

TURNING CANCER DISCOVERIES INTO TREATMENTS

FRONTIERS

PELTONIA SPECIAL EDITION 2014



The James



THE OHIO STATE UNIVERSITY
COMPREHENSIVE CANCER CENTER

NCI
CCC

A Comprehensive Cancer
Center Designated by the
National Cancer Institute

UPFRONT

The Director's Perspective

Pelotonia Turns 6

Time often passes faster than the countryside on a Pelotonia downhill.

I find it amazing that Pelotonia, our annual grassroots bicycle tour to raise money for cancer research at the OSUCCC – James, will turn 6 years old in August. Even more remarkable is the incredible response the community shows at each event, the growing number of riders and volunteers, and the people along the road cheering the riders on.

Also telling is the extraordinary support reflected in the money the ride generates. We originally hoped to raise \$39 million within our first five years. Then the community responded, and we surpassed that goal in four years, raising more than \$42 million. As of last year, Pelotonia has raised more than \$61 million.

That is an extraordinary sum, and this special Pelotonia issue of *Frontiers* gives a good idea of how we are using it. It supports work that is making new discoveries, new

treatments, new ways to diagnose and prevent cancer, and new strategies for improving quality of life.

These advances are coming from talented people at the OSUCCC – James who live right here in Ohio. They could be neighbors, friends and fellow Pelotonia participants. Pelotonia funds also help us recruit new talent and expertise to build on these incredible minds and to advance research at our cancer center.

Pelotonia 14 will happen Aug. 8-10, and it will be especially memorable. It precedes an important phase in the history of Ohio State's cancer program. In September we will receive the keys to the new James Cancer Hospital and Solove Research Institute, which will open to the public in December. The new hospital has



MICHAEL A. CALIGIURI, MD
DIRECTOR, COMPREHENSIVE CANCER CENTER; CHIEF EXECUTIVE OFFICER, JAMES CANCER HOSPITAL AND SOLOVE RESEARCH INSTITUTE, THE OHIO STATE UNIVERSITY; JOHN L. MARAKAS NATIONWIDE INSURANCE ENTERPRISE FOUNDATION CHAIR IN CANCER RESEARCH

many design innovations that more closely unite our triple mission of research, patient care and education.

Please join me this August as a rider, a virtual rider or a volunteer in Pelotonia. And when you come to Columbus, watch for our stately, stunning and solid new 21st century cancer hospital. When you do, know that Pelotonia helps support the expertise and research that that building represents. Working together, we can move closer to our ultimate goal of a cancer-free world.

THE OHIO STATE UNIVERSITY COMPREHENSIVE CANCER CENTER – ARTHUR G. JAMES CANCER HOSPITAL AND RICHARD J. SOLOVE RESEARCH INSTITUTE (OSUCCC – JAMES)

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FRONTIERS

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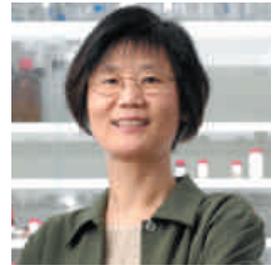
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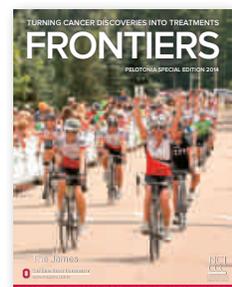
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Riders cross the finish line during Pelotonia 13



Pelotonia 5-Year Total Surpasses **\$61 Million**

Riders, virtual riders and donors in Pelotonia 13, the annual grassroots bicycle tour that generates money for cancer research at Ohio State, raised a record \$19,007,104, easily exceeding the Pelotonia 12 total of \$16.87 million.

Pelotonia staff presented a check for the new total – which pushes the overall five-year tally for this popular event to more than \$61 million – to OSUCCC Director and James CEO Michael A. Caligiuri, MD, at a ceremony in early December.

Thanks to Pelotonia's generous sponsors – including Limitedbrands Foundation, Huntington, and Richard and

Peggy Santulli – every cent raised by riders, virtual riders and donors will support cancer research at the OSUCCC – James.

The money supports projects addressing many aspects of cancer, including diagnosis, treatment, psychosocial issues and prevention. Projects funded by Pelotonia include a fellowship program for student researchers working in the labs of faculty mentors, “idea” grants for teams of faculty researchers, sophisticated equipment to aid researchers in their work, and recruitment/retention of top cancer researchers and programs.

Pelotonia 13 took place Aug. 9-11 with routes between

Columbus and Kenyon College in Gambier, Ohio. The event drew a record 6,723 riders from 41 states and nine countries, as well as 3,451 virtual riders and more than 2,300 volunteers.

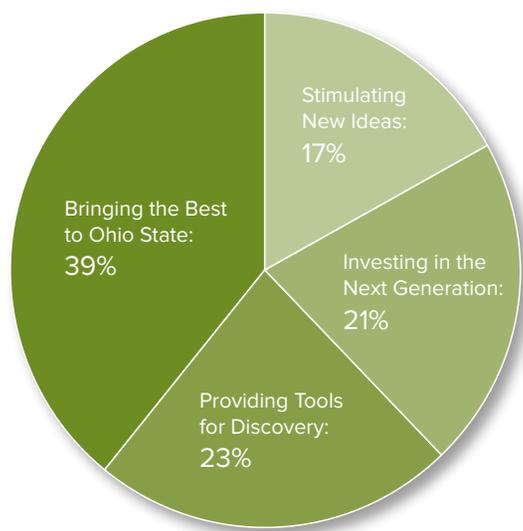
Among the Pelotonia 13 participants were 1,914 members of Team Buckeye, the official superpeloton (riding group) of The Ohio State University. Team Buckeye consisted of 1,178 riders in 90 pelotons, as well as 614 virtual riders and 122 volunteers. The collective Team Buckeye fundraising total was \$2,269,222.

Registration is open at www.pelotonia.org for Pelotonia 14, which will unfold from Aug. 8-10. 



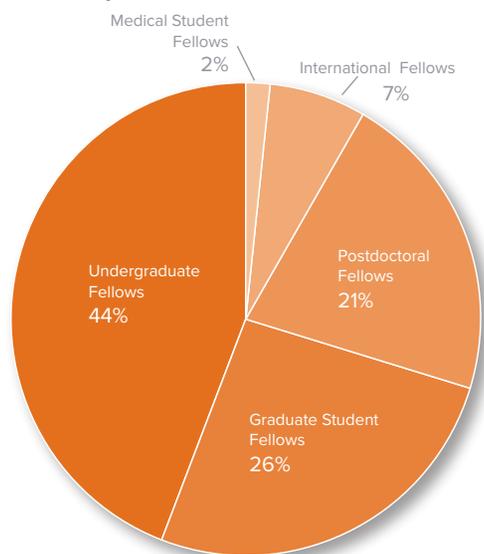
4-Year Pelotonia Financial Summary

Allocations of Funding For Pelotonia 09, 10, 11, 12



Pelotonia, the annual grassroots bicycle tour established in 2009 to raise money for cancer research at the OSUCCC – James, generated more than \$42 million in its first four years through rider pledges and donations. Thanks to the event’s generous underwriters, every dollar raised by our riders since Pelotonia began has been used to advance cancer research, as shown in the chart to the left.

Fellowship Grants Awarded



Bringing Knowledge to Bear in the Fight Against Cancer

Multiple colleges at Ohio State, listed below, as well as Nationwide Children’s Hospital and Cincinnati Children’s Hospital Medical Center, have received Pelotonia funding for cancer research:

- College of Public Health
- College of Medicine
- College of Law
- College of Nursing
- College of Pharmacy
- College of Food, Agricultural and Environmental Sciences
- College of Engineering
- College of Veterinary Medicine
- College of Human Ecology
- College of Dentistry
- College of Arts and Sciences
- Nationwide Children’s Hospital
- Cincinnati Children’s Hospital Medical Center

Investing in the Next Generation: Pelotonia Fellowship Program

To date, the Pelotonia Fellowship Program has awarded more than \$7 million in cancer research funding for Ohio State students at all levels of scholarship – undergraduate, graduate, medical school and postdoctoral fellow.

Drug Approved for Chronic Leukemia

Ohio State Research Played Significant Role in Ibrutinib Approval, Along With Pelotonia-Supported Clinical Trial

On her 70th birthday in June 2012, Judy Hileman, a Kansas native with a PhD in nursing, was diagnosed with chronic lymphocytic leukemia (CLL). After two chemotherapy regimens failed, Hileman's condition worsened to ultra-high risk CLL, and her oncologists searched for clinical trials around the nation that might help her.

Hileman opted for a Pelotonia-funded phase II clinical trial at Ohio State of the drug ibrutinib.

Ibrutinib (Imbruvica®) is the first drug designed to target Bruton's tyrosine kinase, a protein essential for CLL-cell survival and proliferation. CLL is the most common form of leukemia in the Western Hemisphere and is currently incurable.



Judy Hileman and granddaughter Lane.

The trial, directed by principal investigator Kami Maddocks, MD, will help identify whether ibrutinib works in high-risk patients like Hileman as well as it works in patients with better-risk disease. It will also help determine why some patients don't respond for long to the drug.

Maddocks' trial (OSU-11133) accepts patients with CLL/small lymphocytic leukemia (SLL) who have not responded to or who have relapsed after standard treatment. Open only at Ohio State, the trial is part of a larger body of research at Ohio State's Comprehensive Cancer Center – James Cancer Hospital and Solove Research Institute (OSUCCC – James) that has shown ibrutinib has strong potential as a safe and effective agent for patients with CLL or mantle cell lymphoma (MCL).

The Ohio State studies played a significant role in the drug's approval by the Food and Drug Administration (FDA) in February 2014 for patients with relapsed or refractory CLL. (In November 2013, the FDA approved ibrutinib for patients with relapsed or refractory MCL, as well.)

Much of the clinical and basic-science research that led to the CLL approval was conducted at the OSUCCC – James, in part using Pelotonia dollars.

And much of the Ohio State work was led by John C. Byrd, MD, who holds the D. Warren Brown Designated Chair in Cancer Research and directs the Division of Hematology at Ohio State. Other key leukemia team members include: Amy

Johnson, PhD; Jason Dubovsky, PhD; Jeffrey Jones, MD, MPH; Joseph Flynn, DO, MPH; Jennifer Woyach, MD; Kristie Blum, MD; Michael Grever, MD; and Maddocks.

“Our clinical studies consistently suggested that ibrutinib is a highly active oral drug that produces a high rate of durable remissions in patients with relapsed and refractory (resistant to treatment) CLL,” says Byrd, who also co-leads the Leukemia Research Program at the OSUCCC – James. “Patient responses can last many months, partly because patients are willing to remain on the drug since the side effects are tolerable.”

Pelotonia funds have also indirectly supported clinical trials of ibrutinib through their allocation to the OSUCCC – James Clinical Trials Office, which oversees all cancer clinical trials at Ohio State.

Happily, Hileman did benefit from Maddocks' trial. She began improving almost immediately upon taking ibrutinib. After 15 weeks her lab tests began to normalize, her energy returned, and she was able to “resume my normal life.” Hileman remains on the trial, taking three capsules daily. She returns to The James every three months for a check-up.

“Ibrutinib has changed so many lives,” she says. “One of the nurses told us they have never seen so many folks do so well on a clinical trial drug. For many patients, like me, that drug may be their last hope.” 

Encouraging Inquiring Minds

Pelotonia Fellowships Help Students and Trainees Pursue Cancer-Research Interests

Perhaps the greatest benefit of the Pelotonia Fellowship Program is fueling interest in cancer research among Ohio State students at all levels of training.

The program enables promising students who might one day become independent cancer researchers to explore their interests in the labs of faculty mentors.

The program had awarded 225 student fellowships by the end of 2013. The awardees included 99 undergraduate students, 59 graduate students, four medical students, 48 postdoctoral fellows and 15 international scholars.

The awards are made by a Pelotonia Fellowship Committee that includes some of Ohio State's most distinguished cancer researchers. Visit the program website (<http://go.osu.edu/pelotoniafellowships>) for information about all fellowship recipients to date. Here's a glimpse at three recent recipients.

DANIEL BROOK

Earning a Pelotonia fellowship was a personal goal for Daniel Brook, a junior in biomedical science who plans to attend medical school and become a physician scientist.

During his first year of college, Brook, a Cincinnati native, joined the lab of OSUCCC Director and James CEO Michael A. Caligiuri, MD. There, he gained enough experience to apply for the fellowship.

His project investigates the effect of the mixed-lineage leukemia (*MLL*) gene on the rate of cancer development within an acute myeloid leukemia (AML) mouse model developed by the Caligiuri lab. Brook also is working to obtain



DANIEL BROOK

evidence “for the hypothesis that *MLL* acts like a tumor suppressor in our mouse model.”

A member of the Triathlon Club at Ohio State, Brook has ridden the full 180-mile circuit in Pelotonia 11, 12 and 13.

MONICA LINDGREN

While working with cancer patients and families at a James-affiliated outpatient clinic that provides end-of-life psychotherapy services, Monica Lindgren saw how depression can affect patients' responses to cancer.

“These experiences sparked my interest in the effects of depression and social support on treatment adherence and quality of life among cancer patients with less-advanced disease,” says Lindgren, a graduate student in Psychology. Her mentor is Janice Kiecolt-Glaser, PhD, a Distinguished University Professor of Psychiatry and of Psychology at Ohio State and a member of the OSUCCC - James.

Lindgren's project examines how depression, social support, treatment adherence and quality of life influence one another in breast cancer patients. She hopes her work will lead to psychological and behavioral interventions for patients.

Lindgren, who has an undergraduate degree in Psychology from the University of North



MONICA LINDGREN

Carolina, plans to become a clinician and researcher in academic psychiatry.

Even with no bike training, she rode 50 miles in Pelotonia 13 and plans to ride this year.

KARA KEPLINGER, MD

Columbus native Kara Keplinger, MD, is working to become a surgical oncologist at the OSUCCC - James and is taking a two-year hiatus from her Ohio State surgical residency to study basic science relating to oncology.

She joined the lab of Matthew Ringel, MD, co-director of the Thyroid Cancer Unit at the OSUCCC - James. “Dr. Ringel's lab is exploding with ideas and projects,” Keplinger says.

Her project evaluates the effectiveness of new agents to treat papillary thyroid cancer (PTC), the most common type of thyroid cancer. “My project will help determine whether these molecular inhibitors might be useful for PTC,” Keplinger says.

She says her experience as a rider in Pelotonia was like no other. “There was an intense energy at the ceremony and the day of the ride that made my fellowship feel more personal,” she explains. “It makes me want to push harder at my project. I can't wait for the next ride.” 



KARA KEPLINGER, MD



Maintaining Momentum

Pelotonia Idea Grants Help Discoveries Happen

Cancer research is a process. A researcher or physician-scientist makes an observation in the laboratory or clinic, then asks, “Why did that happen?” Or, “How can we improve that?” He or she will gather with colleagues and develop a hypothesis that answers the question. Then they will conduct experiments to test their hypothesis.

That’s how discoveries are made. It’s how we build a cancer-free world. That is, if the researchers have financial support for their work.

Federal funding for cancer research has fallen annually since 2006. Grants are fewer in number, smaller in amount and more difficult to obtain. Furthermore, the more novel the idea, the more difficult it is to compete for funding—big ideas hold great

promise but often lack the data needed to compete for scarce dollars. It’s a paradox: Exciting ideas need data to obtain funding, but funding is needed to obtain the data.

Idea Grants funded by Pelotonia break that cycle at the OSUCCC – James. So far, in 2014, nine Pelotonia Idea Grants have been awarded to innovative projects developed by OSUCCC – James investigators. Three of those projects are described here (to read about the other Idea Grants, visit <http://cancer.osu.edu/pelotonia>).

Loneliness and Breast Cancer Development and Progression

Breast cancer is the second-leading cause of cancer death among women in the United States

and worldwide. Studies have shown that women with weak social networks have worse treatment outcomes than women with strong social support.

A Pelotonia Idea Grant has been awarded to a team of OSUCCC – James researchers to test their hypothesis explaining how this happens.

The study by OSUCCC – James breast-oncologist **Maryam Lustberg, MD, MPH**, director of Breast Cancer Survivorship at the Stefanie Spielman Comprehensive Breast Center; **Courtney DeVries, PhD**, professor of Neuroscience and of Psychology who specializes in links between social behavior and health; and **Cynthia Timmers, PhD**, director of the Solid Tumor Translational Science Shared Resource, focuses on a gene that normally protects the body against cancer.

Pelotonia Helps Physician Pursue Passion for Ending Cancer

Apart from caring for his wife Kari and their six children, defeating cancer is the life-passion of **Theodoros (Ted) Teknos, MD**.

After seeing how much Pelotonia contributes to that goal, he is compelled to do his best every year as a rider in the annual grassroots bicycle tour.

“Since it started in 2009, I have participated in every Pelotonia tour as a rider on Team Head and Neck (a part of Team Buckeye, Ohio State’s official superpeloton),” says Teknos, professor and vice chair of the Department of Otolaryngology – Head and Neck Surgery, and director of the Division of Head and Neck Surgery, at Ohio State.

He always rides the full 180-mile circuit and annually attains the event’s “high roller” status for raising at least \$4,000.

“I will ride until I drop,” Teknos says. “And then I will be a virtual rider.”

He admits that, before Pelotonia, he was not an avid cyclist. In fact, he hadn’t ridden a bike at all since he was a teen.

“I stopped riding bikes when I got my first car,” Teknos says. “I picked it up again for Pelotonia, and now I am hooked.”

Finding his way back didn’t take long.

“It was remarkably easy to get reacclimated; it was like riding a bike!” he grins. “The camaraderie of preparing with my James family made it fun.”

As each event draws nearer, he keeps to a rigorous training regimen.

“I start riding in earnest in April, primarily on weekends,” Teknos explains. “Then I step it up in the summer and take a weeklong vacation to train in July.”

His wife also rides with him. “It’s a great family activity,” he says.

Teknos’ dedication to training for Pelotonia is all the more amazing in light of his demanding workload as a cancer clinician and researcher at Ohio State, where he also holds the David E. Schuller, MD and Carole Schuller Chair in Otolaryngology, and is a member of the Translational Therapeutics Program at the OSUCCC – James.

His clinical interests include head and neck cancer, head and neck benign neoplasms, skull-base surgery, microvasculature reconstructive surgery, and thyroid and parathyroid surgery.

His research focuses on cancer stem-cell biology, cancer cell signaling, predictors of treatment response, and prevention of cancer metastasis (spread).

Teknos believes everyone who works at the OSUCCC – James benefits from Pelotonia funding, because a significant share of the money is used to recruit and retain some of the top minds in cancer research and care.

“Pelotonia funds bring tremendous new scientists to our institution, some of whom I have recruited,” he says.

Teknos considers Pelotonia “a life-changing experience.”

“There are few times in life when you know you are participating in an event that is pure and good,” he says.

“By taking part in Pelotonia, you really feel the generosity and power of our community.”



From left, Pelotonia riders Eric Hansen, Milan Hansen, Ted Teknos, MD, and wife Kari Teknos.

This gene, called *PTEN*, is often inactivated in breast cancer. In mice, reducing the activity of this gene by 20 percent makes the animals more susceptible to cancer development. Animal studies by the OSUCCC – James researchers suggest that social isolation can reduce *PTEN* activity by 50 percent.

The researchers hypothesize that levels of a hormone called oxytocin, which is released during social interaction, drop when mice are socially isolated. That reduces the activity of the *PTEN* gene in mammary tissue and makes mice more susceptible to cancer development.

Their Pelotonia Idea Grant will help the researchers learn whether a similar association exists between social isolation and *PTEN* activity in humans.

The study will recruit 100 women undergoing breast biopsy at Ohio State’s Stefanie Spielman Comprehensive Breast Center. The researchers will establish the women’s social networks using questionnaires, and they will test the breast tissue for *PTEN* activity. The researchers will also test whether *PTEN* levels in skin reflect the gene’s levels in breast tissue. If so, it might mean that a simple skin sample can be used to gauge *PTEN* activity in breast tissue in future clinical trials.

“This study could help us understand individual differences in breast-cancer susceptibility and progression, which could lead to

(continued on page 10)

Physician-Researcher Rides to Make Strides

In the 1980s it took 10 years for a scientist to study one gene. Today, scientists can study 20,000 genes in a week. That change emerged during Sameek Roychowdhury's medical training and sparked his interest in genomics and its potential for treating cancer based on the gene changes in a patient's tumor.

"Currently, it costs \$5,000 to \$10,000 to sequence all of a patient's genes," Roychowdhury says. "It's not cheap but it's feasible, and Pelotonia has helped us make genomics-based cancer medicine happen here at Ohio State."

Sameek Roychowdhury, MD, PhD, is a physician-scientist and medical oncologist who specializes in cancer genomics, genomics-driven cancer clinical trials, and precision cancer medicine. This year he will take to his bike as he has for the past three years to ride in Pelotonia to support Ohio State cancer research.

"Pelotonia is an amazing event that grew in just a few years to become the largest bike ride in the nation for cancer research," he says.

Roychowdhury pedals the full 180-mile route both for patients who might benefit from his research and for personal reasons. "My mother-in-law was a breast cancer survivor, and my father was a prostate cancer survivor," he says.

He organized a peloton that includes much of his lab. Last year, the team raised \$10,000, with \$5,000 coming from T-shirt sales alone. This year, the T-shirts are \$20, and 100 percent of the proceeds go directly to Pelotonia. The message they carry plays off the Ohio State/Michigan rivalry: "Two Goals: Beat Michigan, Beat Cancer."

Roychowdhury notes that a portion of the dollars raised by Pelotonia supports high-risk, high-reward research. "That's one way Pelotonia is making a difference," he says. "High-risk, high-reward research can more rapidly advance progress against cancer."

Pelotonia funds helped recruit Roychowdhury and other researchers who specialize in precision cancer medicine, which relies heavily on genome sequencing and sophisticated equipment. "Pelotonia funding has been crucial in bringing that technology to Ohio State and in making genomics available to patients," he says.

Using genomic sequencing to characterize a patient's tumor enables physician-researchers at the OSUCCC — James to choose a clinical trial that is appropriate for that particular patient based on the molecular changes in his or her tumor. "It enables us to get the most effective treatment to the patient while also facilitating drug development," he says.



Sameek Roychowdhury, MD, PhD

There are many ways to participate in Pelotonia and work toward the goal of ending cancer, Roychowdhury notes. "Anyone can contribute as a rider, a virtual rider, a volunteer or a supporter.

"One of the most exciting things about the event is the support of people in Ohio. You're riding through the countryside; the houses are hundreds of yards apart; it's the middle of the summer and hot – and you see people sitting in lawn chairs beside the road, offering lemonade, cookies and cheering us on because we are all on the ride together.

"The kind of effort that people have put into this goal of ending cancer is magical."

(continued from page 9)

new diagnostic, therapeutic and prognostic tools for breast cancer prevention and treatment," Lustberg says.

She notes that the results might also apply to endometrial, thyroid, prostate, brain, pancreatic and colon cancers, which are also influenced by *PTEN*.

The Right Therapy For the Right Glioblastoma Patient

Glioblastoma (GBM) is the most common and lethal form of brain cancer in the United States. Even with aggressive therapy, patients survive only 15 months on average. Recent research has shown that particular molecular changes in some GBM tumors correlate with treatment outcomes. It raised the hope that treating the disease with drugs that target these changes would extend patients' lives.

But the drugs have not helped as expected, in part because new methods are needed to accurately identify GBM progression and the molecular targets that identify patients for personalized therapy.

A Pelotonia Idea Grant is helping a team of OSUCCC – James physicians and researchers in neuro-oncology, neurosurgery, neuropathology and engineering to pool their expertise and help develop those techniques.

The research team includes neuropathologist **Jose Otero, MD, PhD**; Biomedical Informatics and image analysis specialist **Metin**

Gurcan, PhD; director of Neuro-oncology at the OSUMC and OSUCCC – James **Vinay Puduvalli, MD**; neurosurgeon **Brad Elder, MD**; and associate professor of Chemical and Biomedical Engineering **Jessica Winter, PhD**.

They are developing new strategies to improve diagnostic accuracy of GBM, including innovative digitized-image-analysis techniques that accurately distinguish false tumor progression from true progression.

“We are harnessing technology to improve the treatment of an intractable and deadly form of cancer,” says Elder. “Our study is building a new approach to tissue analysis that has great potential for use in clinical trials and possibly with other types of tumors.”

“Targeted therapy for cancer will be the standard treatment of the future, and it will lead to the control and, eventually, to the cure of cancers,” says Puduvalli.

“However, efforts at consistently identifying the targets—there may be more than one in a single tumor cell—has hit a roadblock because currently available tests lack the precision to accurately detect such targets,” he adds. “Our study will bring a next-generation technology to the fight against cancer and a new level of accuracy to the detection of cancer targets.”

The study will also generate critical data needed to apply for external grant funding. The Pelotonia-funded study will ultimately help develop new

techniques to personalize the therapy and guide the management of GBM patients.

Targeting Oncogenes for New Liver Cancer Therapies

Hepatocellular carcinoma (HCC) is the most prevalent form of liver cancer. Worldwide, it caused an estimated 746,000 deaths in 2012, making it the second-leading cause of cancer death. The disease is usually associated with hepatitis, fibrosis, cirrhosis and other liver diseases.

Liver cancer mortality is high because the disease lacks effective therapy. “The liver works to clean toxins from the blood, making it challenging to develop drugs that can penetrate the liver and reach cancerous cells,” says **Kalpana Ghoshal, PhD**, associate professor of Pathology.

Ghoshal was awarded a Pelotonia Idea Grant to investigate a strategy for treating HCC.

Research by Ghoshal and others has shown that a molecule called microRNA-122 (miR-122) is critical for normal liver function and that it protects against cancer. Cancerous liver cells often stop producing this molecule, an event that is associated with poor prognosis, tumor recurrence and metastasis.

Animal studies by Ghoshal have shown that restoring miR-122 in liver cancer cells causes the malignant cells to die. Normally,



“Results from these studies could lead to a phase I clinical trial in liver cancer patients of two experimental drugs in combination with miR-122 for treating a human cancer.”

— *Kalpana Ghoshal, PhD*

miR-122 suppresses the activity, or expression, of two genes that play an important role in cell proliferation. When liver cells lose miR-122, those two genes become much more active, contributing to tumor growth.

Ghoshal is investigating whether use of a targeted drug to block either of the two cancer-promoting genes, plus a drug that restores miR-122 levels, will inhibit liver cancer growth and offer a potentially effective therapy for the disease.

“Results from these studies could lead to a phase I clinical trial in liver cancer patients of two experimental drugs in combination with miR-122 for treating a human cancer,” Ghoshal says. ■

from Ideas to Impact

Discoveries Made With Pelotonia Support

The promise of Pelotonia is revealed in part by the discoveries made by teams of OSUCCC – James researchers who receive support from the annual event. Here are four examples.

STRESS GENE HAS ROLE IN TUMOR METASTASIS

With a Pelotonia Idea Grant as partial support, a team of OSUCCC – James researchers has linked a stress gene called *ATF3* in immune cells to the spread of breast-cancer cells from a tumor to other parts of the body. The spread, or metastasis, of cancer cells is the leading cause of death in cancer patients.

The findings, published in the *Journal of Clinical Investigation*, suggest that *ATF3* may be a crucial link between stress and cancer. Previous studies have shown that stress is a risk factor for cancer. This research suggests that cancer cells, by acting as stress signals, coax immune cells that have been recruited to a tumor to express *ATF3*.

Though it's unclear how, *ATF3* promotes the immune cells to act erratically and give cancer an escape route from the tumor site to other areas of the body.

“If your body does not help cancer cells, they cannot spread as far,” says senior author **Tsonwin Hai, PhD**, professor of Medicine

and a member of the OSUCCC – James Molecular Biology and Cancer Genetics Program. “So the rest of the cells in the body help cancer cells move to distant sites. And one of the unifying themes is stress.”

Hai says this stress gene could one day serve as a target for drugs to combat metastasis.

LOSS OF A CRITICAL TUMOR-SUPPRESSOR GENE IS EXPLAINED

OSUCCC – James researchers have discovered a mechanism responsible for the loss of a critical tumor-suppressor gene in rhabdomyosarcoma and other soft-tissue sarcomas. The findings could guide the development of more effective therapies for these rare cancers, which strike mainly children and often respond poorly to treatment.

The researchers discovered that the tumor-suppressor gene called *A20* is silenced not by mutation, as in many other cancers, but because a second molecule is lost – a small molecule called microRNA-29. They also found that microRNA-29 normally protects *A20* from destruction. When microRNA-29 is missing, *A20* is degraded. Loss of *A20*, in turn, leads to a rise in levels of a protein called NF- κ B and to tumor progression.

The findings were published in the journal *Science Signaling*.

“We know that NF- κ B promotes tumor growth, but we don't know why it is upregulated in many cancers,” says principal investigator

Denis Guttridge, PhD, professor of Molecular Virology, Immunology and Medical Genetics. “Our study indicates that it involves a regulatory circuit between NF- κ B, microRNA-29 and the *A20* tumor-suppressor gene. It also identifies NF- κ B as a therapeutic target in sarcoma, and *A20* and microRNA-29 as potential biomarkers for sarcoma.”

Guttridge notes that the findings move research a step closer toward developing microRNA-29 therapy against NF- κ B activation in cancers.

A NEW PROGNOSTIC MARKER AND TREATMENT TARGET FOR ACUTE LEUKEMIA

A study supported in part by Pelotonia dollars identified microRNA-155 as an independent prognostic marker and treatment target in certain patients with acute myeloid leukemia (AML). The study focused on patients whose leukemia cells, when viewed under a microscope, have normal-looking chromosomes. This category of AML is called cytogenetically normal acute myeloid leukemia (CN-AML).

The study found that when microRNA-155 is present at abnormally high levels in CN-AML cells, patients are less likely to have a complete remission, and they experience a shorter disease-free period and shorter overall survival.

The researchers say that miR-155 would be relatively easy to measure at diagnosis, suggesting that it could be a good marker for identifying patients at greater risk of



TSONWIN HAI, PhD



DENIS GUTTRIDGE, PhD



CLARA D. BLOOMFIELD, MD



GUIDO MARCUCCI, MD

recurrence.

“Our findings indicate that miR-155 expression is a strong and independent prognostic marker in CN-AML, and they provide clinical validation of data from preclinical models that support a crucial role of miR-155 in leukemia,” says senior author **Clara D. Bloomfield, MD**, a Distinguished University Professor at Ohio State, where she also serves as cancer scholar and senior adviser to the OSUCCC – James.

The findings also suggest that miR-155 plays a role in CN-AML development and could be a target for an emerging class of drugs designed to inhibit microRNAs, says first author **Guido Marcucci, MD**, professor of Hematology, a leukemia specialist and associate director for translational research at the OSUCCC – James.

SEVEN-GENE SCORE MIGHT HELP DETERMINE BEST AML TREATMENT

Pelotonia funding also helped Bloomfield, Marcucci and collaborators develop a novel method that might help guide the treatment of CN-AML patients.

Currently, doctors use chromosome markers and gene mutations to determine AML treatment. This study, published in the *Journal of Clinical Oncology*, developed a score based on seven mutated genes. Along with gene mutations, this AML score includes another gene alteration that influences cancer development

called DNA methylation. Healthy cells use DNA methylation to reduce or silence a gene’s activity. Abnormal DNA methylation can shut down important tumor-suppressor genes and promote cancer development.

“To date, disease classification and prognostication for AML patients have been based largely on chromosomal and genetic markers, and changes that affect gene expression have not been considered,” says Bloomfield, who also holds the William Greenville Pace III Endowed Chair in Cancer Research at Ohio State.

“Here we show that DNA methylation in previously recognized and prognostically important mutated genes can identify novel patient subgroups, which might better help guide therapy,” she says.

Most adults with AML are not cured by current therapies. Only about 40 percent of patients younger than age 60, and about 10 percent of patients 60 and older, are alive after three years, so new strategies for treating the disease and for matching patients with the most promising treatment are needed, Bloomfield says.

The researchers computed the seven-gene score based on the number of genes in the panel that were highly expressed in patients’ AML cells, and retrospectively tested the score in two groups of older patients (age 60 and up) and two groups of younger patients (age 59 and under).

“For this seven-gene panel, the fewer highly expressed genes, the better the outcome,” says first author Marcucci. “In both younger and older patients, those who had no highly expressed genes, or had one highly expressed gene, had the best outcomes.” ■

For more discoveries made with the help of Pelotonia funds, go online to the OSUCCC – James Media Room (<http://cancer.osu.edu/mediaroom/>). On the left, click “Research Findings Supported by Pelotonia.”

New Hope

Pelotonia Funding for Clinical Trials

Clinical trials demonstrate the safety and effectiveness of new treatments. Here are two Pelotonia-supported trials at the OSUCCC – James. For more information about these or other trials at The James, call The James Line toll free at 1-800-293-5066.

INNOVATIVE 2-DRUG COMBO FOR AML

Adult and pediatric patients with acute myeloid leukemia (AML) have a poor prognosis overall. New treatments that target the causes of AML and have minimal toxicity are needed.

Alison Walker, MD, an assistant professor in the Division of Hematology at Ohio State and a member of the Translational Therapeutics Program at the OSUCCC – James, is leading a phase I (first-in-human) clinical trial for one such treatment: a two-drug combination that could significantly improve AML remission rates. The trial is supported by Pelotonia funds.

“We have previously reported on the use of a drug called decitabine in older patients with AML,” Walker says. That earlier study showed the drug was well tolerated and helped 47 percent of patients who received it achieve remission.

They also observed that patients with higher levels of a substance in their blood called miR-29b had a



ALISON WALKER, MD

better response to decitabine than those with lower levels.

The researchers have also discovered that a drug called AR-42, which was designed by OSUCCC – James researchers led by **Ching-Shih Chen, PhD**, increases levels of miR-29b in leukemia cells.

In this new clinical trial, patients first receive AR-42 to raise their miR-29b levels, then they receive decitabine therapy. Walker and colleagues want to determine whether this combination will help more patients achieve complete remission.

The trial is open to adult and pediatric patients who meet the study’s eligibility criteria.

A NOVEL DRUG COMBINATION FOR TRIPLE-NEGATIVE BREAST CANCER

Triple-negative breast cancer (TNBC) is an aggressive malignancy that carries a high risk of recurrence and death within five years of diagnosis. To meet the need for new treatments, OSUCCC – James researchers are investigating novel combinations of targeted agents.

“TNBC accounts for approximately 20-25 percent of all breast cancers and is characterized by a lack of estrogen receptors, progesterone receptors and HER-2 receptors,” says **Erin Macrae, MD**, assistant professor of Medical Oncology at Ohio State and a breast cancer specialist at the OSUCCC – James.



ERIN MACRAE, MD

Oncologists use the three hormone receptors to help determine treatment for breast cancer. “In other forms of breast cancer, treatments can be directed against these targets, but that’s not possible with TNBC,” Macrae says.

Macrae is principal investigator for a new phase II clinical trial (OSU-13117) – supported by Pelotonia funds – in which patients with TNBC initially receive a drug called trametinib, followed by trametinib in combination with a drug called GSK2141795. The investigators hypothesize that these agents may stop the growth of tumor cells by blocking enzymes needed for the cells to grow.

“TNBC is an important challenge because these tumors fail to respond to the targeted regimens that are currently available,” Macrae says. “Our study is exploring a novel regimen that we hope will help these patients.” 

Drug Development Institute

Pelotonia Funds Support the Development of Anticancer Agents by OSUCCC – James Researchers

In 2011, the OSUCCC – James collaborated with the colleges of Medicine, Pharmacy and Business to organize The Ohio State University Drug Development Institute (DDI). The institute guides the development of promising anticancer drugs produced by OSUCCC – James researchers.

Timothy Wright, a former executive of several pharmaceutical companies, directs the institute in conjunction with **Bence Boelcskevy, PhD**, also a former pharmaceutical executive. They fast-track promising compounds through the testing needed for use in clinical trials. Currently, the institute has six anticancer agents in its pipeline. The DDI receives Pelotonia funds to facilitate their further development. Following is a brief description of each of these agents.



TIMOTHY WRIGHT

PRMT5 INHIBITOR

PRMT5 is an enzyme that plays a vital role in cancer-cell growth. It is highly expressed in lymphoma, acute leukemia and other hematologic malignancies, and in solid tumors, including head and neck, lung, melanoma and brain. OSUCCC – James researchers have developed a first-in-class PRMT5 inhibitor that they believe will effectively stop tumor growth. The inhibitor is now in preclinical testing.

CHEMOBODIES

Chemobodies are a special class of small molecules that can perform antibody-like functions, either alone or after combining with a protein inside the cell. They have the potential to block protein-protein interactions, which are extremely important drug targets but have been unreachable by conventional agents. OSUCCC – James researchers have developed chemobodies that inhibit K-Ras, a protein implicated in about 30 percent of all cancers.

EPSTEIN-BARR VIRUS VACCINE

Epstein-Barr virus (EBV) is a common viral infection that causes mononucleosis. It is also associated with Hodgkin's lymphoma, Burkitt's lymphoma and other cancers; with conditions associated with HIV infection; and with certain autoimmune diseases. If EBV is present in a blood stem cell or in a donated solid organ, it can cause post-transplant lymphoproliferative disease (PTLD). This often-fatal complication can follow a stem-cell or organ transplant. OSUCCC – James researchers are developing an EBV vaccine to prevent PTLD and to potentially help other EBV-related conditions.

STAT3 INHIBITOR

Tumor growth can be promoted or suppressed by various signaling pathways in cancer cells, including STAT3. The tumor-suppressor role of STAT3 has been reported in human glioblastoma, or brain cancer. Recent studies have shown that STAT3 has an inhibiting role in colon carcinogenesis depending on tumor stage. OSUCCC – James researchers are collaborating with Nationwide Children's Hospital in defining the STAT3 effects in sarcoma, and they are initiating a multi-pronged research program in melanoma, lung and pancreatic cancer.

NUCLEOSIDE ANALOG

Hepatitis C virus (HCV) infection is a primary cause of liver cancer, which is the second-leading cause of cancer death globally and a growing problem in the United States. Effective treatments are needed. Nucleoside analogs are a special class of small molecules that inhibit HCV infections. OSUCCC – James researchers and the DDI are developing a promising nucleoside analog that eradicates HCV and removes a critical driver that can lead to liver cancer.

FENRETINIDE ORAL PATCH

About 300,000 Americans annually develop precancerous lesions in the mouth that can progress to oral cancer (nearly 36,000 people in the United States develop oral cancer yearly). Currently, these lesions are removed surgically, but they tend to recur. A team of OSUCCC – James researchers has developed a patch that adheres to the lesions and releases a drug to treat them. The drug, fenretinide, is a synthetic derivative of vitamin A and has highly promising anticancer properties. The patch could provide an alternative to surgery and reduce the incidence of oral cancer.

Instruments *of* Progress

Pelotonia Funds Help Purchase Sophisticated Technology and Preserve Priceless Tissue Samples

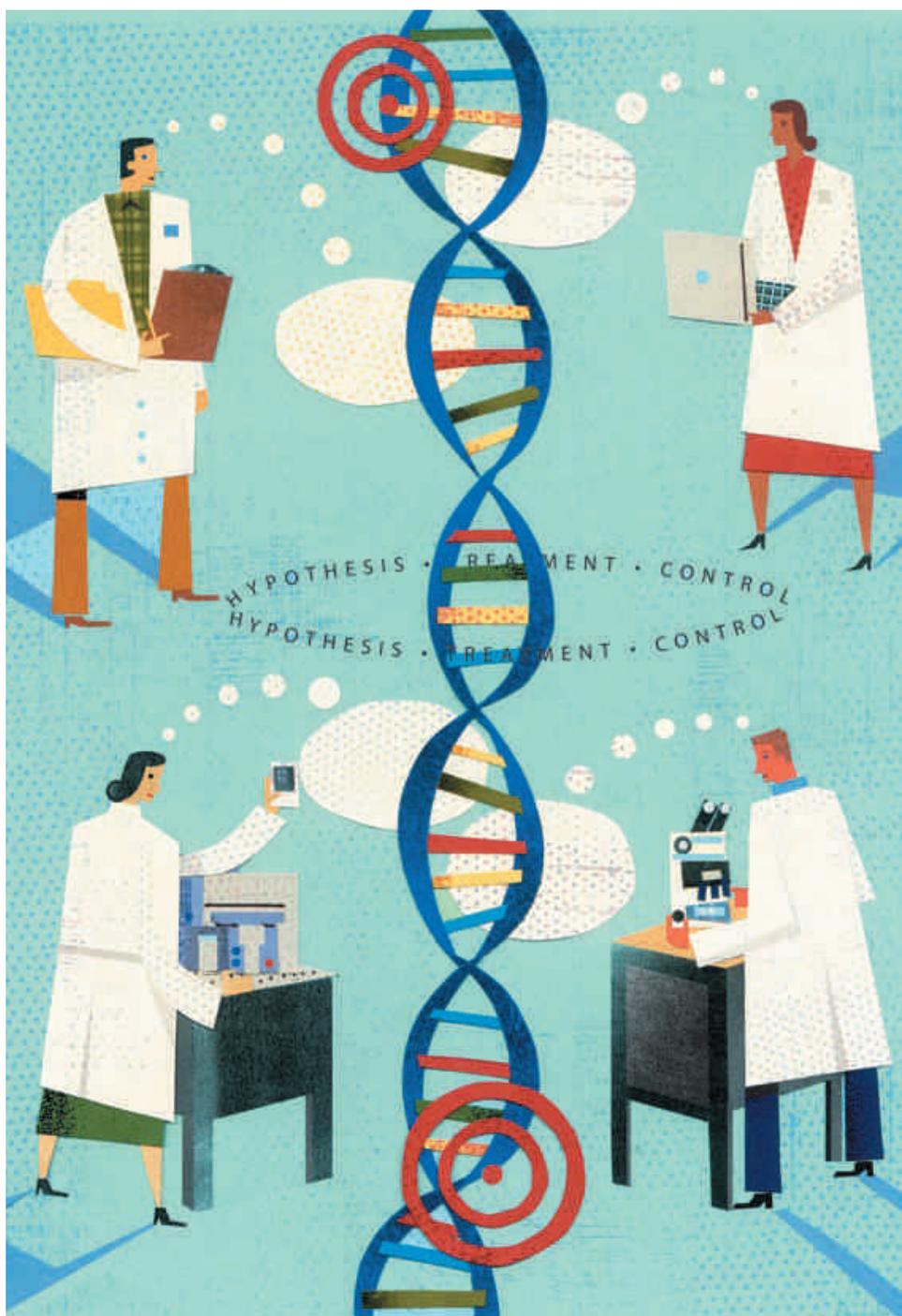


ILLUSTRATION BY RICHARD LILLASH

Progress in cancer research – the process of moving from an observation made in the laboratory or clinic to discoveries that help patients – requires expensive technology and priceless biological samples such as tumor tissue and blood from patients. These samples must be stored under stringent conditions to preserve the fragile molecules their cells contain.

Pelotonia funds this past year were used in both areas. They supported the purchase of instruments that help decode cancer genomes, and a system that helps keep precious tissue samples viable for research. These examples of equipment purchased in 2013 with support from Pelotonia can benefit the more than 300 investigators at the OSUCCC – James.

SCICLONE NGS WORKSTATION

The Sciclone NGS (Next Generation Sequencing) Workstation fits on the laboratory bench and can robotically prepare batches of cancer samples for high-throughput genome sequencing. Genome sequencing reveals how cancer hijacks normal cell functions via mutations and other structural changes in DNA and RNA.

The device helps convert long lengths of DNA extracted from cancer cells into short pieces that are readable by high-throughput

sequencers. The resulting collection of DNA fragments is called a sequencing library.

To generate a sequencing library, scientists first extract DNA from cancer cells, break it into fragments and attach the fragments to tiny metal beads. The goal is to duplicate, or amplify, the number of fragments in preparation for sequencing. Producing high-quality sequencing libraries is a tedious process that can involve more than a dozen steps, each of which must be done with precision.

Enter the robotic device. The instrument uses a magnet to gather the DNA-laden metal beads together, then uses multiple pipette tips to draw off the used solution and replace it with reagent needed for the next step.

The robotic system can prepare eight to 96 samples at a time while ensuring consistency and freeing lab personnel for other tasks.

OSUCCC – James researchers are working to develop protocols needed for particular components of the genome, such as RNA-seq libraries and exome libraries.

DIAGENODE IP-STAR

DNA sequencing can reveal gene mutations present in cancer cells that influence their growth and might determine the most effective therapy for that particular patient. In addition to gene mutations, other genomic alterations happen to DNA that

contribute to cancer development.

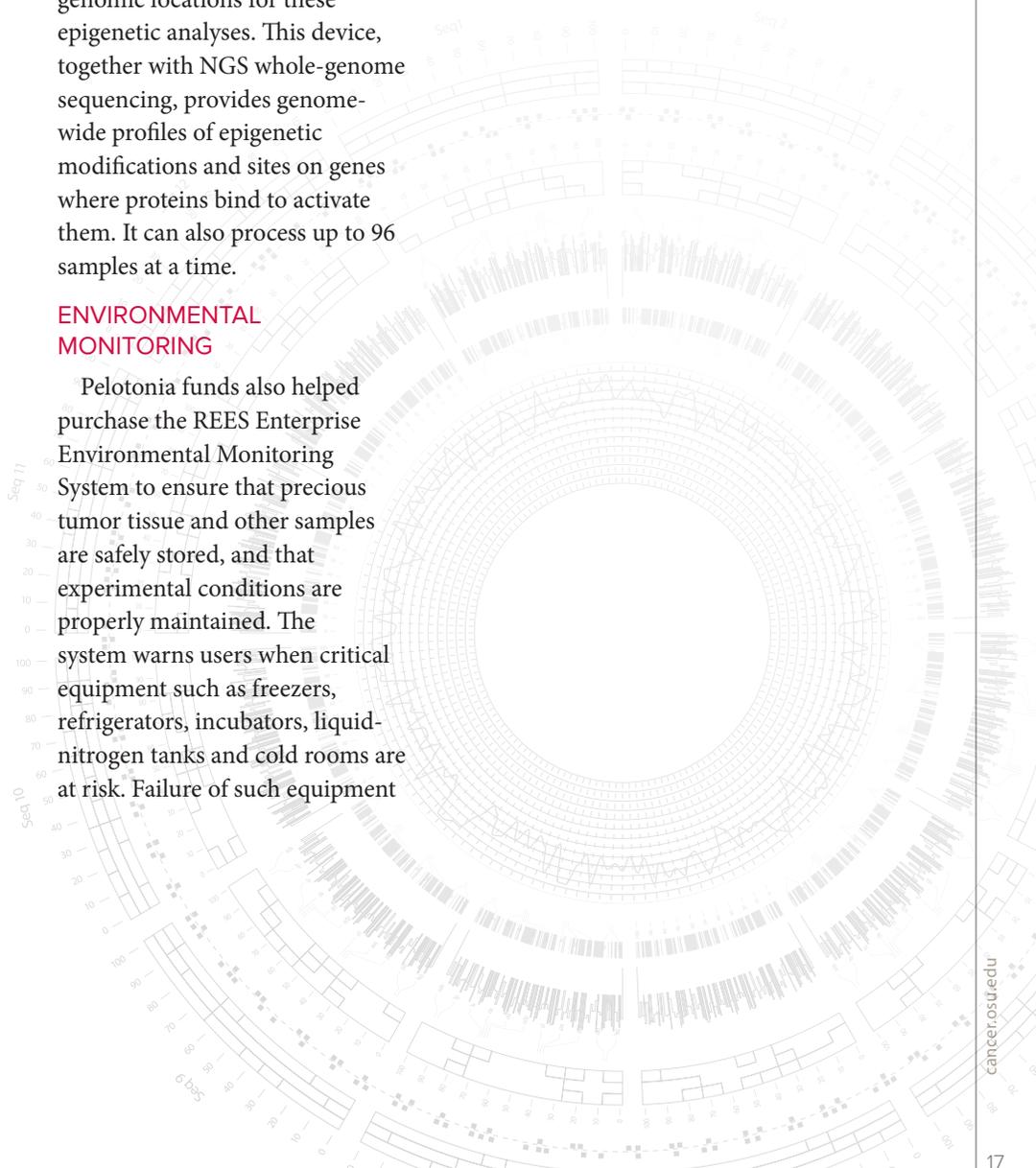
Genome sequencing can detect these “epigenetic” changes in tumor and tissue samples by customizing how sequencing libraries are generated. Pelotonia funds were used to help purchase a Diagenode IPStar Compact unit, a robotic device that automates the enrichment of genomic locations for these epigenetic analyses. This device, together with NGS whole-genome sequencing, provides genome-wide profiles of epigenetic modifications and sites on genes where proteins bind to activate them. It can also process up to 96 samples at a time.

ENVIRONMENTAL MONITORING

Pelotonia funds also helped purchase the REES Enterprise Environmental Monitoring System to ensure that precious tumor tissue and other samples are safely stored, and that experimental conditions are properly maintained. The system warns users when critical equipment such as freezers, refrigerators, incubators, liquid-nitrogen tanks and cold rooms are at risk. Failure of such equipment

can render large numbers of patient and animal samples unusable, and this can translate into years of lost work.

The system monitors critical parameters such as temperature, humidity, oxygen and carbon dioxide. 



From Pool to Pelotonia

Champion Swimmer and Cancer Survivor Rode to Raise Research Revenue

(Editor's Note: A profile of Emily Marsh-Fleming, a courageous cancer survivor who rode in Pelotonia despite her diagnosis of incurable metastatic breast cancer, was written and set to run in this issue of Frontiers. On March 7, Emily died of her disease. With the permission of her husband, Scott, we are including her story here to recognize Emily's inexorable spirit and her refusal to let cancer dim her hopes or diminish her life.)

Emily Marsh-Fleming, 38, a national champion synchronized swimmer while an Ohio State undergrad from 1994-97, was well into her cancer journey when she decided to participate in Pelotonia 11.

Until then, her only biking experience involved riding to the pool, classes and home as an Ohio State student. "The first time I set out on my bike, which my dad had disassembled and mailed to me in my freshman year, the seat dropped to the frame because I hadn't tightened it well enough on the stem," she recalled. "My legs are long, so it was a hilarious sight, me sitting on the low seat, pedaling across the Oval, knees up to my ears."

At the time of her death in March 2014, however, she was a veteran of three Pelotonias, riding with a steely resolve to support Pelotonia's goal of ending cancer.

A resident of Yellow Springs, Ohio, Marsh-Fleming approached cycling with the same determination that made her a nine-time national event champion, a four-time All-American and national team champion, and a 1997 finalist for the Big Ten Conference Medal of Honor as a superb student-athlete. (She had earned a bachelor's in microbiology and, in 2004, a master's in food science and nutrition from Ohio State.)

In 1997-2000, Marsh-Fleming trained with the U.S. National Synchronized Swimming Team and was selected as an alternate for the 2000 Summer Olympic team. In 2003 she was inducted into Ohio State's Sports Hall of Fame, and in 2013 she was admitted to the United States Synchronized Swimming Hall of Fame.

But never in the aquatic arena did she face a challenge as formidable as breast cancer. She was diagnosed in 2009 at age 34 while six months pregnant with her son Bryce. Five weeks after giving birth, she began chemotherapy at Ohio State's James Cancer Hospital and Solove Research Institute. Marsh-Fleming then returned to her job at Wright-Patterson Air Force Base and began radiation therapy in Dayton.

When she learned about Pelotonia, she rode the 43-mile route from Columbus to Amanda in 2011.

Marsh-Fleming described her cancer journey as a bumpy but fairly straight road—until it dropped into a canyon in January 2012: A CT scan showed that her cancer had spread to her bones and liver.

Emily Marsh-Fleming, Pelotonia 13



Upon absorbing this news and learning that there was no cure, she declared, "I have to ride 100 miles in Pelotonia." She bought a new bike, endured weeks of training with riding pal Jodi Chaiten – also a Pelotonia rider – then completed the 100-mile circuit in Pelotonia 12 as a member of the Pedal Me Pink peloton (riding group), a part of Team Buckeye, Ohio State's official superpeloton.

"My 2012 ride was driven by a need to prove something to myself, my doctors and every person who might question the mental integrity of a stage-four cancer patient who hops on a bike and sets out to ride 100 miles," she said.

Hoping to contribute even more to Pelotonia 13, Marsh-Fleming formed The Noble Circle Pedalers peloton, which included several cancer survivors from the Dayton area. "I wanted to help grow the Pelotonia family: more funds for cancer research, which my life depends on; more inspiration for our doctors, patients, families and caregivers; and more healing for our riders," she explained.

Health complications just before Pelotonia 13 limited Marsh-Fleming's ride to 75 miles; she met her team "at the top of a hill and we finished together. It was purely emotional spirit and strength."

Marsh-Fleming's story has inspired others. Ohio State's current synchronized swimming team and coach Holly Vargo Brown organized a Sync Cancer swim-a-thon last November in which current and former team members and others registered to swim one mile for \$25 each. It raised \$5,000 to support Team Buckeye in Pelotonia 14, in which Marsh-Fleming planned to participate.

"It's my intention to ride in Pelotonia every year I am on this Earth until Pelotonia has realized its goal," she said. "My favorite thing about it is the camaraderie around a single lofty goal that no one shies away from."

Emily Marsh-Fleming certainly didn't. Her husband, Scott, plans to ride 100 miles this year and to continue the Noble Circle peloton in her memory. **F**

Bringing the Best to Ohio State

Funds raised by Pelotonia have helped recruit and retain some of the brightest minds in cancer research to Ohio State. Here, we highlight two of the renowned senior physician-scientists formerly at MD Anderson Cancer Center who were recruited to Ohio State in the past year with Pelotonia funds.



RAPHAEL E. POLLOCK, MD, PhD, is a globally respected cancer surgeon, researcher and educator of physicians-in-training. On Sept. 1, 2013, Pollock became a professor and director of the Division of Surgical Oncology at Ohio State. He also serves as chief of surgical services at the OSUCCC – James. Pollock came to Ohio State after spending 31 years at The University of Texas MD Anderson Cancer Center in Houston, where he held several leadership positions. Pollock's clinical practice and laboratory research focus on soft tissue sarcoma, a rare cancer in adults but more prevalent in children. He is principal investigator of an \$11.5 million National Cancer Institute Specialized Programs of Research Excellence (SPORE) grant to support collaborative sarcoma translational research. The grant is one of the largest awards ever for the study of sarcoma. Pollock's SPORE research component is now located at the OSUCCC – James.



VINAY PUDUVALLI, MBBS, is a noted authority on developing therapies for patients with brain and spine malignancies using a combined approach of targeted therapies, innovative clinical trial designs and rational combinations of anticancer agents. Puduvalli, who serves as professor and director of the Division of Neuro-Oncology in the Department of Neurological Surgery, was recruited to Ohio State in December 2012 from The University of Texas MD Anderson Cancer Center, where he held several leadership posts. His research focuses on understanding the role of epigenetics in brain tumor and glioma stem-cell biology, and on translating findings to new treatments. His lab team also works to identify mechanisms of treatment resistance, including resistance to cell death and to signaling pathway inhibitors in brain tumors. In this context, he leads several clinical trials involving epigenetic therapies and novel targeted agents.



APPLY NOW FOR PELOTONIA POSTDOCTORAL FELLOWSHIPS

The Pelotonia Fellowship Program at Ohio State provides two-year research fellowships to promising postdoctoral candidates from any discipline – from the traditional sciences to such fields as history, business, engineering and humanities – who want to help cure cancer.

The fellowships pay a competitive annual stipend based on National Institutes of Health (NIH) guidelines for postdoctoral fellows. Applications, which are due three times per year, are scored on:

- Applicant strengths and research potential (emphasis is given to clinical fellows and to applicants who received their doctorate within the past year and will be new to Ohio State, or who have been at the university less than one year, and who have the potential to become independent scientists);
- Mentor/adviser qualifications and training record;
- Innovativeness and impact of the project on cancer research.

For more information, including eligibility guidelines and an application, visit <http://cancer.osu.edu/go/pelotoniafellowship> and click on Postdoctoral Fellowships, or send an email to jeffrey.mason@osumc.edu.



REGISTER NOW FOR PELOTONIA 14

Anyone wanting to participate in Pelotonia 14 as a rider, virtual rider or volunteer should visit <http://pelotonia.org/register/> and sign up for this year's tour, to be held Aug. 8-10. Riders may choose from routes of varying distances, with the longest extending from Columbus to Gambier, Ohio, home to Kenyon College. There also will be second-day return routes for those who wish to ride farther.

Visit the Pelotonia website shown above for details and online forms for registering as an adult (16 or older), as a minor (those of ages 14 or 15 may ride the 25- or 50-mile routes), as a virtual rider or as a volunteer. Riders must agree to raise the amount of funds specified for their chosen route. Thanks to generous event sponsors, all money raised by riders, virtual riders and donors will go directly to cancer research at the OSUCCC – James.

Pelotonia 13 drew a record 6,723 riders from 41 states and nine countries, as well as 3,451 virtual riders and more than 2,300 volunteers. The event raised a record \$19,007,104, boosting the five-year total for this grassroots event to more than \$61 million. Questions? Contact Karl Koon, director of development/Pelotonia at the OSUCCC – James, at karl.koon@osumc.edu.

INSIDE THE NEXT FRONTIERS

TOBACCO RESEARCH

Ohio State's new Center for Excellence in Regulatory Science is funded by a five-year, \$18.7 million grant from the National Institutes of Health and the U.S. Food and Drug Administration. The developing research program will take into account the biological, psychological, economic and public health implications associated with tobacco use and the marketing of tobacco products. The center's 18 scientists come from the OSUCCC – James and six Ohio State colleges.

PRECISE CANCER MEDICINE

Studies suggest that cancer is a genetically heterogeneous disease, and that personalized therapy will be superior to the "one size fits all" approach. Personalized therapy requires identifying unique and shared genetic changes in patients' tumors. OSUCCC – James researchers are merging clinical and basic science expertise, and sequencing individual cancers in real time, to develop and apply genetic biomarkers through innovative clinical trials. The goal: to bring precision cancer medicine into the clinic.