2023 Belfer Center Annual Report

Robert and Renée Belfer Center for Applied Cancer Science
Introduction

The Robert and Renée Belfer Center for Applied Cancer Science at Dana-Farber Cancer Institute helps to improve patient outcomes by discovering and advancing the most effective cancer therapies in collaboration with pharmaceutical and biotechnology partners. With cutting-edge capabilities at their fingertips, Belfer Center investigators, under the leadership of Pasi Jänne, MD, PhD, David Barbie, MD, and Cloud Paweletz, PhD, work to solve the most challenging scientific and drug development problems with rigor and efficiency.

Over the years, the Belfer Center’s leadership has been recognized in a number of ways. In November 2022, Jänne was named the David M. Livingston, MD, Chair at Dana-Farber. Named after the former Dana-Farber director, physician-in-chief, and prominent expert on the molecular origins of breast and ovarian cancer, the chair honors Jänne’s exceptional work as an investigator, mentor, teacher, and clinician who emulates the example Livingston set in his work and life.

In October 2022, Barbie was named co-chair of 2023 II-ON, the International Immuno-Oncology Network, a peer-to-peer collaboration between Bristol Myers Squibb and academia to advance immuno-oncology science through translational medicine and improve patient outcomes.

Your investment in the Belfer Center’s research is bringing hope to patients with challenging cancers who have few effective treatment options. Thank you for your partnership in this important work.

Strategic Alliances

The Belfer Center collaborates with pharmaceutical and biotechnology companies to bring basic scientific breakthroughs to market in the form of new therapeutic products. Recent partnerships include:

ASTRAZENECA

In collaboration with AstraZeneca, the Belfer Center is optimizing and characterizing combinations of osimertinib, the company’s flagship lung cancer drug, and antibody-drug conjugates (ADCs) to treat non-small cell lung cancer. Antibody-drug conjugates deliver chemotherapy drugs directly to tumor cells by attaching them to antibodies that bind to proteins on the
surface of cancer cells. Scientists will use patient-derived explant models (see sidebar) in conjunction with single-cell RNA sequencing, a method to isolate individual cells to determine their function and behavior, and other technologies to investigate responses to osimertinib/ADC combinations.

### BICYCLE THERAPEUTICS

Natural killer (NK) cells are the shock troops of the immune system and the body’s first defenders against infection and disease. The Belfer Center is working with Bicycle Therapeutics to study the mechanism and utility of NK cell engagers, molecules that engage targets that have historically been resistant to conventional therapies, to destroy tumor cells. Researchers will use the Belfer Center’s “tumor-on-a-chip” technology, also known as patient-derived organotypic spheroids, to study how tumors respond to the NK cell engagers and combinations with other drugs.

### BRISTOL MYERS SQUIBB

Most patients with non-small cell lung cancer acquire resistance to tyrosine kinase inhibitors such as osimertinib. With Bristol Myers Squibb, Belfer Center scientists are investigating a new treatment strategy, called bispecific ADCs, that targets two tumor antigens simultaneously and have the potential to increase the potency of ADCs. To maximize the therapeutic effect of bispecific ADCs, target pairs must be broadly co-expressed across tumors with limited expression in normal tissue. This project will identify target pairs capable of inducing ADC therapeutic efficacy in EGFR-mutated non-small cell lung cancer samples that are resistant or develop resistance to tyrosine kinase inhibitors.

### KINNATE BIOPHARMA/VERTICAL BIOSCIENCES

Overexpression of the MET gene, which makes a protein involved in cell growth and survival, frequently occurs in a range of cancers and is associated with poor prognosis. Up to 35% of patients treated with an approved c-MET inhibitor develop resistance, leaving them with limited treatment options. With Kinnate Biopharma, the Belfer Center is evaluating the company’s investigational c-MET inhibitor, KIN-8471, in preparation for an upcoming clinical trial. The drug targets acquired resistance mutations across a variety of solid tumors, including non-small cell lung cancer, in which MET is overexpressed.
The Belfer Center is working with Vertical Biosciences on another drug to overcome MET resistance. Unlike small-molecule inhibitors that block the activity of a protein, VERT-1 is an antibody that totally eliminates MET from cells. The drug, which has shown efficacy in non-small cell lung cancer and gastric cancer models, has potential efficacy in cancers resistant to MET tyrosine kinase inhibitors.

**GSK**

The Belfer Center is collaborating with GSK (GlaxoSmithKline) on the development of a novel drug that inactivates a protein that allows cell replication to continue so that cancer cells can survive. The drug targets POLQ, which provides a vital repair mechanism in cancer cells that are unable to repair DNA gaps using a common method called **homologous recombination** (HR; see sidebar). The drug is being tested in solid tumors that are HR deficient, including those with BRCA mutations. Previously, in collaboration with Alan D’Andrea, MD, the Belfer Center showed that the antibiotic novobiocin has specific POLQ inhibitory activity in HR-deficient ovarian cancer models. Additionally, the researchers observed that increased POLQ levels predict novobiocin sensitivity and that BRCA-deficient ovarian tumors with acquired resistance to PARP inhibitors (see page 8) are sensitive to the antibiotic. This sensitivity increases when used in combination with PARP inhibitors.

**Publications**

One method researchers use to advance scientific knowledge is by sharing their findings in peer-reviewed journals. Over the past year, Belfer Center scientists have published papers in numerous leading journals.

**REACTIVATING THE STING PATHWAY**

In the October 2022 issue of *Cancer Cell*, a Belfer Center team led by Barbie showed that inhibiting MSP1, a master regulator of cancer cell behavior, may potentially re-engage the **STING (STimulator of INterferon Genes) pathway** (see sidebar) in non-small cell lung cancers that are resistant to immune checkpoint blockade. They found that a single course of decitabine, a leukemia drug that can increase the activity of cancer-killing T cells, followed by MSP1 inhibition enhanced anti-PD-1 efficacy and resulted in long-term responses and few significant side effects. These findings may facilitate the development of clinical trials to treat non-small cell lung cancers and other cancers that are resistant to immune checkpoint blockade.

Homologous recombination is a phenomenon in which genetic material is exchanged between two similar or identical molecules of DNA. It is most widely used by cells to accurately repair harmful breaks that occur in both strands of DNA, known as double-stranded breaks.
Immunotherapy has limited effectiveness in patients with EGFR-mutant lung cancer. In the November 2022 edition of Cancer Research, Belfer Center investigators reported that MET amplification (see sidebar) upregulates a protein that promotes tumor growth by limiting anti-tumor T cell immunity and suppresses STING activation in EGFR-mutant lung cancers that do not respond to standard treatments. The researchers found that pemetrexed, the most frequently used chemotherapy drug as EGFR-mutant lung cancers become resistant to osimertinib, enhances immunogenicity (the ability to provoke an immune response) by reactivating the STING pathway. The findings identify a strategy to stimulate an immune response in these cancers and improve outcomes.

**DRUGGING A ONCE-UNDRUGGABLE PROTEIN**

Colorectal cancers with KRAS G12C mutations are rare but have a dismal response to chemotherapy and a poor prognosis. KRAS has long been considered “undruggable,” and there are no approved drugs that target the KRAS G12C mutation. In a phase I/II trial, scientists, including Paweletz, found that the Food and Drug Administration-approved KRAS G12C inhibitor adagrasib demonstrated greater efficacy when combined with cetuximab, an approved EGFR antibody, in heavily pretreated patients with KRAS G12C-mutated colorectal cancer. The study, published in the January 2023 issue of the New England Journal of Medicine, supports the ongoing clinical investigation of this combination therapy.

In the July 2023 edition of Clinical Cancer Research, Paweletz, Jänne, and their colleagues reported that noninvasive monitoring of circulating tumor DNA (ctDNA)—fragments of DNA that are shed into the bloodstream as tumors die—could help predict clinical response to therapy. The scientists conducted droplet digital PCR, a technology that amplifies small pieces of DNA, and next-generation genetic sequencing at different timepoints on 60 patients with KRAS G12C-mutated lung cancer treated with adagrasib. Most patients showed decreased or complete KRAS G12C clearance by their second cycle on the drug, and the overall response rate and overall survival improved markedly. The results support assessing KRAS G12C ctDNA at approximately three weeks to anticipate the likelihood of a favorable clinical response.

While KRAS G12C inhibitors have been approved for clinical use, less than half of patients with lung cancer respond to them, and their responses are temporary. In the June 2023 Journal of Clinical Investigation, Belfer Center researchers revealed two new promising strategies for KRAS-mutant lung
cancers. The researchers found that combining a KRAS G12C inhibitor with an inhibitor of a protein complex that promotes a cancer cell malignant phenotype dramatically enhances the effects of the anti-KRAS drug. In addition, they showed that a MEK inhibitor similarly synergizes with a KRAS G12C inhibitor to increase its effectiveness. The findings offer new hope for patients with KRAS-driven lung cancer.

IDENTIFYING CLL RESISTANCE MECHANISMS

Chronic lymphocytic leukemia (CLL) remains largely incurable despite the development of drugs, such as venetoclax, that target cancer cells’ pro-survival proteins. In collaboration with Jennifer Brown, MD, PhD, Paweletz and colleagues analyzed tumor samples from 11 patients with CLL to uncover multiple potential resistance mechanisms in patients whose disease progressed while being treated with venetoclax. The findings, published in the May 2023 Blood, identify potential therapeutic targets that may help to overcome or avoid venetoclax resistance in CLL.

Presentations

By presenting findings at conferences, Belfer Center scientists share their most recent results prior to publication, as well as their scientific expertise.

At the September 2022 ESMO (European Society of Medical Oncology) Congress in Paris, Jänne chaired sessions on the current and future use of immunotherapy for non-small cell lung cancer and creating a new stage between early and metastatic lung cancers. ESMO is Europe’s leading professional organization for medical oncology.

Liquid biopsies for ctDNA are becoming an integral part of early cancer detection, diagnosis, therapy selection, resistance detection, and response and relapse monitoring. At the November 2022 Agilent Technologies Engager meeting, Paweletz was part of a panel discussing the role of liquid biopsy in the development of biomarker-driven targeted cancer therapy.

Barbie discussed targeting innate immunity to restore lung cancer immunogenicity at the November 2022 Parker Institute for Cancer Immunotherapy Retreat in Montecito, Calif. Dana-Farber and the Parker Institute, the leading network of immuno-oncology experts in the world, have partnered to better understand the tumor microenvironment across cancer types and translate these basic discoveries to the clinic as impactful cancer immunotherapies.
At the April 2023 meeting of the American Association for Cancer Research (AACR), Elena Ivanova, PhD, reported on a new paradigm for determining drug response prior to prescription using patient-derived organoids, which are 3D cultures of tumors cells from an individual patient that can be used to evaluate therapy regimens. Personal organoids from a patient with low-grade serous ovarian cancer were developed and used to test 13 standard and non-standard of care anti-cancer therapies. Tests included BH3 profiling, which determines if a drug is inducing cell death, and a cell viability test to determine whether cells are alive or dead. The organoids showed sensitivity to two drugs, navitoclax and venetoclax, reducing cell viability by about 90% and showing high scores of cell death induction. The study shows proof-of-concept that this method is an effective means of determining how well a patient will respond to a drug, before it is prescribed.

Also at AACR, Barbie and his colleagues reported on a promising strategy to overcome chemotherapy resistance in small cell lung cancer, the most lethal type of lung cancer. They found that targeting TREX1, which degrades tumor-derived DNA that would otherwise activate the STING pathway, with certain drugs re-sensitizes chemoresistant small cell lung cancer cells to chemotherapy. Thus, inhibiting TREX1 might be a promising therapeutic strategy to treat the disease.

In 2023, Jänne also presented on new strategies for the treatment of EGFR mutant non-small cell lung cancer at the 20th Annual Meeting of the Japanese Society of Medical Oncology in Fukuoka, Japan, and at the Centro Nacional de Investigaciones Oncológicas in Madrid.

Barbie gave presentations in 2023 on utilizing ex vivo models to develop novel immunotherapies at the 1st IMMUNO-model COST Action Conference in Barcelona and on targeting innate immunity to enhance lung cancer immunotherapy response at the University of North Carolina Lineberger Comprehensive Cancer Center Seminar.

**Dana-Farber Collaborations**

The achievements of Dana-Farber researchers are due in part to a special environment that fosters collaboration among investigators from different disciplines. These partnerships help to transfer research innovations from the lab to the clinic, where they benefit patients.
COMBINATION THERAPY FOR OVARIAN CANCER

CDK7, a protein involved in regulating the process by which cells grow and divide, is overexpressed in many cancers and is associated with poor clinical outcomes. In collaboration with Panagiotis Konstantinopoulos, MD, PhD, the Belfer Center is testing the activity of an investigational CDK7 inhibitor, YKL-5-124, in combination with the PARP inhibitor (see sidebar) olaparib in patient-derived xenograft (PDX) models of ovarian cancer, which retain the biologic, molecular, and clinical features of human cancers. The researchers anticipate that CDK7 inhibition alone, or in combination with the PARP inhibitor, will elicit tumor responses in the PDX models, confirming results obtained in established cell lines that have displayed sensitivity to CDK7 inhibitors. Additionally, they will test whether the synergy between the anti-CDK7 drug and the PARP inhibitor is mediated by CDK7-induced inhibition of homologous repair, a phenomenon widely used by cells to accurately fix harmful breaks that occur on both strands of DNA.

TARGETING DNA DAMAGE

In another project with the Konstantinopoulos lab, Belfer Center scientists are investigating inhibition of ATR, a protein involved in DNA damage repair, with combination chemotherapy in ovarian cancer PDX models. Several studies have shown that ATR inhibitors may be synergistic with paclitaxel, which is widely used to treat multiple solid tumors and is particularly relevant in certain cancers driven by errors in DNA damage repair genes such as ovarian, breast, prostate, and pancreatic cancer. The researchers are studying the investigational ATR inhibitor ART0380, alone or in combination with paclitaxel, to determine its mechanism of action and evaluate its effectiveness in PDX models of high-grade serous ovarian cancer.

OPTIONS FOR HIGH-GRADE ENDOMETRIAL CANCER

Treatment options for high-grade endometrial cancers (see sidebar) remain limited, despite an increase in incidence and mortality. In collaboration with Joyce Liu, MD, MPH, the Belfer Center is evaluating a novel strategy for targeting two genetic abnormalities—the WEE1 protein and the ATR damage response gene—in these difficult-to-treat cancers. The Belfer Center will develop patient-derived organoids to help predict drug responses. The study may identify novel targeted therapies for high-grade endometrial cancer, with the potential to improve outcomes and address health disparities for women with this aggressive disease.
The Impact of Your Philanthropy

Cancer is an incredibly complex set of diseases, with different mechanisms by which malignant cells grow and survive. With your philanthropic support, the Belfer Center is able to take scientific research to the next level, addressing many of today’s most important challenges in cancer research and care. By integrating academic and industrial research, this revenue-generating work is improving the lives of patients everywhere. Thank you for your commitment to Dana-Farber’s lifesaving mission.

Report written by Scott Edwards.
Dana-Farber Cancer Institute has been the top-ranked cancer hospital in New England by *U.S. News & World Report* for 23 consecutive years, and is the only cancer center in the country ranked in the top 5 for both adult and pediatric cancer programs.

Dana-Farber Cancer Institute was named the #4 cancer center in the world by *Newsweek* in its World’s Best Specialized Hospitals ranking.

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