Cancer Center

Beth Israel Deaconess Medical Center

HARVARD MEDICAL SCHOOL TEACHING HOSPITAL

# For Your Information

*News and Information about the Cancer Center @ Beth Israel Deaconess Medical Center*

December 2016 • Volume.3, Number 2

Dr. Pier Paolo Pandolfi

**FROM THE DIRECTOR**

BIDMC Cancer Researchers Harness the Body's Own Defense

*See page 2*

## IN THIS ISSUE




Learn how immunotherapy saved a life. Go to bidmc.org/cancercenter

## BIDMC Cancer Center Offers Immune Therapies

Over the past several years, immunotherapy has grown increasingly important for the treatment of a growing number of cancers. Unlike chemotherapy and radiation, which bluntly and indiscriminately kill cancer cells, immunotherapy acts on a patient's own immune cells to help them selectively attack these cancers. It's a big story that's getting bigger.

The BIDMC Cancer Center has long been at the forefront of the field of immunotherapy. BIDMC's programs in biologic therapies and cancer vaccines, under the direction of David McDermott, MD, and David Avigan, MD, are widely recognized, both nationally and internationally, for significantly advancing the field and providing cancer patients with promising new treatment options.

"Decades ago, when there was still skepticism about immunotherapy, BIDMC researchers had already established

*Continued on page 19*

FROM THE DIRECTOR

# BIDMC Cancer Researchers Harness the Body's Own Defense

Dr. Pier Paolo Pandolfi, Director, BIDMC Cancer Center and Cancer Research Institute

For many years our therapeutic arsenal against cancer has relied on chemotherapies that target the highly proliferative nature of many cancer types. More recently, we have turned to a variety of precision drugs that target very specific tumor alterations, including genetic mutations that cause cancer. With this approach we have gone after the cancer itself, as we try to slay this monster with a multitude of new drugs available to us.

Yet the body has its own defense -- the immune system -- a highly efficient and vigilant patrol that protects us from both external and internal assaults to our wellbeing.

It is now becoming evident that another highly effective way to combat cancer is to harness the immune system, activating and facilitating it so that it quickly recognizes cancer as foreign and eradicates it. The development of "immunotherapy," as it is known, can have significant impact on patient outcomes. Equally important, the immune system continues to remain vigilant long beyond clinical intervention.

Here at BIDMC, the Cancer Research Institute (CRI) includes several well-established research programs that strive to understand how the immune system functions and malfunctions in the context of cancer. Critically, our research studies go hand in hand with clinical efforts and help to gain insight into how best to implement immunotherapy in the cancer setting.

In addition to a number of pioneering immunotherapy related approaches that we discuss in this edition of *FYI*, research teams at the CRI are carrying out immune landscaping studies using mouse models of cancer to allow us to understand the immune cells that infiltrate and may be harnessed to combat a variety of tumor types. Importantly, these mouse studies are revealing that cancers with specific genetic makeups harbor distinctive and often unique immune cell populations, and that the presence or absence of such infiltrating immune cells can have a direct impact on therapeutic outcomes.

We are actively examining the role of T cells, an important immune cell type that can identify and eradicate cancer cells, and the innate immunity, to understand how they can be harnessed for therapy. Understanding how to unleash T cells, macrophages or granulocytes to target cancer cells currently holds great promise for treatment of many cancers.

Our researchers and clinical investigators are also pioneering the development and the clinical use of cancer vaccines: the ultimate form of "personalized" immune therapy available to our patients. In this approach, we are using dendritic cells in order to train them to eliminate cancer cells, as well as to help our bodies develop a long-lasting memory of a patient's cancer, thereby preventing its recurrence.

These research efforts are of tremendous clinical relevance and the results obtained in the clinic are extremely promising. As the field of immunotherapy moves forward, our work here at BIDMC will help bring these advances to the clinic in our quest to eradicate cancer.

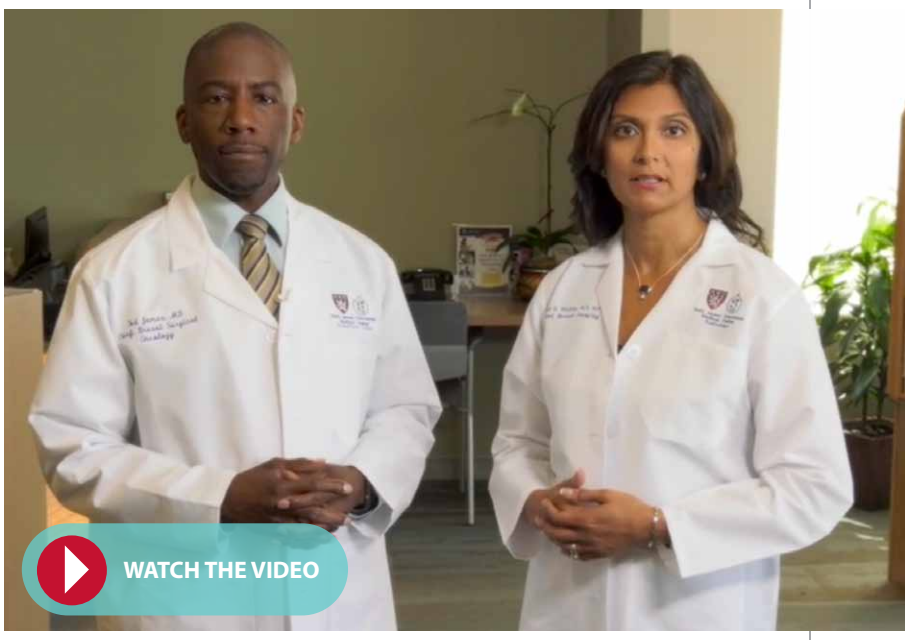
CLINICAL CARE

# BreastCare Center Enhances Focus on Patient-Centered Care

With new leadership and a freshly renovated facility, the BreastCare Center at BIDMC is doubling down on its existing commitment to patient-centered care.

"Our program is already known for delivering excellent, compassionate care," said Ted James, MD, who arrived in August from the University of Vermont as BIDMC's Chief of Breast Surgical Oncology and Co-Director of the Joseph M. and Thelma Linsey BreastCare Center. "We are now preparing to enhance our offerings based on empirical studies and input from our patients about their experiences and expectations."

Research shows a strong association between the patient experience on the one hand and clinical outcomes and post-treatment quality of life on the other, according to James. The term "patient experience" refers to how patients perceive critical aspects of the way care is delivered, including communication with their doctors, understanding treatment plans and coordination of healthcare needs.




Learn more about the Center from Dr. Ted James, left, and Dr. Tejas Mehta. Go to bidmc.org/breastcarecenter

## What Do Patients Want?

James said studies reveal that some key desires of cancer patients are convenient care in one building; support programs to aid with symptom management; a single point of contact to help them navigate the complexities of their care; and clinics that deliver multidisciplinary care.

Already at BIDMC, "Our recent renovation has improved the physical integration of our breast screening area on Shapiro 4 and the surgical consultation suite on Shapiro 5," said Tejas Mehta, MD, Chief of Breast Imaging and James's Co-Director of the Breast Care Center. "We now have a physical space that matches our multidisciplinary approach to breast care."

The BreastCare Center renovation was completed in May 2016. Its nature-themed, light-filled interior is designed to soothe while new surgical consult rooms on the breast imaging floor offer patients a degree of comfort and convenience when they receive their diagnoses.

In addition, this fall, a new BreastCare Center opened at Beth Israel Deaconess Hospital-Needham to provide quality screening and care in a convenient suburban location with free parking. [See story, page17]

## Patient-Centered Initiatives

James outlined several additional patient-centered initiatives that are underway in Boston.

**Breast oncology nurse navigator** – The BreastCare Center has recruited a full-time breast oncology nurse navigator to expand the center's capacity to coordinate and facilitate patient care. The existing patient navigators will continue to work closely with the nurse navigator, providing Chinese and Spanish language translation and culturally sensitive support.

*Continued on next page*

# New Breast Care Leadership, Facility

*Continued from page 3*

Renovated mamography room on Shapiro 4

**Breast Cancer Committee focus** – A new committee within the BIDMC Cancer Center's Cancer Care Committee will develop ways to solicit patient input and respond to it. Planned approaches include working with patient representatives on redesigning care processes, conducting patient focus groups, developing a patient-shadowing program and providing faculty development in patient-centered care.

**Shared decision-making resource** – Staff will create new informational resources, such as tablet-based educational programs, to support patients in making difficult choices.

**Surgical outcomes database** – Data collection will help the center track outcomes, monitor patient experiences and help translate outcomes research into best practices for delivering patient-centered care.

## New Treatment Options

James noted that the BreastCare Center has recently begun offering patients access to new surgical options, another important element in patient-centered care.

**Concealed scar surgery** – This new technique significantly minimizes visible scar tissue after mastectomy and lumpectomy for breast cancer.

**Lymphedema procedures** – Plastic surgery at BIDMC now offers surgical treatments to prevent or ease lymphedema. This non-life threatening but uncomfortable swelling in the arms can sometimes result from breast surgery or radiation. [See story, page 15].

James noted that studies demonstrate that women with breast cancer are particularly discerning when it comes to seeking care based on perceptions of quality, and will preferentially choose centers based on service quality.

"Word of mouth about the care experience has a huge impact on where patients decide to receive treatment," James said. "Ultimately, the goals of the BIDMC BreastCare Center are to excel in the delivery of patient-centered care and to provide each patient with an exceptional care experience."

**More info:** bidmc.org/breastcarecenter

Renovated waiting room on Shapiro 5

## CALENDAR

**January 5, 2017**
BIDMC Cancer Center Distinguished Lecture Series
*BRCA1 sustains mammary differentiation through DNA damage control*
A lecture by David Livingston, MD, of Dana-Farber Cancer Institute
4-5 pm at the Leventhal Conference Room, BIDMC

**February 2, 2017**
BIDMC Cancer Center Distinguished Lecture Series
*Regulation of Cell Death and Inflammation by RIPK1*
A lecture by Junying Yuan, PhD, of Harvard Medical School
4-5 pm at the Leventhal Conference Room, BIDMC

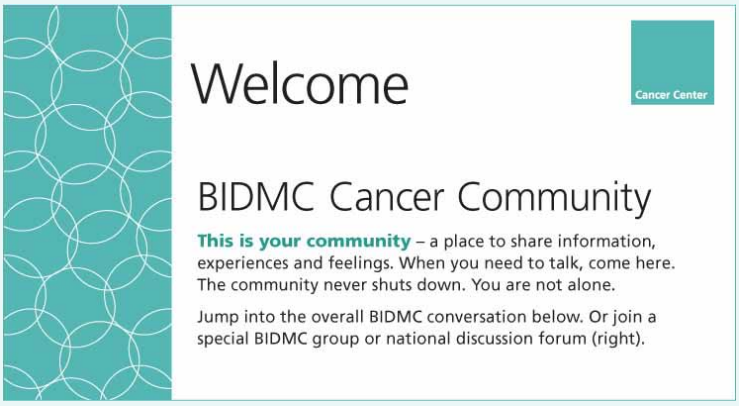
**March 2, 2017**
BIDMC Cancer Center Distinguished Lecture Series
*Oncogenic Ras-dependent Determinants of Tumor Fitness*
A lecture by Dafna Bar-Sagi, PhD, New York University Langone Medical Center
4-5 pm at the Leventhal Conference Room, BIDMC
**More info:** bidmc.org/cancercenter

**April 27, 2017**
RNAMEDICINE2017 Symposium
Joseph B. Martin Conference Center, Harvard Medical School
Registration opens January 2017

**More info:** bidmc.org/cancerevents

## NEWS

# Cancer Center Builds Online Community




To join, go to cancercommunity.bidmc.org

*"I will soon have surgery to remove one third of my right lung …"*

*"When I was really down, I tried to take it one step at a time, and even one breath at a time …"*

*"I underwent a very successful robot-assisted prostatectomy one year ago …"*

*"The worst thing probably was said by a close relative: 'How did you let this happen to you?'"*

Every person with cancer has a story. Many who have been treated at the BIDMC Cancer Center have reached out to share theirs with others, using a new online tool called the BIDMC Cancer Community.

The community can be found at www.cancercommunity.bidmc.org. Essentially a website that hosts a series of online discussion groups, the community is free and open to all. The community welcomes patients, friends, caregivers and anyone else whose life has been touched by cancer. Affiliation with BIDMC is not required.

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# Cancer Center Builds Online Community

*Continued from page 5*

"Cancer can be very isolating," said Hester Hill Schnipper, LICSW, Program Manager of Oncology Social Work at BIDMC and founder of the site. "Building community to help people support each other is the basis of many of our traditional services such as support groups. The BIDMC Cancer Community expands this opportunity by helping people connect with each other any place and any time."

The community's home page summarizes its mission by saying, "When you need to talk, come here. The community never shuts down. You are not alone."

The BIDMC Cancer Community consists of several BIDMC-focused discussion groups and national groups organized more than 40 topics. It is built on a software platform developed by the nationwide CancerConnect network.

The BIDMC groups are moderated by experienced BIDMC staff: oncology social workers, cancer nutritionists and the chaplaincy director. National groups are moderated by CancerConnect professionals.

## Special-Interest Discussion Groups

Hester Hill Schnipper

BIDMC groups include:

- Blood Cancers
- Breast Cancer
- Caregivers
- Cancer Nutrition
- Gynecologic Cancer
- Living with Cancer (general discussion)
- Prostate Cancer

The community also has the capacity to serve as a center of activity for online support groups, ask-the-expert sessions, educational videos and other helpful services.

The community opened in January and has since attracted 341 registered users. The busiest discussion groups are the general "Living with Cancer" and breast cancer groups. Patients are provided with information about the community in waiting rooms, during care visits and at cancer-related events.

"We tested the concept for a few months and discovered that the community operated very smoothly and in a real spirit of mutual helpfulness," said Schnipper. "In 2017, we will be reaching out to encourage more people to join the conversation."

**More information and sign-up**:
cancercommunity.bidmc.org

Cancer Center

Beth Israel Deaconess Medical Center

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***For Your Information***

News and information about the Cancer Center at BIDMC and its affiliates for referring physicians, scientists, colleagues, patients, employees, donors and other members of the BIDMC Cancer Center Community

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*FYI* welcomes comments, story ideas and subscription requests (specify electronic or print edition). Please email cancercenter@bidmc.harvard.edu.

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NEWS

# Cancer Symposium Speakers Describe Advances in Cancer Research

Breaking all previous attendance records, the BIDMC Cancer Center's Ninth Annual Cancer Symposium brought 500 attendees to the Joseph B. Martin Center at Harvard Medical School on November 2. Featuring10 presentations by various leaders in the field, the daylong program, titled "Pathways to Cure," focused on some of the newest frontiers in cancer research, including immunotherapy and cancer genomics.

"This symposium has become a fantastic forum to discuss new advances – trail-blazing advances – with a specific and particular attention on translating these advances into therapy, but importantly, into cures," said Cancer Center Director Pier Paolo Pandolfi, MD, PhD. "We use the word 'cure' on purpose because we want to cure cancer and not simply treat cancer."

David McDermott, MD, Director of the Biologic Therapy and Cutaneous Oncology programs at BIDMC's Cancer Center, gave an historical overview of cancer immunotherapy research. BIDMC researchers James W. Mier, MD, and Michael B. Atkins, now of Georgetown University, contributed to one of the earliest cancer immunotherapy drugs, approved by the FDA in 1992. But while it produces a durable remission for a certain subset of patients, said McDermott, it is "a very toxic drug that doesn't work for most people."

## Newer Immunotherapies

Since then, researchers have developed immunotherapies that are much more tolerable and apply to a number

Symposium speakers


of different kinds of tumors, including kidney, lung, melanoma and bladder cancers, McDermott said.

"Over the last ten to 15 years, we've gotten a much better understanding about the different, complex and sometimes overlapping ways in which tumors can evade and suppress the immune system," said McDermott, who is also leader of the Dana-Farber/Harvard Cancer Center Kidney Center Cancer Program and an Associate Professor of Medicine at Harvard Medical School.

While the new treatment approach is incredibly promising, one puzzle dating back to the 1990s persists.

"Most patients don't develop durable responses to immune therapy," McDermott said. "Some do, but it's a subset. How can we identify those patients? At BIDMC, we're trying to focus on improving outcomes by improving our ability to identify patients more likely to benefit. We are also developing novel approaches for those patients who fail immune therapy."

## From Basic Science to Cures

"I'm going to use the word 'cure' unabashedly here," said James Allison, PhD, Executive Director of the Immunotherapy Platform and Chair of the Department of Immunology at MD Anderson Cancer Center at the University of Texas. He followed McDermott's talk by describing the mechanisms and data supporting the many new immunotherapy treatments hitting the market in recent years.

"These drugs are being approved at almost an exponential rate," Allison said. "We got here by understanding the

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## Cancer Symposium Speakers Describe Advances in Cancer Research

*Continued from page 7*

fundamentals of the immune system, and we did that through basic science, something that is being lost in the trend toward translational science. Translational science is important, but there won't be anything to translate if we don't do basic science."

"We ended up coming to the same conclusions, telling the same story, but from fundamentally opposite positions," Scully said.

A pioneer in her field, Columbia University's Carol Prives, PhD, weighed in on the P53 tumor suppressor gene—the most frequent genetic error detected in cancer. Prives described how the gene regulates the metabolic pathway responsible for lipid synthesis. She has found that the mutant form of p53 stimulates the expression of the pathway, creating more aggressive tumors. By contrast, wild type (or normal) p53 dampens this pathway. Many drugs – such as the statins developed to treat high cholesterol – already target this pathway, Prives said, and may be used to target this cancer-causing pathway.

In the day's last session, Celeste Simon, PhD, of the Perlman School of Medicine at the University of Pennsylvania discussed the relationship between hypoxia and tumor progression, and Howard Hughes Medical Institute investigator, George Q. Daley, MD, PhD, of Boston Children's Hospital described the Stem Cell Pathways that drive cancer.

Other speakers included Edwin Liu, MD, of The Jackson Laboratory; Ralph Scully, PhD, of BIDMC; Elaine Mardis, PhD, of Nationwide Children's Hospital; Benjamin Ebert, MD, PhD, of Brigham and Women's Hospital; and Irving Weissman, MD, of Stanford University.

The 2017 Symposium will be November 8.
**More info:** bidmc.org/cancerevents

**NEWS**

# BIDMC to Join Transformative Pancreatic Cancer Trial

Dr. Manuel Hidalgo

"What would it look like if researchers, clinicians and diagnostic and drug developers created an unprecedented model of collaboration and data sharing to address one of the nation's deadliest cancers, pancreatic cancer?"

That question was posed by Julie Fleshman, President and CEO of the Pancreatic Cancer Action Network (PanCan), in October when she announced the first large-scale precision medicine trial designed to dramatically improve outcomes for patients with pancreatic cancer.

PanCan initially has committed $35 million over four years for its Precision Promise trial, which is expected to begin in spring 2017 at Dana-Farber/Harvard Cancer Center members including BIDMC. In addition, a series of grants will support translational research.

Manuel Hidalgo, MD, PhD, Clinical Director of the BIDMC Cancer Center and Co-Director of the Pancreas and Liver Institute at BIDMC, is a member of the Stromal Disruption Working Group spearheading the trial in one of its priority areas.

"The studies will be done in 12 institutions across the country," Hidalgo said, "and we will be leading one of them. I don't know which trial we will lead yet. Not all studies will take place at each center."

Hidalgo described Precision Promise as "an investigator-driven, philanthropy-supported initiative aimed at basically doubling the survival of pancreatic cancer patients by 2020. The way this will be accomplished is a series of integrated clinical trials combining novel compounds in the areas of stroma, immunology and cancer genetics, to be really effective. They will be combined in different ways and studied in different populations."

The trial leaders are hoping for robust patient enrollments. Participation in clinical trials is only 4 percent for pancreatic cancer patients, because the disease claims so many lives so quickly. The survival rate is 8 percent at five years.

Precision Promise will offer patients multiple treatment options under a single trial protocol that allows for quickly shifting to another option if one proves ineffective.

"This is a world class project," Hidalgo said. "It's transformative."

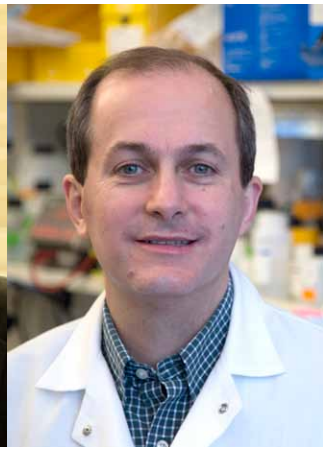
NEWS

# JAX-BIDMC Partnership Targets Triple Negative Breast Cancer

A research partnership between two scientists that sprang from the affiliation between the BIDMC Cancer Center and The Jackson Laboratory (JAX) has produced a grant to continue pursuing promising breast cancer studies together.

The United States Army Medical Research and Materiel Command has awarded $1.8 million over three years to Edison Liu, MD, President and CEO of The Jackson Laboratory, and Ralph Scully, PhD, a BIDMC cancer researcher. The grant will support studies aimed at characterizing the molecular basis of triple-negative breast cancers.

Dr. Edison Liu



Dr. Ralph Scully

> *'We hope our research will significantly improve prognoses for women with triple-negative breast cancer'*
>
> Dr. Edison Liu

The investigators hope their collaboration will result in the identification of a biomarker that can predict clinical response to cisplatin and other existing and new drugs used to treat triple-negative breast cancer and related ovarian and endometrial cancers. Their work is directed at understanding a unique genomic feature known as the tandem duplicator phenotype, which is found in women with triple-negative breast cancer. Triple-negative tumors resist targeted therapy because they lack three common receptor targets.

"Focusing on a genome-based tandem duplicator score, we hope our research will significantly improve prognoses for women with triple-negative breast cancer," said Liu. "Our goal is to find ways to identify and treat patients with the best drug possible, providing more precision and effectiveness."

"This type of breast cancer is extremely aggressive and difficult to treat because it is so complex," said Scully. "Our preliminary work shows that the tandem duplicator phenotype results in genetic damage that drives tumor growth. We're hoping a more precise understanding of the phenotype will make it possible to develop personalized treatments and save lives."

Scully and Liu met during a series of meetings between JAX and BIDMC cancer scientists that explored the potential for collaboration after the institutions' affiliation was announced in 2013. Liu is a cancer biologist with a focus on translational research, particularly in breast cancer. Scully is a cancer biologist with a focus on the basic science of DNA repair, especially the BRCA1 and 2 breast cancer genes.

"We became interested in the tandem duplicator phenotype completely independently and were excited to learn that we had come to similar conclusions about its potential for targeting triple-negative breast cancer," Scully said.

Scully and Liu began working together in 2015 as one of seven teams that secured grants through a special JAX-BIDMC pilot program designed to encourage collaborations.

NEWS

# MATCH Trial: New Options for Refractory Cancer

The many types of cancer are popularly known by the part of the body where the tumor is located: the breast, the prostate, the lung, the liver, the blood. Most cancer specialty programs, including those at the Cancer Center at BIDMC, are also commonly organized and named according to cancer sites.

This system of nomenclature is a bit misleading, however.

"Cancer is often a mutation-driven disease, not just a site-specific disease," said oncologist Glenn Bubley, MD, Director of the Genitourinary Cancer Program at the BIDMC Cancer Center. "The sequencing of the human genome now allows us to identify cancer-causing 'driver' mutations, and this, in effect, is the basis of personalized medicine. The newer way of treating cancer is that you don't start with the drug, you start with the mutation."

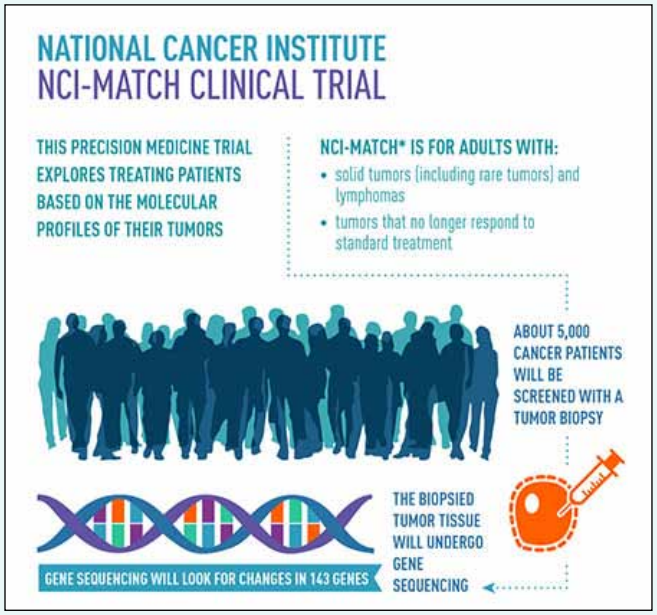
In an ideal world, every patient would receive personalized therapies that precisely target the molecular basis of his or her cancer. But this is not an ideal world.

## Addressing Barriers to Progress

Many cancer-causing mutations—including some related to big cancer categories like prostate cancer—are too rare for the pharmaceuticals industry to economically develop therapeutic agents. Even when there is a chance that "off-label" use of a drug already under development for a different cancer would help a patient with a less-common disease, the cost of sequencing the patient's genome is prohibitively expensive given the low odds of success.

In April 2015, the National Cancer Institute addressed this problem. It opened an innovative study called Molecular Analysis for Therapy Choice, popularly known as the MATCH trial. MATCH at first consisted of 10 arms corresponding to a range of 10 drugs, some already approved by the FDA for specific cancers only and others still in development. After a pause for reassessment, the trial reopened in 2016 with 24 arms, each with an enrollment goal of 35 patients. The number of arms will eventually grow to 30. MATCH pays for the genomic sequencing and—when a "match" is found—provides the drug.

In early December, the MATCH trial opened at BIDMC, with Bubley as the on-site site principal investigator. Already, Bubley has identified a metastatic prostate cancer patient whose genome has been sequenced and who appears to have a genetic mutation that may respond to a drug on the MATCH list.




National Cancer Institute infographic

"The criteria for participating is that the patient has to be more than 18 years old and that the cancer either never responded to standard therapy or responded and then began growing again," Bubley said.

## Searching for Matches

Only a handful of patients from BIDMC are likely to be "matched" to a treatment protocol, although many more patients will have their tumors biopsied and sequenced. During the first segment of the trial, 500 patients were screened, but contrary to expectations, only 9 percent were found to have "actionable" mutations that matched one of the drugs on the list, and only 5 percent actually entered the study.

Despite the challenges of successful matchmaking to date, however, Bubley is certain the MATCH trial is a promising addition to the BIDMC Cancer Center.

"If you know the driver, it's worth trying to treat the cancer," he said. "This trial offers patients new treatment options for which there is every reason to think there could be durable responses."

**More info:** https://www.cancer.gov/about-cancer/treatment/clinical-trials/nci-supported/nci-match

DEVELOPMENTS

# From Midlife Crisis to a Fight for Survival

## How immune therapy saved Jody Simes – and how he is saying "thanks"

*Jody Simes is an investment manager who lives in Newton. Below, he tells the story of his cancer, his immunotherapy at BIDMC and his gratitude to David Avigan,MD, Director of the BIDMC Cancer Center's Hematologic Malignancies Program.*

By Jody Simes

I am a 47-year-old man with a wonderful wife and three children. I live in Newton and I am a portfolio manager for a mutual fund company. When I turned 40, I had a mid-life crisis. I decided I was getting fat and out of shape. Over the next few years I began exercising and eating a very healthy diet. At the age of 43 I was in the best shape of my life, my career was going great and my family life was fantastic. I thought I was on top of the world.

Then I caught the flu. I couldn't get rid of it. I stubbornly refused to go to the doctor, so my wife made an appointment for me. She was concerned that I was not okay, and she was right.

My doctor took one look at me and I could tell even he was scared. He had me X-rayed immediately and called the same day to tell me I had cancer. I was in complete shock, and it took me a while to accept that I was sick. My biggest concern was my wife and kids. And so began my odyssey to defeat cancer.

I had Hodgkin's lymphoma, a very treatable form of cancer with a 90% cure rate. I always thought I would be one of the good statistics, and I immediately started chemotherapy with Dr. David Avigan at BIDMC.

> ***Avigan:*** *When I met Jody and we initially laid out our plan, we were hoping it would be straightforward treatment that would not require anything more complicated than chemotherapy.*

I failed my first chemo protocol, and my second, and my third. Next up was radiation therapy. I received 22 rounds, which left me with a partial response and a nice sunburn on my back.

When you fail chemotherapy as I have, your chance of a full cure becomes very remote. My best chance to survive was a bone marrow transplant. Luckily, my brother was an exact match. I began the long and dangerous process of a transplant. During all of these treatments I endured several bouts of pneumonia, mystery infections, pneumonitis and a couple months on oxygen. I was in and out of the hospital over a long, long time.

Jody Simes, center, with his family

At this point, I was really starting to feel I was getting my money's worth out of Dr. Avigan. But wait, there's more: a few months after the bone marrow transplant, the cancer came back. More chemo followed.

Then things got really scary. I was admitted to the hospital with severe back pain. Tumors were pressing on my spinal cord. I am an optimist, but for the first time I really thought I was going to die. Fortunately, more radiation therapy shrank the tumors, and I started to feel much better.

I was still in very deep trouble and Dr. Avigan was working tirelessly to find a solution. There was a new immune based therapy called Opdivo that had showed some promising results on a small group of Hodgkin's patients, but it was not yet approved for a patient like me with

*Continued on next page*

# From Midlife Crisis to a Fight for Survival

*Continued from previous page*


a bone marrow transplant. The danger was that the treatment could easily cause a deadly case of graft versus host disease, where my brother's immune system would attack my healthy organs. There was virtually no data on this drug with people in my condition.

Dr. Avigan spent countless hours consulting with other doctors, and managed to find a few doctors in the country who had tried Opdivo on patients with a bone marrow transplant. He gained enough comfort to consider ordering the drug for me. He didn't know if insurance would cover it (in the end it did) or if it would kill me. We discussed the pros and cons in detail, and I pressed him to go forward. I told him I wanted him to cure me or kill me trying. I was going to play offense, to take the most aggressive treatment available, no matter the risk.

***Avigan:*** *Bone marrow transplant from a donor may be effective in blood cancers that are resistant to standard treatments. The potency of the treatment is based on the donor's immune cells seeing the patient's cancer cells as foreign and eliminating them. As such, this is essentially a crude but effective form of immune therapy. However, Jody's tumor started to grow again. We decided together to try Opdivo therapy, a novel way of activating the immune system by blocking one of the pathways that tumors use to create tolerance to it. However, using this approach after a bone marrow transplant was unknown territory and could unleash a very strong donor immune response against the patient's normal tissue. But given the difficult situation Jody was in, we decided to take a deep breath and take the leap together.*

I started Opdivo last summer, and I have been getting stronger ever since. Recently I received results from a CT scan. For the first time in over three years of nonstop treatments, I am thrilled to be in remission. I have graft vs. host disease, like most transplant recipients, but it is mild. Dr. Avigan found the silver bullet. Ironically, Dr. Avigan's own scientific work in immunotherapy takes a vaccination approach, which is different from the checkpoint inhibitor approach that saved me.

***Avigan:*** *There has been a real revolution in our understanding of how the immune system and cancer cells interact, and the development of novel therapeutic agents to boost the immune system's recognition of cancer. BIDMC is a leader in that revolution.*


Dr. David Avigan

*These strategies include cancer vaccines, which seek to educate the immune system to see cancer cells as foreign and to launch an immune response to target and eradicate the cancer. Our vaccine model is being studied in a first of its kind national trial in melanoma. Its use in acute myeloid leukemia has resulted in more than 70% of patients remaining in remission at five years in a population in which less than 20% are expected to remain in remission.*

*Other strategies available at BIDMC include use of*

*Continued on next page*

*genetically engineered "CAR T-cell" to target lymphoma; and studies involving checkpoint blockades alone or in combination with other agents that take the brakes off the immune system as in Jody's case. The latter has shown dramatic response in several solid tumors including melanoma, kidney cancer, lung cancer and Hodgkin's disease. They have been approved by the FDA so they are readily available, and now there are studies combining them with other novel agents to further amplify responses.*

I am truly grateful to have such an outstanding and dedicated doctor to help me fight cancer. I made a contribution to help Dr. Avigan establish a laboratory that will be a center for growing vaccines for patients who are being treated at cancer centers all over America. I wanted to help him build something that's going to change a lot of lives.

***Avigan:*** *Jody has been on an incredible journey. He has shown tenacity and perseverance in fighting his illness and his response has been amazing. Jody's story shows the power of immune therapy to save lives.*

## Support the BIDMC Cancer Center

Your donation helps to fuel scientific discoveries, provide world-class care to patients and their families and educate the next generation of cancer physicians and researchers.

**Learn more or make a donation:**
Loren Feingold at (617) 667-7357
or lfeingol@bidmc.harvard.edu

**NEWS**

# Charest Brings Brain Cancer Research Expertise to BIDMC

Dr. Alain Charest

Biochemist Alain Charest, MSc, PhD, has joined the Cancer Research Institute and the Division of Genetics at BIDMC, where he will use his expertise in genetic engineering of human cancers in mice to perform research in brain cancer.

Charest arrived in June, bringing with him a four-member laboratory and three brain cancer research grants from the National Institutes of Health.

He will tap the services of the Mouse Hospital developed by Pier Paolo Pandolfi, MD, PhD, to help identify new pharmacological approaches to glioblastomas. He will also work closely with BIDMC Cancer Center neuro-oncologist Eric Wong, MD, using mouse models to develop new treatment protocols.

"Having clinical input is key for anyone trying to do translational therapeutics with mouse models of cancer," Charest said. His interests include co-clinical trials, in which patient tumors are introduced and treated in mouse avatars to identify potential therapies and likely outcomes.

Charest, a native of Quebec, was until recently an Associate Professor in the Department of Neurosurgery at Tufts Medical Center and Tufts University. He earned his PhD in biochemistry at McGill University and completed his postdoctoral research during a fellowship at Massachusetts Institute of Technology.

Charest is currently co-principal investigator or lead principal investigator of three projects:

**exRNA Released by Glioblastoma Alters Brain Microenvironment**
The project is investigating RNA-mediated intercellular communication using malignant glioma as a model system. The dynamics of extracellular RNA production, release and uptake are being studied using genetically engineered mouse models of glioblastoma.

**Experimental Therapeutics and BioMonitoring for Brain Tumors**
The program supports and assists members with their animal models of gliomas using strains and models derived in Charest's laboratory.

**Molecular Wiring and Therapeutic Targeting of EGFR and PDGFRα Signaling Networks**
The project is studying the consequences of the order of accumulated genetic mutations on tumor physiology and resistance/sensitivity to therapeutic interventions in preclinical mouse models of glioblastoma. It uses quantitative phosphoproteomics and biocomputational analyses.

NEWS

# Textbook Spreads the Word about TTFields Brain Cancer Therapy

Neuro-oncologist Eric T. Wong, MD, has just published the first textbook on Tumor Treating Fields in oncology, and already he can practically feel the increased heft of a possible second edition in his hands.

"This is new technology," said Wong, who edited *Alternating Electric Fields Therapy in Oncology: A Practical Guide to Clinical Applications of Tumor Treating Fields*. "I hope in three to five years I will have the opportunity to write a second edition because so much data emerges that will need to come out."

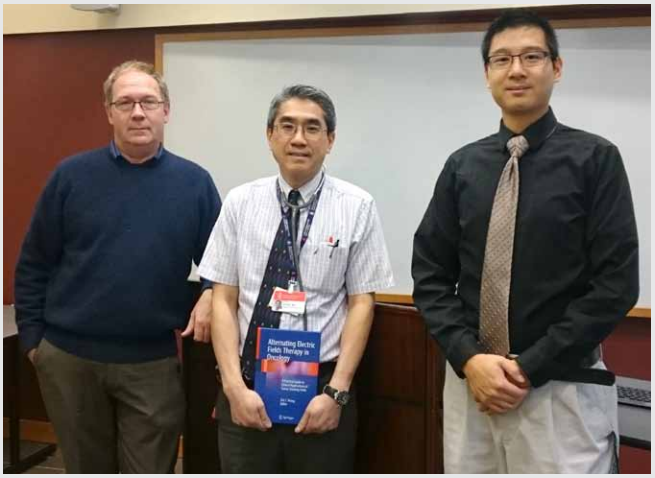
Evidence is already accumulating about the effectiveness of tumor treating fields (TTFields) in targeting glioblastoma—a common, aggressive and difficult-to-treat form of brain cancer that claimed the life of U.S. Senator Edward M. Kennedy. Research in which Wong has participated showed that TTFields extends the median survival of people with glioblastoma by five months and can stabilize the disease for as much as two years. In addition, there is growing evidence that TTFields may be applicable to lung, ovarian, pancreatic and other tumors.

## Form of Electromagnetic Therapy

Wong, Director of the Neuro-Oncology Unit and Co-Director of the Brain Tumor Program at BIDMC, has treated more than 70 patients with TTFields, a form of electromagnetic therapy. The patient's head is shaved and ceramic discs with electrodes are placed on the scalp to deliver low-intensity, medium-frequency electrical current that passes through the skin, skull and brain tissue into the tumor. The therapy stresses and ultimately destroys tumor cells. Patients receive TTFields in combination with surgery, radiation and chemotherapy.

With the recent publication of his textbook by Springer International Publishing, Wong said, "I hope I can interest more people to do this type of research so we can really understand the mechanisms behind this technology."

The book for the first time assembles in one place 10 chapters chosen to guide clinicians when treating brain and other cancers with TTFields. Articles were authored by Wong, his longtime BIDMC collaborators—cell biologist Kenneth D. Swanson, PhD, and physicist Edwin Lok, PhD—and other colleagues in the United States and other countries.



Left to right: Dr. Kenneth D. Swanson, Dr. Eric T. Wong and Dr. Edwin Lok

TTFields was approved by the FDA for use in recurrent glioblastoma in 2011 following a clinical trial sponsored by the Israeli company Novocure. The findings were somewhat controversial because the trial was conducted without a control group that received a placebo—a debate Wong considers ridiculous because cancer clinical trials do not treat patients with placebos. The FDA later approved in 2015 TTFields for newly diagnosed glioblastoma in based on positive progression free survival and overall survival benefits.

Wong said he expects a new trial to open at BIDMC this winter in which TTFields will be evaluated as a therapy for metastatic small-cell lung cancer that has spread to the brain.

## TTFields is exciting for many different reasons

"Usually treatments start with other branches of oncology and are applied to neuro-oncology," said Wong. "TTFields is one of only two treatments (the other is stereotactic radiosurgery) that started in neuro-oncology and is branching out to other disease sites."

**Where to buy:** Amazon.com

# Around the Cancer Center

## Zerillo Named to Oversee Quality and Safety

Jessica Zerillo, MD, MPH, has been named Director of Healthcare Quality for the Cancer Center at BIDMC.

Dr. Jessica Zerillo

In this role, Zerillo supports a culture of safety and promotes quality initiatives. She works to improve data collection and measurement of quality with the aim of reducing unnecessary variation in care.

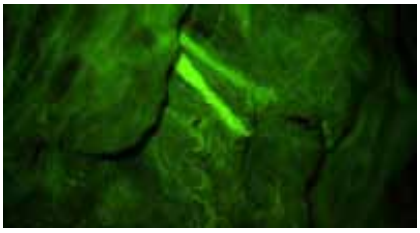
"One of my goals is to consolidate and coordinate quality efforts across the Cancer Center," said Zerillo, who is also a medical oncologist specializing in gastrointestinal cancers.

Zerillo's activities include coordinating accreditations and certifications, including Quality Oncology Practice Initiative and Functional Assessment of Cancer Therapy, and participating in Cancer Center quality efforts and committees. She chairs the Hematology/Oncology Patient Safety Committee. In addition, Zerillo has been appointed to the Department of Medicine Patient Safety Core Faculty to develop quality and safety education for trainees, including fellows.

Zerillo has begun convening a series of Safety Town Halls, aimed at surfacing safety-related concerns, training staff how to report events and assuring that processes are in place to achieve continuous improvement.

Zerillo completed a fellowship in Hematology/Oncology at BIDMC and a fellowship in Patient Safety and Quality at Dana-Farber Cancer Institute in June. She joined BIDMC in 2015 with a clinical focus on gastrointestinal malignancies.

## New Surgical Techniques Ease Lymphedema



Green dye in lymphatic channels

Plastic surgeons at Beth Israel Deaconess Medical Center (BIDMC) are bringing new hope to cancer patients by offering innovative procedures for preventing and treating lymphedema.

Although not life-threatening, lymphedema is an uncomfortable and painful swelling that can commonly occur in a person's extremities (arms or legs) after treatment for breast and other cancers. Lymph node removal can cause lymph fluid to accumulate in the extremity, resulting in lymphedema. Radiation treatment further increases the risk. The traditional treatment, physical therapy, is not always effective.

Dhruv Singhal, MD, Director of Lymphatic Surgery, arrived at BIDMC in September, bringing with him new surgical techniques for easing lymphedema.

**Lymphovenous bypass** is a preventive procedure. During the removal of lymph nodes by a surgical oncologist, a fluorescent green dye is injected into the closest extremity, which makes the lymphatic channels glow. That glow can then be followed to figure out where the lymphatic channel was cut during the removal of the lymph nodes. Using a special microscope, the surgeon re-routes the lymphatic channel to other veins so that the risk of swelling is minimized.

**Vascularized lymph node transfer** surgery can be performed well after a patient has developed lymphedema, if physical therapy isn't working. Surgeons relocate healthy lymph nodes to the affected extremity.

"Patients who have been living with lymphedema for many years have shown such incredible progress after having lymph node transplants," says Singhal. "I've performed this procedure on patients who had lymphedema for many years. Within six months of treatment, we have seen great improvements."

## NP Delivers Keynote at PurpleStride Walk

Once a year, the Boston chapter of the Pancreatic Cancer Network organizes a "PurpleStride" walk to raise awareness and funds to support research and provide support to individuals with this difficult disease. And each year, members of the BIDMC Pancreatic Cancer Program participate to express support for patients and their families. Rebecca A. Miksad, MD, MPH, the Director of Gastrointestinal Oncology at BIDMC, served on the 2016 Boston

PurpleStride Executive Committee, as did A. James Moser, MD, FACS, Co-Director of the BIDMC Pancreas and Liver Institute (PLI), in 2015.


Adrienne Terra

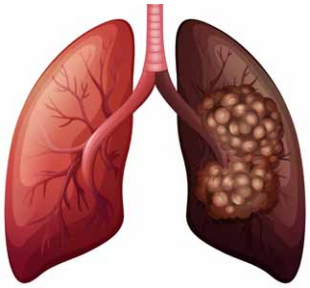
BIDMC's impact on the walk was greater than ever at the August 14, 2016, walk on Boston Common with a heartfelt keynote speech delivered by Adrienne Terra, MSN, a nurse practitioner in the Gastrointestinal Oncology Program. The 40-member BIDMC team organized by Miksad included BIDMC staff, grateful patients and their family members. A BIDMC grateful patient donated 100 large purple cookies decorated with the pancreatic cancer ribbon and the PLI logo; the cookies generated much excitement when team members handed them out to PurpleStride participants.

Terra was asked to speak by the daughter of a beloved patient, the late Jack Jackson of Needham. Her speech wove together two threads–the story of Jackson's quest for survival and the story of her own growing interest in working with pancreatic cancer patients, which Jackson encouraged. He lived an unusual three years after diagnosis.

The two met while Terra was working at BIDMC but still in training. They kept in touch and became friends. Partly inspired by Jackson, Terra set a goal of becoming a nurse practitioner working with pancreatic cancer patients. Two days before she was to start work in this job, after obtaining her NP degree, Jackson passed away.

"This last intersection of our paths–his passing coinciding with my new role–-felt like he was passing a torch on to me," she told the PurpleStride crowd. "I feel like it is my job to keep his legacy alive … Today, I walk in honor of Jack and all of our patients."

## BIDMC Offers Lung Screening Program



BIDMC now offers low dose CT lung cancer screening, the only cost-effective test shown to reduce mortality by detecting lung cancer in Stage I.

The LungHealth Program performs the test with a dedicated low-dose CT technique. There is no contrast administration and the examination is usually completed in 10 minutes. BIDMC was a study site for the clinical trial that validated LDCT screening.

Eligible patients must meet these criteria:

- 55 to 77 years old
- Current or former smokers who quit no more than 15 years ago
- Have at least a 30 pack-year smoking history

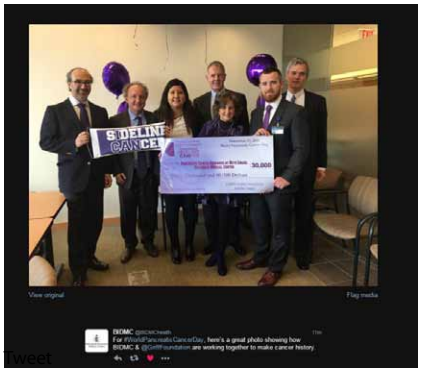
At the time of screening, patients should be free from symptoms suggestive of lung cancer.

There are three ways to enroll patients:

- Reminder alert: The smoking history tab on OMR now allows calculation of pack years but you must update "smoking status" to see the calculator. If your patient meets the criteria, you will see this reminder on the patient's front page.
- New order entry via OMR > Testing/Services > CT Lung Cancer Screening
- Complete paper order and fax to 617-667-5715

**More info:** Lauren Taylor at 617-667-5712 or LungHealth@bidmc.harvard.edu

## World Pancreatic Cancer Day at BIDMC



Tweet

The Pancreas and Liver Institute (PLI) observed World Pancreatic Cancer Day November 17 with educational lectures and a tweet to tell the world about a generous donation from the Griffith Family Foundation.

## A Reason to Ride Raises Research Funds

The annual A Reason to Ride event organized by a grateful BIDNC cancer patient on September 10 raised almost $100,000 to support cancer research at BIDMC.

The patient, Tom DesFosses, has been treated for Primary CNS Lymphoma, a form of brain cancer, by BIDMC neuro-oncologist Eric T. Wong, MD. DesFosses was diagnosed 10 years ago and credits Wong with saving his life.

"Year after year, we are overwhelmed by Tom's generosity and dedication," said Wong. "The hundreds of thousands of dollars he has raised over the past decade support research that will help other cancer patients."

The North Shore bike-a-thon is organized by DesFosses, his wife Judy, and a number of friends and supporters. The presenting sponsor is Fuddruckers Restaurant. The event attracted among the largest-ever numbers of participants this year, including about 60 BIDMC doctors, nurses and staff.

For the first time, the 2016 event also included a 5K walk.

Watch the A Reason to Ride web site for the yet-to-be chosen date of the September 2017 event.

**More info:** areasontoride.com

## New Name in Needham


The Beth Israel Deaconess Cancer Center in Needham—an integral part of the BIDMC cancer Center—recently received a new name. The words "Lank Cancer Center" have been installed on the building in recognition of the generosity of Althea and Buddy Lank. The Lanks are members of a family that over many decades has supported BIDMC and Beth Israel Deaconess Hospital-Needham, where the Lank Cancer Center is located. The building includes both a state-of-the-art Cancer Center and a new Surgical Pavilion. The Lanks' gift was the largest in the history of BID-Needham.

## Needham BreastCare Center Opens

This fall, Beth Israel Deaconess Hospital–Needham opened a new BreastCare Center, a comprehensive program that offers both screenings and the full range of care for benign and malignant breast disease.

This new space brings the entire patient-care team — encompassing radiologists, technologists, nurse practitioners, breast surgeons, a nurse navigator and a social worker — together under the same roof. Its multidisciplinary approach is based on a model similar to that of the BreastCare Center at BIDMC in Boston.

Co-Directors of the center are breast surgeon Mary Jane Houlihan, MD, who practices in both Boston and Needham; and Tejas S. Mehta, MD, MPH, Chief of Breast Imaging and Co-director of the BreastCare Centers at both BID–Needham and BIDMC.

The Needham BreastCare Center facility was designed with patient input. The center offers 3D mammography, breast MRIs and ultrasounds, read by the same radiologists who also practice at BIDMC. When screening results in a potential diagnosis, patients can meet with breast surgeons within the BreastCare Center.

BID–Needham's Cancer Center and Surgical Pavilion provide patients with immediate access to breast surgery and reconstruction, as well as ongoing treatment and support services. The close connection to the Cancer Center at BIDMC in Boston offers patients in Needham access to the latest clinical trials and research.

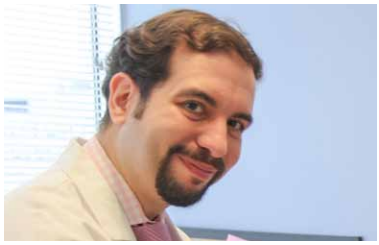
BIDMC's world-renowned breast pathology team reviews every surgical biopsy performed at BID–Needham. When a cancer diagnosis is made, the breast pathologist, along with the breast surgeon, radiation and medical oncologists, radiologist and social worker, create a care plan that is individualized to the patient.

**More info:** bidneedham.org/breastcare

**Screening appointments:** 781-453-3800

# Costa Named Clinical Trials Medical Director

Daniel B. Costa, MD, PhD, MMSc, has been named Medical Director of the Cancer Clinical Trials Office, a role in which he is responsible for the conduct of cancer trials at BIDMC.



Costa helps support the BIDMC Cancer Center as a premier clinical research center of worldwide renown. He assures that innovative clinical studies are conducted in a safe and compliant manner and that the operation is nimble and efficient. He also works toward making clinical protocols available to affiliates throughout the Beth Israel Deaconess network.

Costa succeeds Steven Come, MD, a respected clinical investigator and master clinician. As CCTO Medical Director since 2010, Come was responsible for centralizing cancer clinical trials. He was been instrumental in hiring and recruiting CCTO staff and provided continual and steady stewardship of the program.

An Associate Professor of Medicine at Harvard Medical School, Costa is a thoracic medical oncologist at BIDMC. He holds a number of leadership positions in research and clinical programs and has run clinical trials at BIDMC since 2007. His investigative work focuses on characterizing the mechanisms of sensitivity and resistance to tyrosine kinase inhibitors in lung cancers with oncogenic mutations or rearrangements.

# Three Medical Oncologists Join Staff

**Xiuning Le, MD, PhD**, is practicing thoracic oncology in the Lung Cancer Program.

Earlier this year, while still a fellow at BIDMC, Le received a Young Investigator Award from the American Society of Clinical Oncology. Le's award recognized her research in the mechanisms of resistance to PI3K inhibition in breast cancer.

Le received her medical degree from Peking Union Medical College in China and a doctoral degree in biological and biomedical sciences from Harvard Medical School. She completed her residency at UMass Medical Center and her fellowship in hematology/oncology at BIDMC.

**Myrna Nahas, MD,** specializes in hematological malignancies and bone marrow transplant.

A member of the laboratory of David Avigan, MD, she performs research in immunotherapeutic mechanisms for hematological disease, including acute myeloid leukemia and graft versus host disease. She is currently investigating the therapeutic role of hypomethylating agents in mediating immune responses against acute myeloid leukemia.

Through a Phase I clinical trial for patients with steroid-refractory chronic graft-versus-host disease, Nahas has also analyzed the immunotherapeutic effects of Abatacept, a selective co-stimulatory agent.

Nahas received her medical degree from The University of Texas Health Science Center at San Antonio. She completed her residency in internal medicine at The University of California at Los Angeles David Geffen School of Medicine, and a fellowship in hematology/oncology at BIDMC.

**Eirini Pectasides, MD, PhD**, specializes in the care of patients with gastrointestinal malignancies, with a special focus on patients with gastric and esophageal cancer.

Pectasides' clinical and laboratory research focuses on the development of new, more effective treatment strategies for patients with these diseases. In particular, she is studying the genetics of gastroesophageal cancer in an attempt to develop personalized therapies that exploit the molecular underpinnings of each patient's cancer.

Pectasides received her medical degree and her doctoral degree from the University of Athens Medical School. She completed her residency at Montefiore Medical Center / Albert Einstein College of Medicine and her fellowship in hematology/oncology at BIDMC. She also completed a research fellowship under the mentorship of Adam Bass, MD, at Dana-Farber Cancer Institute.

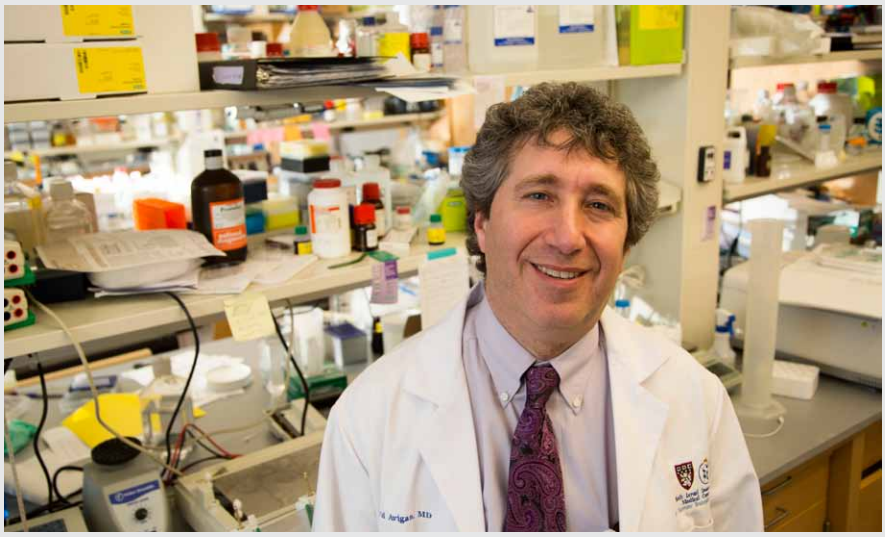
She received a Young Investigator Award from the American Society of Medical Oncologists in 2015 in recognition of her study, "Genomic Heterogeneity: A Barrier to Biomarker Profiling and Targeted Therapy for Gastroesophogeal Cancer."

**Doctor listings:** bidmc.org/findadoc

FEATURE STORY

# BIDMC Cancer Center Offers Immune Therapies

*Continued frompage 1*



Dr. David Avigan

successful research programs in this specialty," says Pier Paolo Pandolfi, MD, PhD, Director of the BIDMC Cancer Center and Cancer Research Institute. "Our clinical investigators believed that the immune system would be a successful tool for the treatment of cancer. And they were right."

The past five years have seen an explosion in new immunotherapy developments and today, at BIDMC, both FDA-approved and experimental treatments are available. They are being used for the majority of cancer types, including solid tumors and blood cancers. Because FDA-approved therapies are widely available in the community, patients are often referred to BIDMC and other academic medical centers to take advantage of experimental protocols. These offer patients new options that go beyond standard treatments.

"It's safe to say that immunotherapy is now considered one of the five pillars of cancer therapy, joining the three longstanding pillars – surgery, radiation therapy and chemotherapy – as well as precision medicines with targeted therapies aimed at repairing the molecular genetic defects specific to various types of cancer," says Pandolfi.

As approved immunotherapies reach increasing numbers of cancer patients, investigators at BIDMC are offering clinical trials with the potential to further extend the benefits of these drugs through a variety of new approaches.

## When to Consider a Referral

"One of the most exciting aspects of immunotherapy treatments today is that patients can often receive treatment in their own communities," says McDermott, Director of the Biologic Therapy Program. Not every patient will have this option, however.

"Often, immunotherapy is used for advanced disease that has not responded to chemotherapy or other treatments," explains Manuel Hidalgo, MD, PhD, BIDMC Cancer Center Clinical Director and Chief of the Division of Hematology/Oncology. In these cases, patients can be referred to BIDMC, where a wide range of clinical trials provide new treatment options.

"Referrals might be considered in a number of situations," says McDermott. Most referrals are made when patients already receiving US Food & Drug Administration-approved immunotherapy or other treatments experience growth of their tumors, or when immunotherapy is not currently the standard of care for the tumor.

"With more than 50 studies that are currently active and enrolling patients, BIDMC is deeply engaged in immunotherapy clinical research, especially cancer vaccines and checkpoint inhibitors for the treatment of a majority of blood cancers and solid tumors," says Daniel Costa, MD, PhD, Medical Director of the Cancer Clinical Trials Office in the BIDMC Cancer Center. BIDMC patients and physicians have access to most of the important immunotherapy trials taking place in the United States today.

Some immunotherapy trials are testing immunotherapies in cancers other than those for which they were originally developed, and others are designed to evaluate the impact of immunotherapies when they are combined together or combined with standard anti-cancer drugs such as chemotherapies.

*Continued on page 20*

# BIDMC Cancer Center Offers Immune Therapies

*Continued from page 19*

Dr. David McDermott

It is important for patients to understand that, despite enthusiastic media coverage, immunotherapies are not magic bullets.

"The reality is that some patients don't respond to immunotherapy treatments, some patients respond and then develop resistance, and for some patients, these drugs can create toxicity problems," cautions Hidalgo.

"In many cases, these novel therapies do not produce remissions of advanced disease," adds McDermott. "But through our clinical trials, we are working to better understand how immunotherapy drugs act on many types of cancer, so that we can determine how best to use these drugs and increase the number of patients who will benefit from them."

## Immune Checkpoint Inhibitors

Immune checkpoint inhibitor drugs are currently the most widely used and widely publicized type of immunotherapy treatment. These new therapies work by targeting "immune checkpoints," the molecular pathways that cancer cells use to evade the immune response. These include pathways known as CTLA-4, PD-1 and PD-L1.

"Immune checkpoints such as PD-1 and CTLA-4 can act as a brake on the immune response to cancer," explains McDermott, whose early work in the Biologic Therapy Program helped pave the way for the field's current success. "These pathways can now be targeted with monoclonal antibodies, the so-called 'checkpoint inhibitors,' which release the brakes and allow the patient's immune system to attack the cancer."

In just the past several years, four new immune checkpoint inhibitors have been approved by the FDA. These include Keytruda (pembrolizumab), Opdivo (nivolumab), Tencentriq (atezolizumab) and Yervoy (ipilimumab). They are given intravenously for the treatment of a growing number of cancers including kidney and bladder cancers, head and neck cancer, advanced melanoma, Hodgkin's lymphoma and non-small cell lung cancer. Checkpoint inhibitor treatment may start with a diagnostic molecular analysis of the patient's cancer cells to determine whether the potential for a response exists.

Over the past decade, BIDMC has been involved in all phases of the development and testing of these checkpoint inhibitor drugs.

"We were part of a group of investigators that showed that CTLA-4 inhibition could improve survival in patients with metastatic melanoma and, more recently, we showed similarly good results with PD-1 and PD-L1 blockade in both melanoma and kidney cancer," says McDermott. BIDMC enrolled more patients than any other center in the clinical trial that led to FDA approval of Yervoy, an antibody that actually produces remissions in some patients with stage 4 disease.

McDermott adds that because these agents work for a number of different cancers, they have helped to revolutionize cancer treatment. "Immune checkpoint inhibitors are more effective and less toxic than earlier cytokine-based immunotherapy agents," he says. "While cytokines, including interleukin-2, are still used for the treatment of kidney cancer and melanoma, their toxicity and limited effectiveness confines their application to select patients."

## Cancer Vaccines and Engineered T Cells

Cancer vaccines, another category of immunotherapy agents, work to reeducate the body's immune system to recognize cancer as foreign and trigger an active immune response against the cancer. BIDMC's Cancer Center provides referring physicians and their patients with one of the largest cancer vaccine and cellular therapy

programs in the country. Under the direction of David Avigan, MD, Chief of Hematological Malignancies and Bone Marrow Transplantation, cancer vaccines have been developed and are being tested for the treatment of multiple myeloma, acute myeloid leukemia and other cancers.

Avigan's work focuses on "personalized" dendritic cell vaccines. In these cases, immune cells are removed from the patient's blood and exposed in the lab to cancer cells or cancer antigens, as well as to other chemicals that turn them into special immune cells called dendritic cells. These custom-made "fused cell" vaccines are then injected back into the patient, where the aim is to cause an immune response to the body's cancer cells. A dedicated clinical immunotherapy facility has been created on-site at BIDMC to develop each of the individually prepared vaccines that are available through several Phase 1, 2 and 3 clinical trials currently open and enrolling eligible patients.

Avigan, Jacalyn Rosenblatt, MD, and colleagues are leading a first of its kind national trial sponsored by the National Institutes of Health and the National Cancer Institute's National Clinical Trials Network for patients with multiple myeloma. Fifteen leading cancer centers around the country are participating in this randomized trial comparing vaccination with dendritic cell/tumor fusions and the standard of care in patients undergoing stem cell transplantation. In an open source format, BIDMC-trained investigators around the country produce the vaccine. BIDMC is serving as the central site verifying vaccine characterization and immune response.

## Vaccine Highly Effective for AML

In a report currently being published in *Science Translational Medicine*, Rosenblatt, Avigan and colleagues have demonstrated that vaccination of patients with acute myeloid leukemia was highly effective in preventing disease relapse in patients with this extremely aggressive blood cancer. A National Institutes of Health-sponsored multicenter, randomized trial is currently being developed to examine the role of vaccine or vaccine with checkpoint blockade as compared to standard of care therapy.

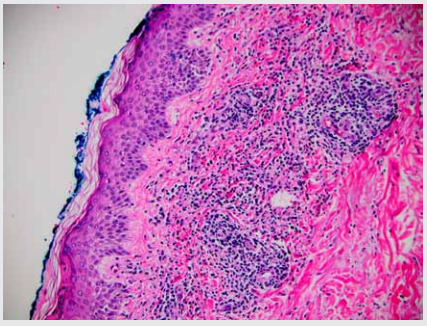
Avigan's group is also testing another immunotherapy approach, known as CAR T-Cell Therapy, which involves engineering a patient's own immune cells to recognize and attack tumors. CAR T cells have been highly effective in treating patients with refractory acute lymphoid leukemia. Trials at BIDMC are now underway to determine the effectiveness of this strategy for patients with lymphoma and multiple myeloma. Combination therapies of immune modulating therapies and checkpoint blockade are also being examined in clinical trials for patients with multiple myeloma.

"At this point, cancer vaccines may be used alone or in combination with chemotherapy or other immune therapies," said Avigan. Over the past 16 years, the program has overseen numerous experimental trials and increasingly positive patient responses.

**More info:** bidmc.org/cancertrials or CCTO Director Jonathan Dinsmore at jdinsmor@bidmc.harvard.edu

## Types of Immune Therapy

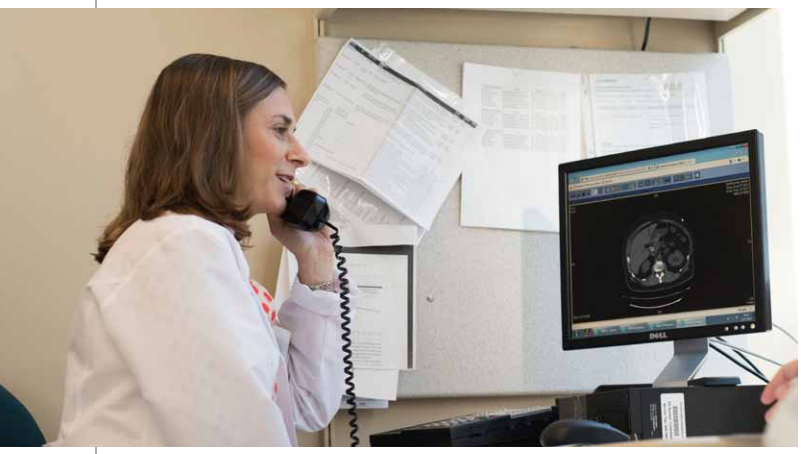
- **Immune checkpoint inhibitors** block a mechanism that cancer cells use to shut down the immune system. This frees T cells – white blood cells that play a role in immunity – to attack the tumor.
- **Cytokine-based immunotherapies** stimulate effector T cell responses and can be quite effective in fighting certain cancers like melanoma and kidney cancer.
- **Therapeutic cancer vaccines** prompt the immune system to attack cancer by presenting it with some piece of the cancer.
- **T Cell therapy** involves removing immune cells and genetically altering them before returning them to the patient.



Immune response at vaccine site

CLINICAL TRIALS

# BIDMC Offers Only Biomarker-Driven, Phase 3 Pancreatic Cancer Trial



Dr. Andrea Bullock

Personalized medicine—in which doctors tailor therapies to the individual based on his or her molecular profile—is revolutionizing treatments and improving survival rates for many cancers. This is truer for some cancers than for others, however, and pancreatic cancer in particular has been a tough nut to crack.

Now a Phase 3 clinical trial that is currently open and recruiting at BIDMC shows promise for certain patients with advanced cases of the most common form of pancreatic cancer. This tumor, pancreatic ductal adenocarcinoma, affects the part of the pancreas in which digestive enzymes are made.

Familiarly known as the "Halo Trial," the study is evaluating the drug PEGPH20, which targets the stroma—connective tissue that supports and surrounds the tumor within the pancreas. By degrading the stroma around the tumor, in halo-like fashion, PEGPH20 is thought to make the tumor more susceptible to pancreatic cancer-fighting drugs.

## BIDMC's Leadership Role

Andrea Bullock, MD, MPH, a pancreatic cancer specialist, is principal investigator for the Stage 3 Halo trial at the BIDMC Cancer Center. She also serves on the steering committee for the overall trial, which will ultimately recruit 420 patients at 200 sites in 20 countries.

"It's an important study because it's changing the paradigm for how we approach pancreatic cancer," Bullock said. "The preliminary results are very encouraging, and we are excited about being a leader in this international effort."

The hopeful outlook comes with a caveat, however. Only a subset of patients responds to PEGPH20: those with the biomarker hyaluronan. The study protocol calls for a biopsy to determine whether the patient's tumor expresses high levels of this long-chain, complex carbohydrate that acts as a tip-off that the pancreas may be receptive to the drug. More than 95% of pancreatic cancer patients are diagnosed with pancreatic ductal adenocarcinoma, according to Bullock, and of these, 30%-40% are thought to have the biomarker.

Phase 2 of the Halo trial, in which Bullock was also a principal investigator, suggested that PEGPH20 does deliver a clinical benefit. The Phase 3 trial compares its use in combination with the chemotherapy drugs nab-paclitaxel and gemcitabine to the same drugs in combination with a placebo.

## Trial Open through 2018

Bullock said 16 BIDMC patients participated in Phase 2, and she is hoping 10-20 will participate in Phase 3. So far, in Phase 3, one patient has been screened, found to have the biomarker and joined the trial. Seven have been found not to have the biomarker and three are currently being screened. The trial will be open through 2018.

"This is the only biomarker-driven Phase 3 study for pancreatic cancer," Bullock said. "This is an exciting time."

Pancreatic cancer trials are difficult to mount, she explained, because the disease affects relatively few people and advances so rapidly, resulting in a small pool of potential trial participants and less financial support for investigation.

The BIDMC Cancer Center is active in gastrointestinal cancer trials, with open and enrolling studies in many areas including colorectal, gastroesophogeal, liver, neuro-endocrine and pancreatic cancers.

**Complete trial listing:** bidmc.org/cancertrials

CONSULT

# Radiology Research on the Rise at BIDMC

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**Will you continue to see patients once the study begins?**

**Pisano:** I will cut back to seeing patients one day every other week. I'm nervous about biting off more than I can chew. We will be recruiting study sites at the Radiological Society of North America annual meeting at the end of November and the trial will begin in mid-2017.

**What else is happening in Radiology research at BIDMC?**

**Pisano:** Dr. Kruskal [Chief of Radiology] is interested in building the department's research operation. In my first six months, we created a strategic plan. We decided to create a Health Services Research Center that will focus on how to deliver care and how we can improve the delivery of care. It makes sense because Dr. Kruskal has been a leader in this area nationally and the Department of Medicine and Harvard Medical School have quite a few researchers in this domain.

We're working on operational issues, including the decision of when to recruit a leader. The Center will focus on quality, safety, economics, evidence-driven care and patient outcomes.

Almost no patient comes to an institution like this who isn't touched by radiology. For a patient, knowing they are getting the highest quality care is extremely important, but unless you look at quality as an institution, you don't know. Using big data to keep track of institutional performance is very important. It's about how we deliver care, not just how we impact the Radiology Department or the bottom line of the hospital. It's about the health of the community.

**You participated in Vice President Joe Biden's Cancer Moon Shot Summit in Washington in June. What is your view of the Moon Shot Initiative?**

**Pisano:** We are saving more people with cancer than we used to, but we need to move faster. That was the theme: Can we get things to move faster? Using the data we already have in a more transparent way will lead to some breakthroughs. There was a lot of agreement and conversation about how to make it happen, and what are the main obstacles--competitive pressures or regulatory problems?

Dr. Etta Pisano

I'm a believer that it's better for patients the more we collaborate. Having worked in Boston twice, it feels too competitive here. By that I mean the research institutions should be collaborating better together. It feels like the walls are up and it's not good for the patients. Thirty years ago, before I left Boston, it was like this, but it was even worse.

**What brought you back to Boston?**

**Pisano:** My husband, Jan Kylstra, had an opportunity so I followed him this time. He is an ophthalmologist and retina surgeon at Massachusetts Eye & Ear Hospital. We were talking about living separately and I was glad to be able to live together. I was at UNC for 21 years and then the Medical University of South Carolina for five years. There is always a crisis when you're in leadership. I'm getting used to research and mentoring people. This is definitely an easier job. There's a lot less stress, and I'm enjoying getting to know people here.

**More info:** bidmc.org/Centers-and-Departments/Departments/Radiology.aspx

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# Radiology Research on the Rise at BIDMC

## An Interview with Dr. Etta Pisano, MD

*Dr. Etta Pisano, a noted diagnostic radiologist and breast imaging researcher, was named Vice Chair of Research for the BIDMC Department of Radiology in November, 2015. She completed her residency here in 1988. For 21 years, she worked as a professor and administrator at the University of North Carolina School of Medicine and from 2010-2014, she served as Dean of the Medical University of South Carolina.*

**You recently received word that the National Cancer Institute will provide $140 million for the Tomosynthesis Mammography Imaging Screening Trial—TMIST—for which you are national principal investigator. Please tell us about the trial.**

**Pisano:** My research centers on development and testing of new technology for breast cancer screening and diagnosis, including digital mammography and other new techniques. My studies assess these technologies for diagnostic accuracy, cost effectiveness and quality of life. I was a principal investigator of the Digital Mammography Imaging Screening Trial—DMIST—which compared film-based mammography to the digital breast imaging that is now common. The results were published in *The New England Journal of Medicine* in 2005. We found that while the overall accuracy of the two methods was similar, digital mammography was more accurate for women under 50 and those with dense breasts.

TMIST is a large trial that will look at screening for breast cancer. Since the last screening trial was completed in 1985, there have been significant changes in technology, including the introduction of digital breast tomosynthesis. "Tomo" uses X-rays to create a 3-D image but is not considered the standard of care. TMIST will compare the use of tomo combined with digital mammography with the use of digital mammography alone. We will screen 165,000 women ages of 45-74 at 90 sites in the United States and Canada. BIDMC likely will have two sites, one here in Boston and the other at Harrington Hospital in Southbridge, where our doctors staff the radiology department. We hope to reach our accrual goal in about three years, and we will follow the women for four-and-a-half to eight years after their initial screening in the trial.


Dr. Etta Pisano with tomosynthesis machine

**A study published in JAMA in 2014 showed that tomo increases detection of cancers by 40% with a 15% reduction in false positives. Why is the TMIST trial needed?**

**Pisano:** There is still a lot of controversy around screening women. For example, we have good evidence that you should start screening at 40, but the US Preventive Services Task Force says the decision should be individualized for women ages 40-49. The ratio of false versus true positives is worse in women in their younger 40s, but women in their late 40s are no different from women in their early 50s. False positives are a risk, but death is a worse risk. I think most women are much more worried about a missed breast cancer.

In TMIST, we will be asking whether tomo finds cancers that are important. If it is advantageous compared to standard digital mammography, we would expect the incidence of advanced breast cancer in the population to drop.

Another important aspect of TMIST is a biorepository of biopsy blood and tissue specimens. This will allow us to determine at the cellular level what genetic properties cancerous lesions share. We will ask participants to give blood samples to help us discover and test new biomarkers.

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