Dr. Rakesh Jain.

Highlights of faculty awards and honors received by Ludwig Center members over the past year include:

Name	Awards and Honors
Sangeeta Bhatia	Selected by STAT News as a member of the inaugural STATUS List Selected by Fierce Pharma as one of the Most Influential People in Biopharma
Yadira Soto-Feliciano	V Scholar Award from the V Foundation for Cancer Research
Matt Vander Heiden	Fellow in the European Academy of Cancer Sciences

- ***Ludwig Graduate Fellowships*** were awarded to five graduate students:

Name	Project Title
Neil Dalvie	"Developing an alternative host for low-cost manufacturing of monoclonal antibodies"
Anisha Datta	"Investigating the effect of anti-AXL treatment on cancer cell survival and recognition by macrophages"
Ellen Kim	"Engineering lentiviruses for gene delivery to antigen-specific T cells "
Jin (Harvey) Yang	"Bottom-up dissection of 3D genome disorganization in cancer"
Colin Fowler	"Understanding the mechanisms of resistance to PRMT5 inhibition and the roles of arginine methylation in cancer"

- ***Ludwig Center Postdoctoral Fellowships*** were awarded to ten postdoctoral associates:

Name	Project Title
Ryuhjin Ahn	"Defining the role of Siglec receptors in glioblastoma"
Charles Couturier	"Understanding mechanisms of plasticity and state determination in glioblastoma"
Whitney Henry	"Functional characterization of ether lipids in cancer progression"
Brendan Horton	"Uncovering the determinants of CD8+ T cell responsiveness to cancer immunotherapy"
Sasan Jalili	"Sampling tissue-resident cancer vaccine responses using noninvasive microneedles"
Nicholas Lamson	"Chemotherapeutic delivery across the blood brain barrier and to glioma cells using nanoparticles electrostatically conjugated with dual targeting peptides"
Edward Miller	"Development of next-generation platinum agents against glioblastoma"
Morgan Stilgenbauer	"Chemical probe discovery for ligases that govern MYC post-translational stability"
Meghan Torrence	"Defining the role of tertiary lymphoid structures in pancreatic cancer"
Parisa Yousefpour	"Self-replicating RNAs for cancer immunotherapy"

For more updates on Ludwig Center activities, please visit https://ludwigcenter.mit.edu/.

RESEARCH HIGHLIGHTS

Selected projects supported by the Ludwig Center at MIT:

Hynes Laboratory: Pancreatic ductal adenocarcinoma (PDAC) characteristically exhibits a collagen-rich, dense extracellular matrix (ECM) that promotes cancer progression and presents a physical barrier to drug delivery. To determine how the regulation of collagen contributes to PDAC malignancy, the Hynes Laboratory previously performed unbiased mass spectrometry on patient tumor samples enriched for the ECM components across all tumor stages. Subsequent data analysis revealed that fibrillar collagens retain their C-terminal pro-domains in the PDAC ECM, suggesting reduced procollagen C-proteinase activity. They further showed that the enzyme possessing procollagen C-proteinase activity, bone morphogenetic protein1 (BMP1), selectively inhibited tumor growth and metastasis in cells that expressed high levels of *COL1A1* – encoding a chain of type I fibrillar collagen. As a secreted proteinase, BMP1 promotes fibrillar collagen deposition from both cancer cells and stromal cells; however, only cancer cell-derived procollagen cleavage and deposition antagonizes PDAC proliferation rate. Overall, these studies highlight a tumor-suppressive role for PDAC-derived fibrillar collagen and suggest patient stratification strategies based on their tumor *COL1A1* expression when considering treatments related to perturbation of fibrillar collagens.

Work in the coming year will focus on a different project: to further optimize a nanotechnology platform that uses small antibodies, referred to as "nanobodies," against the tumor ECM as agents to detect, monitor, and suppress metastases in breast cancer and PDAC. Nanobodies represent a special type of antibody produced by alpacas and other camelids, which display several chemical, biological, and engineering advantages over normal antibodies for such use.

Related publication: Tian, C., Huang, Y., Clauser, K.R., Rickelt, S., Lau, A.N., Carr, S.A., Vander Heiden, M.G. and Hynes, R.O. (2021). Suppression of pancreatic ductal adenocarcinoma growth and metastasis by fibrillar collagens produced selectively by tumor cells. Nat Commun. 2021 12(1):2328. Doi: 10.1038/s41467-021-22490-9. PMID: 33879793 PMC8058088.

Manalis Laboratory: The Manalis Laboratory has developed a fluidics system that can identify fluorescent cancer cells in the bloodstream of live, unanesthetized mice in real time. This technology was originally demonstrated in a collaboration with fellow Ludwig Center members—the Jacks and Vander Heiden Laboratories—and shown to have several key benefits over other methods of enumerating circulating tumor cells (CTCs). Using a genetically fluorescent tumor model, the Manalis team performs a surgical cannulation of the carotid artery and jugular vein of the mouse, allowing temporary access to the circulatory system. The mouse is then connected to an optofluidic platform (fluorescent cell counter), which combines a microfluidic chip with a laser detection setup to enable real-time identification of fluorescent cells from whole blood. This technology may facilitate more accurate studies of CTC dynamics, such as lifespan in circulation and metastatic properties.

The Manalis group has also validated a blood exchange approach whereby the circulation of a tumor-bearing mouse was sequentially connected via the optofluidic platform to naïve healthy mice of the same genetic background. Although this technique was originally designed to detect and transfer rare CTCs within the blood of mice bearing solid tumors, over the past year this has been expanded to study models of hematological (liquid) cancers, which are often thought of as systemic diseases encompassing variable degrees of tumor burden in the blood. The blood exchange method allows for novel ways of understanding how various factors contribute to the circulation kinetics of liquid cancers.

Related publication: Hamza B, Ng SR, Prakadan SM, Delgado FF, Chin CR, King EM, Yang LF, Davidson SM, DeGouveia KL, Cermak N, Navia AW, Winter PS, Drake RS, Tammela T, Li CM, Papagiannakopoulos T, Gupta AJ, Shaw Bagnall J, Knudsen SM, Vander Heiden MG, Wasserman SC, Jacks T, Shalek AK, Manalis SR. Optofluidic real-time cell sorter for longitudinal CTC studies in mouse models of cancer. Proc Natl Acad Sci U S A. 2019 Feb 5;116(6):2232-2236. doi: 10.1073/pnas.1814102116. Epub 2019 Jan 23. PMID: 30674677; PMCID: PMC6369805.

Soto-Feliciano Laboratory: New Ludwig Center pilot member, Professor Yadira Soto-Feliciano, and her group study aberrant chromatin and epigenetic mechanisms, which can impinge on all hallmarks of cancer. These phenotypes may be achieved through silencing of tumor suppressor genes by histone/DNA methylation, activation of oncogenes via enhancer repurposing, or non-physiological cell fate/lineage transitions. One constant among these mechanisms is the requirement for nucleation/assembly of chromatin modifying or remodeling complexes in the right genomic context to support the malignant state. As part of their Ludwig Center-funded research, the Soto-Feliciano group has been working to elucidate the biological impact of cancer-associated mutations in chromatin and epigenetic regulators using a multifaceted approach. To determine genotype-phenotype relationships driven by these mutations, they combine CRISPR saturation mutagenesis (cross-referenced to cancer genomics databases), in vitro and in vivo models, and transcriptomics and epigenomics tools.

PUBLICATIONS

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EXPENDITURES

Use of ***Ludwig Center at MIT*** funds is focused on direct support for research, which includes not only funding for faculty investigators, but also research services provided through the Koch Institute's Robert A. Swanson (1969) Biotechnology Center core facilities to support additional research efforts, and fellowships for graduate students and postdoctoral researchers. Support for the Ludwig Center in fiscal year 2022 was appropriated as indicated in the chart below.