LUDWIG CENTER | MIT

Ludwig Center at MIT: Updates for Fiscal Year 2020 (July 1, 2019-June 30, 2020)

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

In fiscal year (FY2020), the ***Ludwig Center at MIT*** supported the research of 10 faculty members whose work focuses on the critical problems of cancer progression and metastasis. These include Drs. Robert Weinberg and Tyler Jacks, who serve as co-directors of the Center, as well as Drs. Angelika Amon, Sangeeta Bhatia, Michael Hemann, Richard Hynes, Jacqueline Lees, Scott Manalis, Aviv Regev, and Matthew Vander Heiden.

Leaders in their field, Center faculty members regularly receive national and international recognition for their research. Highlights of faculty awards and honors received by Ludwig Center members over the past year:

Name	Awards and Honors
Angelika Amon	Human Frontier Science Program (HFSP) Nakasone Award; Ernst W. Bertner Memorial Award
Aviv Regev	Lurie Prize in Biomedical Sciences
Tyler Jacks	AACR Princess Takamatsu Memorial Lectureship
Matthew Vander Heiden	NIH Outstanding Investigator Award

On medical leave throughout the 2019-2020 year, long-time Ludwig Center member Professor Frank Gertler did not participate in Center activities or receive his usual funding allocation; he announced his retirement at the end of June. Earlier in the spring, center member Aviv Regev announced that she would leave academia over the summer to take on a new role as head of research and early development at Genentech.

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

Name	Project Title
Yash Agarwal	"Enhancing local delivery of cancer immunotherapy with alum adjuvant"
Sachin Bhagchandani	"Toward safe, systemic immunotherapies for treatment of metastatic disease: Developing dendritic cell-biased synthetic TLR7 bottlebrush

	prodrugs (TLR7-BPDs) with precise control over magnitude of immune stimulation"
Ishwar Kohale	"Phosphoproteomic characterization of triple negative breast cancer to develop novel therapeutic strategies"
Mohammed Toure	"Selective degradation of cyclin-dependent kinase 9 in metastatic cancer models"

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

Name	Project Title
Megan Burger	"Elucidating the role of the interferon gamma signaling in lung cancer progression and metastasis"
Jackson Halpin	"Investigation of the design, structure and mechanism of Mena protein interaction inhibitors"
Gavin Kiel	"A modular platform for combination immuno-/photothermal therapy based on carbene-anchored gold nanorods"
Arthur Lambert	"Transcriptional control of cancer stem cells and metastasis by p63/p73"
Pedro Pozo	"Determining the mechanisms of resistance to PRMT5i in tumors"
Shiva Razavi	"Developing a 3D organotypic hepatocellular carcinoma model to probe Wnt regulation of metastasis in vitro"
Elen Torres	"The role of tumor cell-intrinsic Sox2 in the anti-tumor immune response in a metastatic model of non-small cell lung cancer"
Xueyang Yu	"Unraveling the role of MK2 in progression and metastasis of epithelial high grade serous ovarian cancer"

In summer 2020, the Ludwig Center launched a new website (ludwigcenter.mit.edu), which better showcases the center community and its research for scientific and public audiences. Planning for the new website was underway even before the COVID-19 pandemic, which made a revamped online presence even more welcome. In addition to research disruptions, the pandemic necessitated the cancellation of a number of in-person activities for the spring, most notably the Ludwig Center's annual retreat in May.

RESEARCH HIGHLIGHTS

Selected projects supported by the Ludwig Center at MIT:

Hemann Laboratory: Recent work in the Hemann group (Dalin et al, 2019, *Cancer Res*) has focused on drug resistance mechanisms in pancreatic ductal adenocarcinoma (PDAC), for which the deoxynucleoside analog gemcitabine, a modified version of deoxycytidine (a basic building block of DNA), is among the most effective therapies. Yet, nearly all patients treated with gemcitabine either don't respond or rapidly develop resistance. Most of a PDAC tumor consists of stromal (non-cancer) cells, and this accumulation of stroma can contribute to therapy resistance. To better understand this contribution, the researchers investigated microenvironmental mechanisms of resistance to gemcitabine, and found something very surprising. A non-tumor cell present in the stroma called a pancreas stellate cell (PSC) secretes a large quantity of deoxycytidine. This molecule is the same one that gemcitabine, the chemotherapy, is derived from, and both gemcitabine and deoxycytidine are taken up by the same cellular transporters and acted upon by the same cellular enzymes. The net effect of this release of deoxycytidine by PSCs is that this molecule effectively dilutes out the gemcitabine that is administered to treat the cancer.

This finding is noteworthy for two reasons. First, it provides a strategy for overcoming resistance to front-line PDAC chemotherapy, by targeting and blocking the release of deoxycytidine from PSCs. Second, it provides a different way of thinking about chemotherapies, suggesting they may be more targeted than previously thought.

Hynes Laboratory: In a study of metastasis in zebrafish embryos recently published in *Cancer Research* (Benjamin et al, 2020, *Cancer Res*), the Hynes group discovered that activated YAP, an activator of gene transcription they earlier showed promotes metastasis in mice, also does so in zebrafish. Experiments showed the YAP-expressing tumor cells, like the control tumor cells, initially arrest in blood vessels in the tail (the first site of arrest) but, unlike controls, they escape and migrate in the vasculature, transferring to the brain where they seed metastases. Working with collaborators in the Manalis Laboratory, also members of MIT's Ludwig Center, who have developed a device to follow circulating tumor cells in mice, the researchers showed that YAP also enhances increased circulation of tumor cells in mammals. Overall, these results suggest that one mechanism by which YAP, commonly increased in many tumors, promotes metastasis is by enabling tumor cells to disseminate more widely to diverse tissues. These results also show that a specific gene can affect the distribution of tumor cells within an animal, and thereby influence the global pattern of metastasis in that animal. Earlier versions of this work appeared as a featured exhibit in the Koch Institute Public Galleries—read and watch here.

Manalis Laboratory: Existing pre-clinical methods for acquiring dissemination kinetics of rare circulating tumor cells (CTCs) en route to forming metastases cannot provide a direct measure of CTC intravasation rate and subsequent half-life in the circulation, to illuminate how these cells move into the blood stream and how long they stay there.

To address these limitations, the Manalis group (Hamza et al, 2020, *bioRxiv*) developed a novel blood-exchange method between pairs of unanesthetized mice for studying the circulatory dynamics and tumorigenicity of CTCs. Unlike other techniques, this method does not require a permanent surgical connection between the vasculatures of the two mice, and can be used continuously and longitudinally.

In a genetically engineered mouse model of small cell lung cancer, the researchers used their method to study the kinetics of CTCs from tumors that arise de novo in the context of surrounding stroma and a fully functional host immune system. By tracking CTC transfer rates in the model, the researchers extrapolated half-life times in the circulation of 50-100 seconds and intravasation rates between 4,000 and 27,000 CTCs/hour—an average daily shedding rate equivalent to ~0.07% of the total number of primary tumor cells in the lung. Additionally, transfer of 1-2% of daily-shed CTCs from late-stage tumor-bearing mice generated macrometastases in healthy recipient mice.

The team expects their blood-exchange technique and resulting CTC kinetics data can help accurately identify rate-limiting steps in the blood transport phases of the metastatic cascade, and be used to directly and controllably exchange other blood components and study trafficking dynamics of immune cells in various biological contexts. The technology is already being used in collaborations with other Center laboratories, including the Hynes group.

Vander Heiden Laboratory: Researchers in the Vander Heiden Laboratory are working to understand how the environment around a tumor affects cancer cell metabolism, with the express goal, in one of their projects, of targeting breast cancer metabolism to treat brain metastases.

The researchers found that to grow in the brain, cancer cells have to overcome intrinsic limitations for some nutrients in that tissue. Specifically, they have found that the brain microenvironment is very limited in lipids, and thus activation of programs to synthesize lipids is required for cancer cells to grow in this site. Importantly, this creates vulnerabilities to drugs that target lipid synthesis—confirmed by experimentally disrupting lipid metabolism in the cells of breast cancer brain metastases—and may be a therapeutic target to help patients with brain metastases. The evidence suggesting that lipid synthesis was required to form tumors in the brain came from an ongoing collaboration with Rakesh Jain's laboratory at the Ludwig Center at Harvard University (Jin et al, 2020, *Nature*).

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 2020 was appropriated as indicated in the chart below.