LUDWIG CENTER | MIT

Ludwig Center at MIT: Updates from Fiscal Year 2021 (July 1, 2020-June 30, 2021)

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 (FY2021) brought notable changes to the faculty of the Ludwig Center at MIT. Dr. Frank Gertler officially retired from MIT effective July 1, 2020, and his laboratory was officially shut down. Ludwig Center member and cell biologist, Dr. Angelika Amon, sadly passed away in October 2020 at age 53 following a two-and-a-half year battle with ovarian cancer. Her laboratory remained open for the remainder of the fiscal year so that her trainees could wrap up their projects, and other Ludwig Center and Koch Institute faculty members stepped in to serve as their mentors. Dr. Amon made important contributions to the field of cell biology and is sorely missed.

Ludwig Center co-director, Dr. Tyler Jacks, stepped down as director of the Koch Institute, a position he held for almost two decades, and during which he shepherded MIT's NCI Cancer Center through enormous growth. He was replaced as Koch Institute director in April 2021 by Ludwig Center member Dr. Matthew Vander Heiden.

Members Drs. Weinberg and Jacks continue to serve as co-directors of the Ludwig Center; other active Center members are Drs. Bhatia, Hemann, Hynes, Lees, Manalis, and Vander Heiden. Looking ahead to 2022, three new investigators will join the faculties of the Koch Institute and MIT's Department of Biology; they will be assessed, based on their respective research areas, for potential collaborations or membership in the Center.

Meanwhile, current investigators from the Ludwig Center at MIT have continued to collaborate extensively with each other and with members of Ludwig Centers at other institutions. Intra-Center collaborations are facilitated in part by community events and meetings, including the annual MIT Ludwig Center Retreat, which was held on May 24, 2021 via Zoom due to the ongoing pandemic. The virtual format in no way dampened the enthusiasm of more than 75 attendees to gather together; nine presentations, one from each Ludwig Center-supported lab, filled the day and drove engaging discussions.

Inter-Center collaborations this year included ongoing joint work by Dr. Bhatia with Dr. Frank Slack at Harvard; Dr. Jacks collaborates with Drs. Sandro Santagata and Peter Sorger at Ludwig Center at Harvard. Dr. Vander Heiden's lab collaborates with the team from the Ludwig Center at Harvard, under the leadership of Dr. Rakesh Jain, with whom he published three joint paper in this reporting period, including a *Nature Cancer* article entitled "Fatty acid synthesis is required for breast cancer brain metastasis."

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

Name	Awards and Honors
Sangeeta Bhatia	Outstanding Scientist Award, AAISCR Cancer Research Annual Meeting Michael Smith Distinguished Lecturer, University of British Columbia
Michael Hemann	Daily Ho Memorial Award, MD Anderson Cancer Center
Richard Hynes	World Laureates Forum, Shanghai
Robert Weinberg	Japan Prize for Medical Science and Medicinal Science

- ***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 eight postdoctoral associates:

Name	Project Title
Coralie Backlund	"Unexpected mechanisms of cell penetrating peptides enhance peptide neoantigen cancer vaccines"
Jung-Kuei Chen	"Improving the response of metastatic cancer to 5-fluorouracil-based therapies"
Whitney Henry	"Functional characterization of ether lipids in cancer progression"
Josh Hinckley	"Deciphering lymphocyte transcriptome responses in multidimensional cell culture systems to cancer extracellular vesicles using high-resolution single-cell RNA sequencing"
Joomyung (Vicky) Jun	"Pills of PTEN: Traceless delivery of a tumor suppressor into the cytosol"
Bin Liu	"Dually targeted co-delivery of vaccines and adjuvants thorough brush polymers for cancer immunotherapy"
Edward Tan	"Engineering conditional fusogenic liposomes for malignant cancer"
Lauren Zasadil	"Immune clearance of aneuploid cells in vivo"

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

RESEARCH HIGHLIGHTS

Selected projects supported by the Ludwig Center at MIT:

Bhatia Laboratory: To overcome the limitations of the conventional imaging tests and endogenous biomarkers currently used for cancer detection and diagnosis, and with an eye towards designing a future tool capable of

detecting a wide range of tumor types, the Bhatia laboratory has engineered a new type of 'synthetic' biomarker that brings several kinds of materials into a single test. Synthetic biomarkers are an approach to detect tumors by introducing a particle that can then induce a signal, originating from cancer cells, that did not previously exist in the body. These biomarker signals are better able to stand out from the 'noise' of background signals made by healthy cells and, by depending on activation by enzymes present in a tumor environment, the signals can be amplified to be much stronger – together resulting in a diagnostic tool that is both sensitive and specific. Previous uses of synthetic biomarkers were detected as signals excreted in urine, or even exhaled in breath. However, the piece of information that was not captured is where in the body these biomarkers are produced, which would provide information regarding the location of the tumor. To close this gap, the Bhatia group has now engineered protease-responsive imaging sensors for malignancy (PRISM), an approach that combines the delivery of activity-driven synthetic biomarkers with an imaging agent that can be loaded on-demand to enable positron emission tomography-computed tomography (PET-CT) for both in situ and non-invasive disease visualization and monitoring.

PRISM sensors rely on enzyme activity, active proteases known to be present and essential for all invasive tumors, to produce synthetic biomarker reporters. Bhatia group researchers used the acidic pH known to be present at invasive tumor fronts to direct and capture the PRISM particles to the correct physical location. Specifically, they designed their reporter sensor to be produced by the activity of matrix metallopeptidase 9 (MMP9). Positive MMP9-derived urinary tests were then confirmed by a PET-CT test, which is made possible because the PRISM particles can also be loaded with a radioactive tracer that is deposited at the tumor site in the presence of low pH. The researchers compared tumor acidosis-mediated imaging against a standard, clinically-used imaging tracer, and demonstrated long-term monitoring of cancer progression and regression in two models of metastatic colorectal cancer, with and without treatment using a first-line chemotherapy. Providing both tools in a single injection may shorten the regulatory path to bringing a new medicine to patients, and also offers a tool that can help clinicians decide between possible treatment options, even while monitoring for drug response or watching for a post-surgical relapse.

In the upcoming year, the Bhatia group will work to advance their new imaging platform to understand the coupling of tumor acidosis, protease activity and metastatic dissemination as well as how these play out in response to therapy.

Jacks Laboratory: The Jacks laboratory uses an autochthonous mouse model of lung adenocarcinoma previously developed by the group—the $Kras^{LSL\text{-}G12D/+;}$ $p53^{flox/flox}$; $BRG1^{flox/flox}$ mouse—to understand the epigenetic factors that control tumor evolution, with the over-arching goal of translating findings from mouse cancer models for the development of human therapies that inhibit tumor cells from advancing to the metastatic stage. Recent studies seek to illuminate the role of SMARCA4/BRG1 in progression and metastasis.

SMARCA4/BRG1 encodes for one of two mutually exclusive ATPases present in mammalian SWI/SNF chromatin remodeling complexes, and is frequently mutated in human lung adenocarcinoma. However, the functional consequences of SMARCA4 mutation on tumor initiation, progression and chromatin regulation in lung cancer are poorly understood. Using genetically engineered mouse models and epigenomic profiling, Jacks group researchers have demonstrated that loss of Smarca4 sensitizes CCSP+ cells within the lung to malignant transformation and tumor progression, resulting in highly advanced dedifferentiated tumors and increased metastatic incidence. Consistent with these phenotypes, Smarca4-deficient primary tumors lack lung lineage transcription factor activities and resemble a metastatic cell state. Mechanistically, they find that Smarca4 loss impairs the function of all three classes of SWI/SNF complexes, resulting in decreased chromatin accessibility at lung lineage motifs, which presumably accelerates tumor progression. Thus, their work puts forth a model for SMARCA4-mediated lung tumor suppression, wherein SMARCA4 loss in transformed CCSP+ cells directly results in the inability of SWI/SNF complexes to bind to chromatin, and ejects and mobilizes nucleosomes, which prohibit lung lineage transcription factors from exerting lineage-specifying gene expression programs. Absence of lineage specificity, in turn, promotes phenotypic plasticity of Smarca4-deficient cells, and accelerates the sampling and selection of pro-tumorigenic states throughout tumor evolution. Ultimately, this leads to an increase in incidence of high-grade tumors and metastases in Smarca4-deficient murine lung adenocarcinoma, and to highly undifferentiated tumors and poor overall survival in non-small cell lung cancer patients harboring SMARCA4 inactivating mutations.

In the year ahead, the Jacks group aims to further elucidate the mechanisms underlying the tumor suppressive functions of SMARCA4 and investigate potential therapeutic strategies to treat this subtype of lung cancer. Specific aims are to determine epigenetic states that SMARCA4-deficient primary tumor cells must adopt in order to transition into a fully metastatic cell state, and to use their models to test therapeutic strategies that have been proposed for SMARCA4-deficient lung adenocarcinoma, such as CDK4/6 inhibition.

Weinberg Laboratory: Research in the Weinberg group is directed at mechanisms that lead to the formation of metastases, often in the context of breast cancer. Much of this research over the past year has focused on the mechanisms of metastatic re-awakening. After primary breast tumors have been treated and a patient has been declared disease-free, metastatic relapses can erupt at anatomically distant sites months, years and even decades later. These delayed eruptions testify to the existence of nests of breast cancer cells that have been disseminated from the primary tumor but remained in a non-growing, ostensibly dormant state for extended periods.

Work in the Weinberg group has indicated that such dormant micrometastatic deposits may remain in a non-proliferating, but nonetheless viable, state for extended periods of time. The researchers have developed breast cancer cell lines that remain thus indefinitely, until application of an external perturbant—induced localized tissue inflammation, for example—induces such cells to begin active proliferation. The inability of such disseminated cells to proliferate appears to be due to their overly-mesenchymal cell state.

This highly mesenchymal state represents one of several cell states in which carcinoma cells can reside; such states can be arrayed along a spectrum extending from fully epithelial to fully mesenchymal. Weinberg laboratory research has determined that optimal proliferation of such breast cancer cells can only operate if such cells possess subpopulations of cancer stem cells (CSCs), which they have found to reside in an intermediate "quasi-mesenchymal" state located between the two poles of the epithelial-mesenchymal spectrum. CSCs represent unique and specialized cells within larger tumor cell populations, and have the ability to serve as progenitors of entirely new populations of tumor cells. The researchers have found that the awakening of dormant disseminated tumor cells requires an inflammation-induced shift in their cell state from an overly-mesenchymal to a quasi-mesenchymal state, in which they gain proliferative ability and can thus spawn metastases.

Over the next year, the Weinberg group plans experiments to determine whether the paradigm of inflammation-induced awakening of dormant disseminated breast cancer cells can be generalized to a variety of mammary carcinoma cell lines and to other carcinoma cell types beyond breast cancer. In addition, they intend to determine the signaling mechanisms that enable inflamed tissue microenvironment to stimulate previously dormant, overly-mesenchymal disseminated tumor cells to move from this state to a quasi-mesenchymal one compatible with active, robust proliferation.

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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 2021 was appropriated as indicated in the chart below.