THE JACKSON LABORATORY CANCER CENTER

ANNUAL HIGHLIGHTS 2022

THE CANCER CENTER

The Jackson Laboratory (JAX) Cancer Center has been a National Cancer Institute-designated basic laboratory cancer center since 1983, with a sustained focus on deciphering the complex genetics of cancer and to design precision models of the disease.

The unifying theme of our research program is to uncover genetic mechanisms underlying age-related chronic inflammation and cellular dysfunction, and their impact on genetic complexity of cancer, cancer development, metastasis and treatment resistance.

Central to our strategy is the ability to integrate murine and human biology through comparative genomics and computational modeling. The iterative mouse-human, and in silico-laboratory experimentation uncovers new findings and refines contemporary assumptions. This new understanding will lead to innovative therapeutic approaches for both prevention and treatment of cancer.

One of only seven cancer centers with a sole focus on basic research recognized by the National Cancer Institute since 1983.

The Jackson Laboratory
Leading the search for tomorrow's cures

NCI Designated Cancer Center

CEO STATEMENT

Since 1983, The JAX Cancer Center has been an NCI-designated basic science cancer center, currently one of seven in the nation. Our vision is a bold one: to advance the understanding of cancer genomics and to translate that knowledge into new approaches to treatment. Now, more than ever before, we are seeing the impact of our work, not only on the global scientific community but also on clinical practice and patient care. Through our Maine Cancer Genomics Initiative, we are bringing genomic medicine to clinicians and patients in rural communities outside the realm of academic healthcare.

One of my first acts at JAX was to announce the appointment of JAX Cancer Center Director Karolina Palucka, M.D., Ph.D., to an endowed chair newly established in honor of my predecessor and former JAX Cancer Center Director, Edison Liu, M.D. Dr. Palucka, who made the transition from clinical oncology to research because she wanted to help more patients, embodies our determination to transform the future of cancer treatment. The endowed faculty chair she holds - one of JAX's 15 endowed chairs established since 2014 - provides additional support for her work and recognizes her eminence as a leader in cancer research.

"Dr. Palucka, who made the transition from clinical oncology to research because she wanted to help more patients, embodies our determination to transform the future of cancer treatment."

The 35+ donors who came together to establish the Edison T. Liu Endowed Chair in Cancer Research did so because of Ed's tremendous leadership of JAX; because of his own distinguished career in cancer research; and because they were inspired by Ed's vision for how philanthropy could attract talent, accelerate discovery, and amplify impact. This report provides a glimpse into the innovative work we are already doing and the exciting future of cancer research at JAX.

Lon Cardon, Ph.D., FMedSci
President and CEO, The Jackson Laboratory

OUR NEW DIRECTOR

Cancer immunology pioneer and JAX Professor Karolina Palucka, M.D., Ph.D., was named the director of JAX Cancer Center in November 2021. Dr. Palucka specializes in human immunology with a focus on experimental immunotherapy, including vaccines that target cancer.

An internationally recognized clinical oncologist and cancer immunologist, Dr. Palucka came to JAX in 2014 from the Baylor Institute for Immunology Research in Dallas, Texas where she was the Michael A.E. Ramsay Chair for Cancer Immunology Research and Director of the Ralph M. Steinman Center for Cancer Vaccines.

She is the recipient of many honors including a Career Award for Important Contributions to Tumor Immunotherapy from the European Academy of Tumor Immunology. Palucka succeeds Edison Liu, M.D., as JAX Cancer Center Director. Her career trajectory began in the early 1990s as an oncologist in Warsaw, Poland, when she realized the treatments available to her were insufficient to help her patients.

"I was using different combinations of chemotherapy and all the standard treatments," she says, "but, in fact, I was not seeing progress. I was not seeing solutions." She recalls one patient in particular, a woman in her thirties with advanced breast cancer. "She really tipped the balance because I couldn't do much for her. I loved the patients and I think they loved me, but I just could not continue doing that."

Karolina Palucka traded her doctor's coat for a lab coat to explore how to exploit the immune system to fight cancer, and her commitment to cancer patients has never wavered. "I went into research to find novel solutions to help patients," Dr. Palucka says. "Working with my talented and passionate JAX Cancer Center colleagues will allow me to realize that dream."

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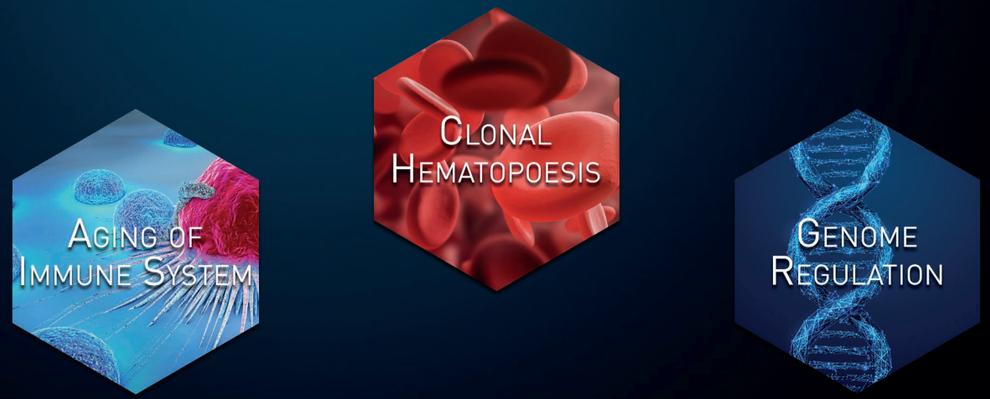
POWER THROUGH COMPLEXITY

Cutting-edge research at the intersection of cancer and aging/geroscience

Aging is the single biggest cancer risk factor and it is associated with progressive cellular dysfunction and heightened inflammation. However, not all older people develop cancer. Identifying the basic mechanisms underlying aging- and tissue-specific inflammation will be transformative in how cancer patients are diagnosed or treated, or how people are prevented from developing cancer. Our goal is to build new transdisciplinary research capacity and catalyze new, joint research programs to more thoroughly explore questions at the intersection of cancer and aging/geroscience.



Innovative therapeutic approaches for prevention and treatment of cancer

Our single Research Program is structured around exploration of four pillars: genomic instability and genetic complexity of cancer; genetic complexity of host; therapeutic resistance; and treatment toxicity.

Central to our strategy is the ability to develop and integrate murine and human biology through comparative genomics and computational modeling.

OUR GOALS

- To discover novel mechanisms underlying cancer development and treatment resistance.
- To achieve the greatest impact on cancer patients' outcomes through our research.
- To recruit the best scientific talent from complimentary and different disciplines to capture synergy from diversity of thought.
- To provide state-of-the-art facilities and advanced technologies at our two academic campuses that empower JAX Cancer Center members to push the frontiers of cancer genomic discovery.
- To establish our own brand of translational research by building partnerships with clinical collaborators at the individual and organizational levels such as the Maine Cancer Genomics Initiative (MCGI).
- To provide a continuum of education opportunities for students, trainees, early career investigators and Maine oncology care providers to enhance success in cancer research and genomic cancer medicine.

OUR APPROACH

Our Research Program, "Genetic models for precision cancer medicine," combines multidisciplinary technical and computational expertise with the institution's unique knowledge of mouse models and human cancer genomics to identify precise therapeutic interventions to prevent and to treat cancers.

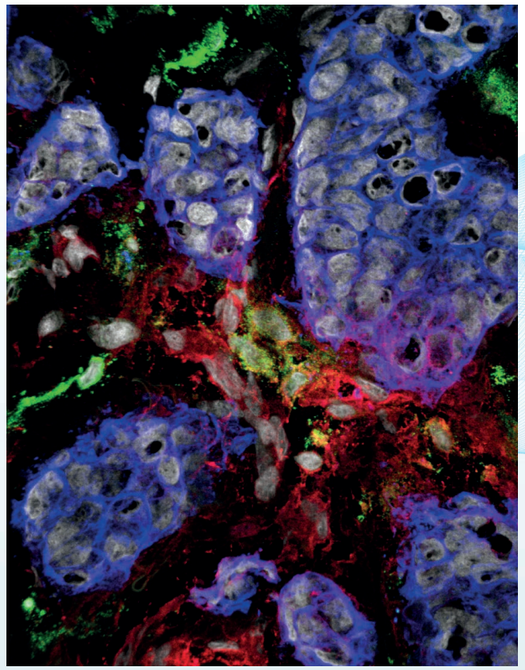
We have members across two campuses in Maine and Connecticut with multidisciplinary expertise who are united in research aimed at understanding and targeting the genomic complexity of cancer.

Genetic models for precision cancer medicine

OUR RESEARCH

The multitude of mutations found in each cancer type limits the development of a common therapeutic, and cancer's genetic diversity and instability leads to resistance to therapies. Moreover, genetic diversity among patients contributes to varied responses to any single treatment.

Researchers at JAX Cancer Center are developing strategies that use this genetic complexity as an advantage to discover new cancer treatments.



Wu et al. Cancer Res. 2018 Volume 15;78(18):5243-5258.

Select scientific initiatives include:

- Develop new animal, cellular and computational models of cancer to accelerate identifying new therapeutic strategies to advance to human clinical trials.
- Explore the genomic instability and genetic complexity of cancer as a novel source of therapeutic targets.
- Investigate how key components of tumor and normal cells interact to influence tumor response to treatment.

JAX CANCER CENTER SUPPORT GRANT 2022 QUICK VIEW

One Research Program:
Genetic Models
for Precision Cancer Medicine

39 Full Members
18 Associate Members
16 Trainee Associate Members

2022 Cancer-relevant Grant Funding*
$5.2M NCI
$17.9M Total Peer-Reviewed
$21.9M Total
*Annual Direct Cost

OUR VISION

Our cancer center seeks to discover precise genomic solutions for cancer medicine by vectoring basic discoveries towards human impact. We realize this vision by focusing on complex genetics and functional genomics, by engaging advanced technologies in scale, and by facilitating integration across disciplines.

Our unique expertise in the development of powerful animal model platforms is complemented by a new translational capacity which iteratively will refine solutions for precision medicine.

OUR MISSION

We seek to discover precise genomic solutions for cancer medicine by making basic discoveries with human impact.

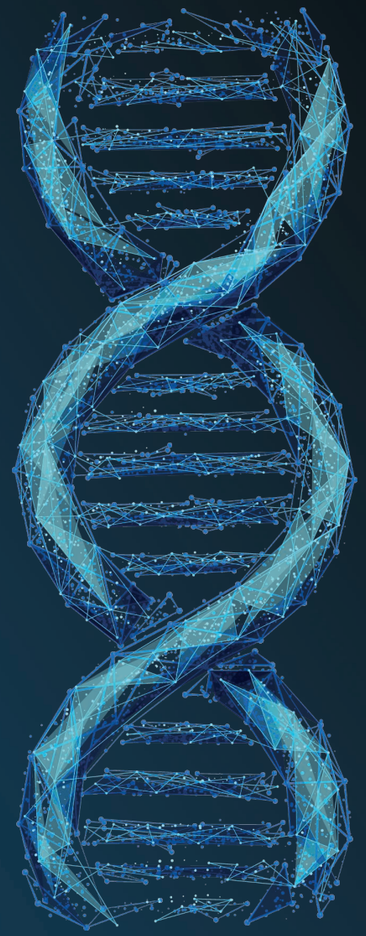
We translate basic cancer research findings to benefit patients through deep partnerships with national, academic, and community clinical entities.

ANNUAL HIGHLIGHTS

FIGHTING CHEMOTHERAPY RESISTANCE

Using patient data, patient-derived xenograft (PDX) mouse models, and engineered cancer cell lines, Professor Edison Liu, M.D., and Research Scientist Francesca Menghi, Ph.D., investigated the mechanisms underlying variable patient responses to platinum-based chemotherapies.

In a *Science Translational Medicine* paper, they contrast cancers with loss-of-function *BRCA1* and/or *BRCA2* mutations versus those with *BRCA1* promoter methylation, which is associated with increased therapy resistance. What they found was that chemo-therapeutic exposure enhances DNA repair in those cancer cells thus counteracting therapeutic effects of chemotherapy.

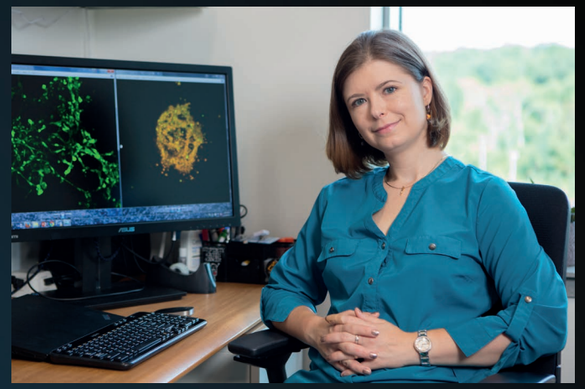


Investigating the mechanisms underlying variable patient responses to platinum-based chemotherapies

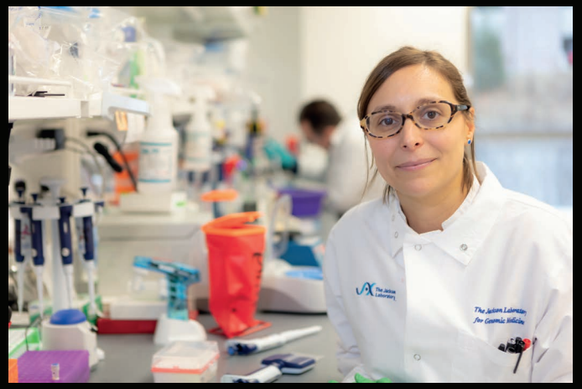
ALTERNATIVE SPLICING IN CANCER

Associate Professor Olga Anczuków, Ph.D., studies alternative RNA splicing, a process allowing a single gene to generate multiple proteins with different functions. In a *Cell Reports* paper, she demonstrates that splicing factors can promote tumor growth by acting in a coordinated network regulated by the well-known cancer gene MYC. This reveals a novel avenue for potential therapeutic targeting of cancers driven by MYC.

Further, with her colleagues at JAX, she is advancing technologies to better detect alternatively spliced isoforms. In a *Science Advances* paper, they develop a long-read sequencing and analytical pipeline that identifies thousands of novel full-length spliced isoforms in breast tumors. These novel isoforms are associated with patient prognosis and represent potential targets for new cancer therapies.



ENDOMETRIOSIS, ONE CELL AT A TIME



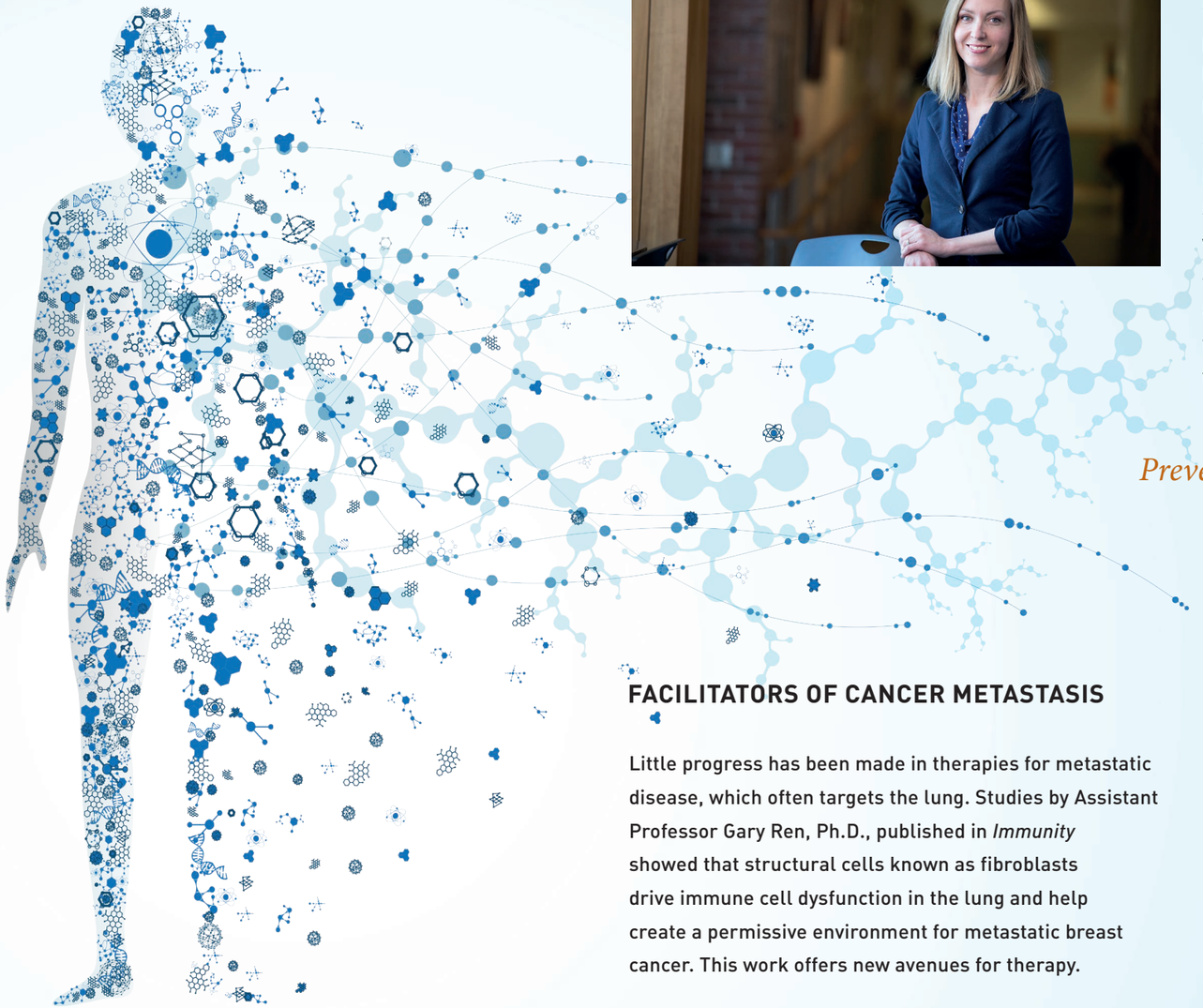
Endometriosis, the growth of endometrium-like lesions outside the uterus, affects about 10% of women worldwide. Nonetheless, there has been relatively little research into its causes or molecular drivers. Elise Courtois, Ph.D., presents, in a *Nature Cell Biology* paper a comprehensive single-cell analysis of endometriosis, providing an essential foundation for future research and therapeutic development.

WORKING WITH GLIOMA PATIENTS

Professor Roel Verhaak, Ph.D., leads an innovative research program looking into the molecular mechanisms that make gliomas, the most common malignant brain cancer, so adaptable and able to resist therapies. Now, working with colleagues at Yale University and the University of Colorado, he is helping address another crucial aspect of glioma research: patient care.

The optimizing engagement in discovery of molecular evolution of low-grade glioma (OPTIMUM) program will gather both primary samples and medical record data from low-grade glioma (LGG) patients in support of basic and clinical research. In addition, the $5.7M, five-year National Cancer Institute grant will focus on the interactions between researchers and patients, enabling bi-dimensional communications concerning the study's progress and outcomes in addition to individual patient results. It will also work to improve messaging regarding the use of genomics in the research in order to improve patient education and, ultimately, improve LGG patient care and wellbeing.

Improving patient care and wellbeing through the use of genomics



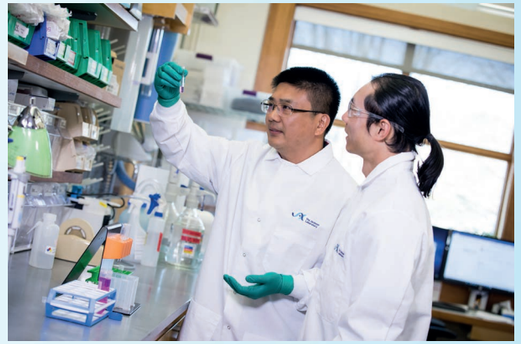
FACILITATORS OF CANCER METASTASIS

Little progress has been made in therapies for metastatic disease, which often targets the lung. Studies by Assistant Professor Gary Ren, Ph.D., published in *Immunity* showed that structural cells known as fibroblasts drive immune cell dysfunction in the lung and help create a permissive environment for metastatic breast cancer. This work offers new avenues for therapy.

TIPPING THE BALANCE IN CLONAL HEMATOPOIESIS

Professor Jennifer Trowbridge, Ph.D., investigates clonal hematopoiesis, a condition acquired by most people as they age. While clonal hematopoiesis usually has little health impact, it can contribute to adverse health outcomes, including leukemia. Conversely, it can also lower the risk of other aging-related diseases. But how? In a *Cancer Discovery* paper, Trowbridge shows how TNF-alpha, a signaling pathway associated with clonal hematopoiesis, can tip the balance. TNF-alpha binds two distinct receptors, with one promoting deleterious effects and the second more beneficial. The findings indicate that a receptor-specific blockade may tip the balance toward improved health outcomes.

Preventing the transition of normal blood cells into blood cancers



LOOKING BEYOND GENE MUTATIONS IN LEUKEMIA

Associate Professor Sheng Li, Ph.D., seeks to understand how genetic and epigenetic changes in the blood stem cells of older adults can increase their risk of developing leukemia. Although aging correlates with the clonal expansion of mutated blood stem cells (a common condition known as age-related clonal hematopoiesis), additional cellular changes are needed to produce leukemia. Thus, Dr. Li is focused on identifying key changes in genomic DNA methylation that transform mutated blood stem cells into leukemia.

Her recent development of the computational tool epihet (*Scientific Reports*) automates the analysis of heterogeneous DNA methylation patterns in cancer cell populations, including leukemia, to identify genes whose expression is impacted by changes in DNA methylation. Epigenetic clonality is directly linked to specific mutations and this epigenetic allele diversity precedes and potentially contributes to malignant transformation (*Cancer Discovery*).

A CONSERVED MOLECULAR SIGNATURE OF AGING

Aging is a major risk factor for cancer. It is associated with chronic systemic inflammation, called “inflammaging”, but what causes this common feature is poorly understood.

To address this, in a recent preprint Associate Professor Duygu Ucar, Ph.D., studied immune cells from diverse mouse strains, representing both long-lived healthy aging and short-lived unhealthy aging. Overlapping these results with data from human blood immune cells, she uncovered a conserved signature of aging: chronic activation of several members of the AP-1 transcription factor complex. This signature may drive inflammaging and may also help explain why older adults have decreased responsiveness to seasonal vaccines.

Improving immune response

PRESERVING FERTILITY IN CANCER PATIENTS

Protecting cancer patients from treatment-associated infertility

Associate Professor Ewelina Bolcun-Filas, Ph.D. investigates the mechanisms underlying oocyte (egg) loss in young female cancer patients following chemotherapies and potential targets for protecting them. Recent research has shown that a protein known as checkpoint kinase 2 (CHEK2) plays a critical role in coordinating the elimination of oocytes following exposure to chemotherapy drugs. Blocking CHEK2 activity using a dual checkpoint kinase inhibitor in ovaries preserves the oocyte reserve, but the specific inhibitor used can be damaging to other ovarian cells, limiting its potential as a protective treatment. Nonetheless, the findings indicate that the development of more selective CHEK2 inhibitors has the potential to yield treatments that effectively provide protection from chemotherapy- and radiation-associated infertility.

Cutting-edge cancer models for precision oncology

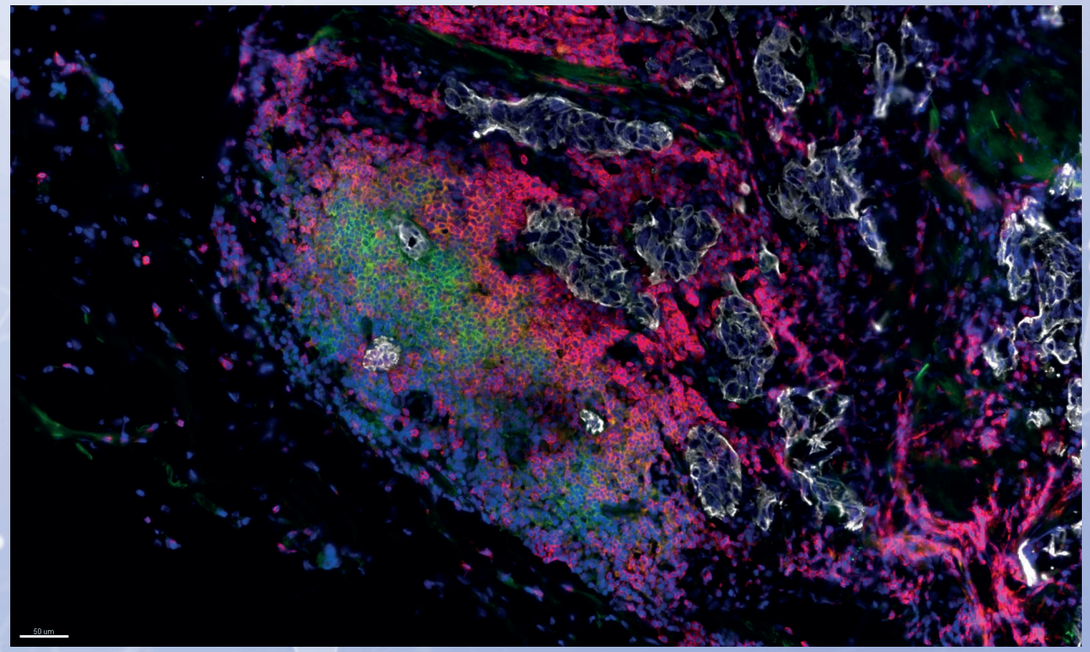
DEVELOPING TUMOR AVATARS MODELS

Three-dimensional cell culturing methods and patient-derived organoids are promising research platforms for both biological discovery and potential precision oncology applications. In "A path to translation: How 3D patient tumor avatars enable next generation precision oncology," published in *Cancer Cell*, JAX Professor Jeffrey Chuang, Ph.D., and colleagues, present how to bring the newest form of patient-cancer modeling (i.e., 3D patient tumor avatars or 3D-PTAs), from the bench to the clinic. Much progress has been made in the field, but standardizing 3D-PTAs and making them repeatable, precise and accurate across institutions, clinicians and tumor types remains a top priority for effective clinical implementation.

CATch PROGRAM

The Cancer Advanced Technology (CATch) program, led by Drs. Jeff Chuang, Gary Ren, Roel Verhaak and Sheng Li, is a Cancer Center initiative to develop transformative cancer science, building on our strengths in technology, computational biology, and cancer models. CATch is deconstructing the complexity of cellular crosstalk through spatial profiling in order to understand how cell-cell interactions influence cancer phenotype and treatment response.

Six JAX teams are working together to develop new concepts and expertise in spatial technologies around how cells influence each other within a tumor microenvironment. The first phase of CATch focused on identifying spatial RNA expression patterns across diverse mouse and human tumor samples, including lung, breast, colorectal, osteosarcoma, melanoma, and glioblastoma tumors . The second phase extends these studies to the protein level, allowing teams to determine how cells functionally interact within these same cancer tissues. CATch projects synergize with JAX's research growth in artificial intelligence, a pillar of JAX's approach toward the general spatial understanding of tissue systems in mouse and human biology.



ENDOWED CHAIR

More than 35 donors contributed over $1.5 million, which has been matched with an additional $1.5 million from JAX, to establish the chair, named in honor of our former director as well as JAX CEO and President Edison T. Liu, M.D. The chair supports a faculty position in the Laboratory's National Cancer Institute-designated Cancer Center Jackson Laboratory. Our new center director, Professor Karolina Palucka, M.D., Ph.D., has been appointed as the first chairholder of the Laboratory's Edison T. Liu Endowed Chair in Cancer Research.

"Dr. Palucka is the natural choice as the first chairholder of this endowed chair," says Liu. "Her significant contributions to cancer immunology that spanned basic sciences and clinical therapeutics, and her successful launch of key initiatives in our cancer center showed not only a creative spirit but strong leadership that has been recognized by all. I was already deeply honored and humbled to have this chair in my name. And when Dr. Palucka accepted the appointment to be the first chairholder, I was overjoyed."

JAX's president and CEO, Lon Cardon, Ph.D., FMedSci, adds, "Cancer research is a foundational discipline at JAX. Karolina Palucka's appointment to Edison T. Liu Endowed Chair in Cancer Research signals our strong commitment to cancer research and to Dr. Palucka as its leader. I can't think of a better person to guide our cancer program into the future."

"I can't think of a better person to guide our cancer program into the future."

"I am honored to be named as this chairholder of The Edison T. Liu Endowed Chair in Cancer Research," says Palucka. "Ed is a dear friend and colleague who has transformed how I think about the study of cancer, and I look forward to continuing our work to understand the basic mechanisms underlying the disease."

TRAINING OPPORTUNITIES

Educational training programs offer opportunities for early career researchers as they begin and progress in their cancer-related careers. Our clinically-oriented and translational educational activities expose basic scientists to core concepts in cancer medicine and train oncologists and related clinicians in the tenets of genomic sciences relevant to their clinical practice.

The JAX Cancer Center Research Training & Education Coordination Core (CRTEC) ensures trainees and junior faculty have access to education and mentoring opportunities that will support them in developing the skills necessary to become leaders in cancer research.

We create opportunities for dialog between basic research, translational and clinical scientists and provide basic researchers with the translational and clinical perspective necessary to identify and tackle the areas of greatest need for fundamental, mechanistic research.

CREDIT AND ACKNOWLEDGEMENT

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The Jackson Laboratory

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