TURNING CANCER DISCOVERIES INTO TREATMENTS
FRONTIERS
PELOTONIA SPECIAL EDITION 2015

The James

The Ohio State University
COMPREHENSIVE CANCER CENTER
Pelotonia 2015

Many of us may remember our younger days of choosing sides for a ballgame or some other monumental competition. Sometimes we’d look across at the opposing lineup and wonder about our chances.

Our global war on cancer is something like that. We face a formidable foe that is rife with biological mystery and mayhem.

But we have a lot going for us, too, including legions of researchers, clinicians, nurses and allied professionals who work tirelessly to solve the riddles of this disease and translate scientific discoveries to better patient care and prevention strategies.

We also have thousands of people who are committed to supporting this effort through incredibly successful events such as Pelotonia, our annual grassroots bicycle tour that raises millions of dollars for cancer research at Ohio State.

Last year’s Pelotonia raised a record $21,049,621, pushing the six-year total for this event to more than $82.3 million. That kind of funding makes a strong difference in our ability to fight cancer, a complex disease that is biologically unique in each patient and must be approached with treatments that target the genetic and epigenetic mechanisms that drive each malignancy.

This special issue of Frontiers, devoted entirely to Pelotonia, offers a look at how money raised by the event’s generous riders, virtual riders and donors is being used at the OSUCCC – James as we pursue our vision of a cancer-free world. It also contains inspirational profiles of a researcher rider, a physician-researcher rider and a cancer-survivor rider.

With so much on our side in our collective quest to end cancer, we shouldn’t wonder about the outcome of this supremely important match. We’re going to win.

Arthur G. James, MD, for whom our hospital is named, once said that he didn’t know when cancer would be defeated, but he was certain the day is coming.

I agree, and so should we all. Thanks to our dedicated efforts, it’s only a matter of time. Let’s roll on toward Pelotonia 15, set for Aug. 7-9. I hope to see you there.
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ON THE COVER:
Justine Boggs, back to camera, and Tanya Knauss at the 100-mile-ride finish line at Kenyon College in Gambier, OH, during Pelotonia 14. Justine went on to complete the 180-mile route.

Read Frontiers online or download an issue at http://cancer.osu.edu/Frontiers.
Pelotonia 6-Year Total Exceeds $82 Million

Riders, virtual riders and donors in Pelotonia 14, an annual cycling event that generates money for cancer research at Ohio State, raised a record $21,049,621 and boosted the six-year total for this event to $82,343,670.

Pelotonia staff presented a check for the Pelotonia 14 total to OSUCCC Director and James CEO Michael A. Caligiuri, MD, at a ceremony in mid-November. The 2014 Pelotonia total outdistanced the 2013 tally by more than $2 million.

Thanks to Pelotonia’s generous sponsors (see box), every cent raised by riders, virtual riders and donors goes directly to cancer research at the OSUCCC – James.

Pelotonia funds support a variety of projects related to cancer diagnosis, treatment, psychosocial issues and prevention. They also provide a research fellowship program for students, idea grants for teams of faculty researchers, new and upgraded technologies to aid research, and support for work by researchers newly recruited to Ohio State.

Pelotonia 15 is scheduled for Aug. 7-9. Registration is open at www.pelotonia.org.

Pelotonia 14 notable numbers
- 7,270 riders from 41 states, 10 countries (a record)
- 3,700 virtual riders
- 2,600 volunteers
- 276 registered pelotons (riding groups)

Team Buckeye, Ohio State’s official superpeloton
- 2,362 members of Team Buckeye
- 100 individual pelotons
- 732 virtual riders
- 202 volunteers

Team Buckeye Fund Raising Total:
- $2,727,856

Key Pelotonia Sponsors

**Major Funding Partners**
- Huntington
- Lbrands Foundation
- Richard and Peggy Santulli

**Supporting Funding Partners**
- AEP
- Nationwide

**Notable Funding Partners**
- Cardinal Health
- Harold C. Schott Foundation
- Scotts Miracle-Gro
- Kenyon College

Total Funds Raised
Six-Year Total $82,343,670

Total Participation
Riders, virtual riders and volunteers
Pelotonia, the annual grassroots bicycle tour established in 2009 to raise money for cancer research at the OSUCCC – James, generated more than $61 million in its first five years through rider pledges and donations. Thanks to the generous underwriters of the event, every dollar raised by riders, virtual riders and donors since Pelotonia began has been used to advance cancer research, as shown in the bar graph to the left.

Bringing Knowledge to Bear in the Fight Against Cancer
Pelotonia research funding has been allocated to investigators in multiple colleges at Ohio State, as well as at Nationwide Children’s Hospital in Columbus and at Cincinnati Children’s Hospital Medical Center:

- 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 Education and 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
The Pelotonia Fellowship Program has awarded more than $9 million in funding for peer-reviewed cancer research projects by Ohio State students who work in the labs of faculty mentors. The trainees are in multiple disciplines and at all levels of scholarship—undergraduate, graduate, medical school and postdoctoral.
The Pelotonia-funded Ohio Colorectal Cancer Prevention Initiative (OCCPI) involves the OSUCCC – James and more than 40 Ohio hospitals working to reduce the number of deaths from and increase screening for colorectal cancer (CRC) across the state.

CRC is the third most common cancer and the third most common cause of cancer death in the United States. Some 5,430 new CRC cases and nearly 2,100 deaths from the disease are expected in Ohio in 2015.

“CRC is highly preventable and treatable when caught early through screening, but many people don’t realize that colonoscopies can prevent CRC by removing polyps in the colon before they become cancerous,” says Heather Hampel, MS, CGC, who heads the prevention initiative.

The OCCPI focuses on screening tumor samples from CRC patients—and also uterine cancer patients at the OSUCCC – James—to learn which patients have Lynch syndrome (LS), a cancer-causing condition that occurs when a person inherits a mutation in one of four genes.

A person with a mutation in one of these genes is almost 100 percent likely to develop CRC, uterine, ovarian, gastric, kidney or other cancer in his or her lifetime, usually at a younger age.

If a person learns he or she has LS before cancer develops, diligent cancer surveillance can prevent some of these cancers or detect them early, when they are easier to treat.

Pelotonia has provided the OCCPI with $3.5 million in support. By mid-April 2015, the project had identified LS or other hereditary cancer susceptibility syndrome in more than 100 individuals. Preventing cancer and the consequent loss of life in these individuals translates into an estimated savings of $40 million in healthcare costs.

Ultimately, the OCCPI will test tumor tissue from 3,000 newly diagnosed CRC patients at the OSUCCC – James and other participating hospitals to see if the four LS genes are working or not. Those subsequently found to have a change (mutation) in one of the LS genes is diagnosed with LS. This can be life-saving information for that person’s siblings, parents and children.

First-degree relatives—parents, siblings and children—of someone with LS have a 50-percent chance of inheriting the same mutation. Hampel and her colleagues have evidence that for every patient diagnosed with LS, three family members on average also carry the mutation.

So when LS is identified in one family member, other family members can be tested for the LS gene mutation that is running in their families. Those found to have LS are counseled to seek regular screening to detect cancer early; those without the mutation can follow the usual screening guidelines.

A second arm of the OCCPI monitors the first-degree relatives of the study’s newly diagnosed CRC patients to learn whether education about the benefits of colonoscopy and providing a personalized prescription for colon cancer screening will improve colonoscopy screening rates and prevent future cancers.

Numbers that mark the OCCPI’s progress as of mid-April 2015:

1,701 participants with CRC enrolled in the study
213 participants with uterine cancer enrolled in the study
49 participants found to have LS (44 CRC, 5 uterine cancer)

Of the 49 people with LS:
44 had genetic counseling
98 have family members who have had genetic counseling and enrolled in the study for genetic testing
33 relatives tested positive for LS
65 relatives tested negative for LS
19 CRC patients were diagnosed with a hereditary cancer susceptibility syndrome other than LS

Heather Hampel, MS, CGC

Saving Lives Statewide

Pelotonia-supported research at Ohio State is preventing colorectal and other cancers
The Pelotonia Fellowship Program annually allots $2 million to help promising Ohio State students with an interest in cancer research work in the labs of OSUCCC – James faculty mentors. Since the program began in 2010, it has awarded 292 fellowship grants to 129 undergraduates, 77 graduate students, four medical students, 61 postdoctoral fellows and 21 international scholars. The awards are peer reviewed and made by a committee of cancer researchers chaired by Gustavo Leone, PhD, associate director for basic research at the OSUCCC – James, and co-chaired by Janice Kiecolt-Glaser, PhD, of the OSUCCC – James Cancer Control Program. Here’s a look at three recent Pelotonia fellowship recipients:

**PETER LYON**

Peter Lyon, a junior majoring in molecular genetics, admits that completing the full 180-mile ride in Pelotonia 14 “was difficult at times, but the end result was well worth it.” He might say the same about the basic research he is conducting in the lab of Amanda Simcox, PhD, a member of the Molecular Biology and Cancer Genetics Program at the OSUCCC – James. Lyon is doing genetic and biochemical analyses of a cellular protein called CG4096/ADAMTS, which the Simcox lab discovered. The protein is part of a signaling pathway called EGFR that helps control cell division and is implicated in many human cancers. Loss of the protein can contribute to the uncontrolled cell growth that fuels tumor development.

“Our findings could lead to new knowledge about the EGFR pathway,” says Lyon, who plans to ride 180 miles again this year. After graduating, he will pursue an MD/PhD and hopes to one day “work at a large research institution like Ohio State.”

**JULIA BEHNFELDT**

Hoping to help reverse a nearly 10-year decline in federal funding for cancer research, Julia Behnfeldt will pursue a science/health policy career after earning her PhD in biomedical research with an emphasis on cancer biology this spring at Ohio State. “Pelotonia has done an exceptional job of easing these funding losses at OSU, but nationwide the research community is suffering,” says Behnfeldt, who rode 25 miles in Pelotonia 14 and will ride 50 miles this year. “I plan to bring my knowledge of science to legislators to highlight the need for a sustained investment in research.”

She’s off to a good start. Earlier this year she was one of three graduate students nationally to receive an honorable mention for the 2015 Emerging Public Policy Leadership Award presented by the American Institute of Biological Sciences. As a Pelotonia fellow in the lab of Joanna Groden, PhD, of the Molecular Biology and Cancer Genetics Program at the OSUCCC – James, Behnfeldt examines how two important DNA-repair proteins interact to prevent chromosomal instability, a driver of cancer formation.

**PRIYA LONDHE, PHD**

Priya Londhe, PhD, is a Pelotonia postdoctoral fellow in the lab of Denis Guttridge, PhD, co-leader of the OSUCCC – James Translational Therapeutics Program. She is working to solve the mysteries of cachexia, the progressive muscle wasting that renders many patients too frail for treatment. Cachexia occurs most often in patients with advanced lung, pancreatic and gastrointestinal cancers. Londhe hopes to find a treatment that will improve quality of life for these patients. “We want to understand how nanosized particles called microvesicles, which are secreted by tumor cells, regulate muscle wasting in cachexia,” Londhe says. “We have shown that these microvesicles cause killing of the muscle cells, which was unknown prior to our work, and we believe that this killing activity contributes to cachexia.”

If this proves to be true, she adds, “It will help us better understand cachexia and pave the way for pharmacological interventions.” Londhe rode 25 miles in Pelotonia 14 and is excited about riding again this year. “I met a lot of cancer survivors and was humbled to see their support for Pelotonia,” she says.
Pelotonia cyclists propel themselves through the August Ohio countryside to personally support cancer research at The Ohio State University Comprehensive Cancer Center – Arthur G. James Cancer Hospital and Richard J. Solove Research Institute (OSUCCC – James).

A share of the funds raised by Pelotonia riders supports idea grants that enable OSUCCC – James scientists to break new research ground and produce data needed to garner grants for larger, more definitive studies.

In the past four years, 67 OSUCCC – James research teams have received Pelotonia idea grants. Awardees are selected through a peer-review process conducted by both internal and external scientists not competing for grants in the current funding year.

Since the program’s inception, $6.6 million in funding has been awarded. The collaborating researchers come from several Ohio State colleges and departments and three academic institutions, including Nationwide Children’s Hospital.

Breaking new ground always involves some risk, but it can hasten the development of safer, more effective treatments and improved prevention strategies. Here are three examples of the Pelotonia idea grants awarded in 2014.

A New Approach to Cervical-Cancer Prevention

Paul Reiter, PhD, MPH, assistant professor of Medicine and member of the OSUCCC – James Cancer Control Program
Mira Katz, PhD, MPH, professor of Public Health in the College of Public Health and member of the OSUCCC – James Cancer Control Program

About 12,900 women in the United States are expected to develop cervical cancer in 2015, and 4,100 are expected to die from the disease, according to the American Cancer Society. Yet, cervical
cancer incidence rates are higher because data suggest that cervical region is important to focus on screening. This geographic or no prior cervical cancer who have received infrequent women from Ohio Appalachia program that will focus on pilot testing an HPV self-testing researchers is developing and this team of OSUCCC – James testing.

at home and mailing them in for collecting samples by themselves testing, which involves women HPV test is through HPV self-strategy for women to receive an every three years. One potential a Pap test and an HPV test that women ages 30-65 receive revisions to include testing for presence of HPV for some women. Current guidelines recommend that women ages 30-65 receive a Pap test and an HPV test every five years, or a Pap test every three years. One potential strategy for women to receive an HPV test is through HPV self-testing, which involves women collecting samples by themselves at home and mailing them in for testing.

With its Pelotonia idea grant, this team of OSUCCC – James researchers is developing and pilot testing an HPV self-testing program that will focus on women from Ohio Appalachia who have received infrequent or no prior cervical cancer screening. This geographic region is important to focus on because data suggest that cervical cancer incidence rates are higher.
Researcher Rider Has Passion for Discovery

Graduate student Emily McWilliams works in the laboratory of OSUCCC – James physician-researcher John C. Byrd, MD, and Raj Muthusamy, DVM, PhD. She is passionate about her work.

“I think about science discovery even when I’m not in the lab,” McWilliams says, “and I’m passionate about cancer research.”

She’s equally fervent about Pelotonia. She first rode in Pelotonia 13, completing the 100-mile route. In 2014, she rode the 180-mile route and plans to tackle that one again this year.

“Pelotonia is a way for me to be passionate about cancer research and also to be part of my community in Columbus,” she says. “I can’t talk with many people about my research because most people won’t understand it. But we can talk about bikes and training rides.

“It’s a way to connect with nearly anyone because nearly everyone has been affected in some way by cancer.”

McWilliams’ Pelotonia training rides often include cancer survivors, some of whom are Byrd’s patients, and many of those were treated with drugs that have been studied in the Byrd lab.

“That is so encouraging,” she says. “Those Saturday morning training rides make me all the more excited to be back in the lab on Monday.”

The Byrd lab focuses mainly on developing new treatments for chronic lymphocytic leukemia (CLL) and other forms of non-Hodgkin lymphoma and for acute myeloid leukemia. McWilliams is a member of the lab’s “antibody group,” led by Muthusamy. She studies antibody therapeutics. “Antibody therapeutics use the patient’s own immune system to attack cancer cells,” she says.

Specifically, McWilliams is studying ways to combine antibodies with drugs to boost an immune response and home in on the cancer cells. She looks at how the antibodies affect cancer cells, on the one hand, and how they affect the ability of immune cells to destroy cancer cells on the other.

McWilliams did her undergraduate work at North Park University in Chicago, earning a degree in chemistry with a minor in business. During her sophomore year, a close friend died at age 18 of a rare cancer called rhabdomyosarcoma.

“Danielle and I grew up together, and we did everything together,” McWilliams says. “She grew sick very quickly, and I wasn’t able to see her once she was diagnosed. I couldn’t do anything for her.

“When Mom called to tell me she had passed, I found myself staring blankly at a wall in my apartment wondering what I could do,” she says. She decided then that she would do cancer research. “I wanted to be part of the cure.”

The following summer, McWilliams did a research-experience program at Loyola Medical School and came to love biological science. She graduated from North Park and entered Ohio State’s Biomedical Science Graduate Program to study with Byrd and Muthusamy.

She learned of Pelotonia during orientation. “I knew right away that Pelotonia was something I wanted to do,” she says. The Byrd laboratory riding group, or peloton, is called Hope Highway, and in 2014 it had more than 50 members, McWilliams says. “Everyone in the lab pitches in, and we help each other raise money.”

Her fundraising efforts carry a personal touch. For example, she plays soccer year round, and during the transition between the indoor and outdoor seasons, she paired up with an indoor gym that gave her a discounted field rental. Her teammates pay $10 for two hours of play. “After 10 people come, the remainder goes toward Pelotonia,” she says.

McWilliams is also a member of the executive board of Team Buckeye Student Riders, which works to increase the number of undergraduate and graduate student riders.

“Pelotonia is not just a one- or two-day event,” McWilliams says. “It’s year round because people become passionate about it. Outside the lab, we come together to help each other reach our Pelotonia fundraising goal; inside the lab, we help each other to find the next great drug.

“The great thing about Columbus and Ohio State is that everybody wants to work together to fight this disease.”

(continued from page 9)

among women living in Ohio Appalachia compared with women living in the rest of the state (8.7 vs. 7.8 cases per 100,000 females, respectively).

The interdisciplinary team is working closely with the Valley View Health Centers of Ohio Appalachia to conduct the study. The findings will provide needed information about the acceptability and feasibility of HPV self-testing as a potential cervical cancer screening strategy.

An Edible Plant Component That Might Help Treat Acute Myeloid Leukemia

Jianhua Yu, PhD, assistant professor of Medicine and member of the OSUCCC – James Molecular Carcinogenesis and Chemoprevention Program

A. Douglas Kinghorn, PhD, DSc, professor of Pharmacy in the College of Pharmacy and member of the OSUCCC – James Molecular Carcinogenesis and Chemoprevention Program

Acute myeloid leukemia (AML) will affect an estimated 20,800 Americans in 2015, and 10,460 are expected to die of the disease. The malignancy affects mainly people aged 65 and over, and the five-year survival rate for this age group remains under 10 percent.

That five-year survival rate of older adults has remained unchanged for 40 years, largely because older patients are less able to tolerate therapies such as
intensive chemotherapy and stem-cell transplantation that are effective in younger patients.

These OSUCCC – James researchers are using a Pelotonia idea grant to investigate a new, less toxic way of treating AML in older patients that uses a compound from plants found in Asia.

The compound is a type of lignin called phyllanthusmin C (PL-C). The researchers have evidence suggesting that PL-C can improve antitumor activity of a type of white blood cell called natural killer (NK) cells, the immune system's first line of defense against cancer cells and viral infections.

The researchers are using their Pelotonia grant to investigate the mechanisms by which PL-C enhances NK cell antitumor activity and to study the effectiveness of PL-C in preventing AML in an animal model.

The researchers note that, to their knowledge, this is the first time that a dietary lignin component has been demonstrated to significantly enhance human NK cell function. They believe their study might open a new avenue for cancer prevention.

Furthermore, because PL-C can come from an edible plant, they believe that if their findings are positive, they could lead quickly to a clinical trial that tests PL-C in humans.

**Personalizing Therapy for Multiple Myeloma**

*Mitch Phelps, PhD, assistant professor of Pharmacy in the College of Pharmacy and member of the OSUCCC – James Leukemia Research Program*

*Ming Poi, PharmD, PhD, assistant professor of Pharmacy Practice and Administration in the College of Pharmacy*

*Craig Hofmeister, MD, associate professor clinical of Hematology and member of the OSUCCC – James Leukemia Research Program*

Multiple myeloma is a leukemia-like cancer of a type of immune cell that produces antibodies. The disease remains incurable, but one treatment that prolongs life for many patients uses a potent chemotherapy drug called melphalan, followed by bone marrow transplantation. The drug kills the cancer cells but at the same time wipes out the immune system, which is restored through bone marrow transplant.

Given in high doses, the drug can stabilize the disease and prevent progression for 30 months on average. Unfortunately, this progression-free period varies greatly from person to person, ranging from six months in some and up to 12 years in a few. In addition, each patient's body handles the drug differently, so the nature and severity of side effects is difficult to predict and avoid.

This OSUCCC – James research team received a Pelotonia idea grant to reduce this uncertainty by developing a method to determine the optimal dose of melphalan for individual myeloma patients.

Their method combines clinical factors such as patient weight and kidney function, with assays to estimate how living cells from patients react to a standard concentration of the drug. The objective is to identify a dose of melphalan that maximizes myeloma-cell killing while minimizing the drug's toxic side effects for each patient.

To read about other research supported by Pelotonia idea grants, visit [http://cancer.osu.edu/research-and-education/pelotonia-funded-research/idea-grants](http://cancer.osu.edu/research-and-education/pelotonia-funded-research/idea-grants).
Discoveries Made With Pelotonia Support

Pelotonia-supported research at The Ohio State University Comprehensive Cancer Center – Arthur G. James Cancer Hospital and Richard J. Solove Research Institute (OSUCCC – James) can lead to important discoveries that might change patient care. Here are three examples of work by OSUCCC – James researchers that received crucial support from Pelotonia and will likely lead to improved care for cancer patients.

LEARNING WHAT WORKS FROM WOMEN COPING WITH CHEMOTHERAPY

A Pelotonia idea grant awarded to OSUCCC – James researcher Kristin Carpenter, PhD, is supporting a clinical trial to identify strategies used by women who cope well with harsh chemotherapy side effects during treatment. The trial is expected to start this summer.

“Historically, health psychology focused on the bad things that happen to people during cancer treatment; variables that make their outcomes worse,” says Carpenter, who is an assistant professor clinical of Psychiatry, of Psychology and of Obstetrics and Gynecology. “We want to learn what helps the folks who do well during treatment.

“Results from several studies in breast cancer have suggested that optimistic patients do a bit better through treatment,” Carpenter says. “Our goal is to investigate the role of optimism and other dispositional variables to ascertain what kinds of things they do that might facilitate better outcomes.”

In addition, she and her collaborators hope to gain insight into whether coping strategies that work well for an optimistic person work as well for those who are less optimistic.

“What excites me about this study is that we have an opportunity to look at what patients do naturally to help them through treatment,” she says. “We will look for patterns that we hope will help us develop more individualized, targeted interventions down the line.”

The researchers will assess patients before they begin chemotherapy, and then several times during treatment to learn what symptoms they experienced and how they coped with them.

In one phase of the study, they will have participants complete a daily “diary” of their symptoms and the strategies they might be using to make themselves feel better, distract themselves, or otherwise offset the problem. “The closer we act to the time when something occurs, the more accurate patient reports are,” she says.

The study will assess participants’ personality, their tendency toward optimism and their general coping style, as well as the presence of depression, anxiety and stress, if any.

“We want to learn what strategies work best and for whom, and how we can develop an intervention...
“Our work presents a novel strategy for treating multiple myeloma, and we hope to bring it to patients as part of a phase I clinical trial as soon as possible.”

—Craig Hofmeister, MD

that makes sense in the long run,” Carpenter says. “We want to translate that into something that will foster better treatment outcomes for patients.”

**ANDROGEN RECEPTOR ACTIVATES DIFFERENT GENES WHEN BOUND TO ANTIHORMONE DRUGS**

A 2011 Pelotonia idea grant helped OSUCCC – James researcher Qianben Wang, PhD, associate professor of Molecular Virology, Immunology and Medical Genetics and a member of the Molecular Carcinogenesis and Chemoprevention Program, lead research that produced a surprising finding about a key receptor for testosterone, a hormone that drives prostate cancer development and progression.

That key molecule in prostate cancer cells is called the androgen receptor (AR). When testosterone activates that receptor, it causes the receptor to activate a particular set of genes.

However, the study published in 2015 by Wang and his colleagues showed for the first time that when the receptor binds with certain drugs used to treat prostate cancer (called bicalutamide and enzalutamide), it activates a completely different set of genes, including some that promote cancer.

The findings provide new insights into AR biology and suggest a novel strategy for treating prostate cancer, which is the most frequently diagnosed cancer in men. An estimated 220,800 new cases are expected in the United States in 2015, along with 27,540 deaths from the disease.

Although initially responsive to antiandrogen drugs (including bicalutamide and enzalutamide), prostate cancer ultimately progresses to a lethal, treatment-resistant state that is currently incurable.

“Our findings suggest that when antiandrogen drugs are used to treat prostate cancer, the treatment should also include agents that inhibit the cancer-causing genes activated by the antiandrogen,” Wang says.

Wang and first author Zhong Chen, a research scientist at the OSUCCC – James, developed most of the study’s scientific concepts.

**AN IMMUNE THERAPY FOR MULTIPLE MYELOMA**

Multiple myeloma is an incurable cancer that forms in white blood cells that produce antibodies. It is expected to affect about 26,000 Americans in 2015, with more than 11,000 dying of the disease.

OSUCCC – James researcher Jianhua Yu, PhD, assistant professor of Medicine and a member of the OSUCCC – James Leukemia Research Program, and multiple myeloma specialist Craig Hofmeister, MD, assistant professor of Medicine and a member of the OSUCCC – James Translational Therapeutics Program, used a Pelotonia idea grant to help develop a way to harness the immune system for treating the disease.

“Despite current drugs and the use of bone marrow transplantation, almost all myeloma patients eventually relapse,” says Hofmeister. “Our work presents a novel strategy for treating multiple myeloma, and we hope to bring it to patients as part of a phase I clinical trial as soon as possible.”

The potential treatment involves altering cancer-killing immune cells called natural killer (NK) cells, and T lymphocytes, or T cells. The researchers modified the cells so that they homed in on a target molecule called CS1, which is found on nearly all myeloma cells. The modified NK and T cells then killed the myeloma cells in laboratory tests. When the researchers injected the modified cells into an animal model, they again killed human myeloma cells.

“Our study shows that we can modify these immune cells to target CS1, and that the modified cells efficiently destroy human myeloma cells,” Yu says.

An important potential advantage to this approach, Yu notes, is that if the therapeutic T cells replicate in the body, they might also prevent the tumor from recurring for a prolonged period.

The researchers published their findings in the journal *Clinical Cancer Research.*
Researchers Detail Reasons for Ibrutinib Therapy Discontinuation in Some Patients With CLL

Basic and clinical research at Ohio State and elsewhere has shown the drug ibrutinib to be highly effective among certain patients with chronic lymphocytic leukemia (CLL), but a study at the OSUCCC – James has shown that about 10 percent of patients discontinued the drug because of disease progression.

CLL is the most common form of chronic leukemia among adults, with 14,600 new cases expected this year. The malignancy remains incurable, but advances in therapy have been made, notably the emergence of kinase inhibitors such as ibrutinib for patients whose disease has recurred or is resistant to other therapies.

Ibrutinib (marketed as Imbruvica®), is the first drug to target Bruton tyrosine kinase, a protein essential for CLL cell survival and proliferation. Work by OSUCCC – James researchers played a key role in gaining FDA approval of ibrutinib to treat certain patients with CLL or mantle cell lymphoma.

Clinical studies of this drug have continued, including a Pelotonia-supported study published in the Journal of the American Medical Association (JAMA) Oncology. The study by OSU hematologists Kami Maddocks, MD, Jennifer Woyach, MD, and colleagues described the outcomes of patients who discontinued ibrutinib therapy during four sequential clinical trials involving 308 patients at the OSUCCC – James.

With a midpoint follow-up of 20 months, the study showed that of the 308 patients:

- 232 remained on ibrutinib
- 45 stopped ibrutinib due to infection, other adverse events
- 31 stopped ibrutinib due to disease progression

The study concluded that this single-institution experience with ibrutinib “confirms it to be an effective therapy and identifies, for the first time, baseline factors associated with ibrutinib therapy discontinuation.” The study also showed poor prognosis for patients who discontinued therapy.

“These data enhance our understanding of how patients do on ibrutinib long-term and who is likely to relapse,” says Woyach, the study’s senior author and a member of the OSUCCC – James Leukemia Research Program. “Many patients have durable remissions with ibrutinib, and understanding which patients are at higher risk helps us select who might benefit from clinical trials on other new agents and combination therapies rather than starting ibrutinib treatment by itself,” she adds. “We have confirmed that specific gene mutations are seen in patients who relapse, which gives us an idea of other drugs that might be effective in these circumstances.”
“...there is a seamless integration between this clinical trial and laboratory study to determine how cancers become resistant to therapy and why some patients respond to therapy and others do not, with a key connection of research tumor samples before and after treatment.”

—Sameek Roychowdhury, MD, PhD

patient’s cancer genes.

Specifically this trial, supported by Pelotonia funds, will determine how well a drug called ponatinib hydrochloride works in treating patients with cancer that has metastasized (spread) to other parts of the body, has not responded to previous therapy, and has one of several alterations, or mutations, in its DNA sequence.

"Ponatinib hydrochloride may stop the growth of cancer cells by blocking some of the enzymes needed for cell growth," says principal investigator (PI) Sameek Roychowdhury, MD, PhD, a specialist in translational genomics and member of the Translational Therapeutics Program at the OSUCCC – James. "It is not yet known whether a patient’s genetic alterations affect how well this drug works."

Roychowdhury says there is a "seamless integration between this clinical trial and laboratory study to determine how cancers become resistant to therapy and why some patients respond to therapy and others do not, with a key connection of research tumor samples before and after treatment."

The investigators will use a “team science” approach to 1) study gene and protein alterations by collaboration between the Ohio State basic science labs of Roychowdhury and co-investigator John Hays, MD, PhD, also of the Translational Therapeutics Program, and 2) complete the clinical trial via collaboration between Roychowdhury and scientists at the University of Michigan.

The trial is open to patients 18 and older with any metastatic cancer that has alterations in a protein called fibroblast growth factor receptor (FGFR).

Roychowdhury describes this study as a “basket trial” because it involves patients with different cancer types that have common gene alterations.

Trial participants orally receive ponatinib hydrochloride once daily for 28 days, and then repeat this course every 28 days in the absence of disease progression or unacceptable toxicity (adverse effects).

The study’s primary objective is to evaluate overall patient response to this drug, which is an FGFR inhibitor.

"While we expect that patients with FGFR alterations will have disease regression, we also anticipate that patients will eventually acquire resistance to single-agent therapy with ponatinib and develop disease progression," the researchers state in their study application. "Despite intensive study of FGFR in cancers, (the cause of) acquired resistance to FGFR inhibition is unknown."

However, they hypothesize that acquired resistance is mediated through genomic or expressed alterations that provide a bypass for FGFR signaling. This study and its methods are designed to address their hypothesis.
Working with the colleges of Medicine, Pharmacy and Business, the OSUCCC – James organized The Ohio State University Drug Development Institute (DDI) in 2011 to guide the development of promising anticancer drugs produced by OSUCCC – James researchers. Using external research-and-development service organizations, the DDI works with OSUCCC – James researchers to fast-track innovative compounds through the required FDA testing that is needed to proceed to clinical trials.

Timothy Wright, a former executive of several pharmaceutical companies, chairs the External Advisory Board for the Drug Development Institute. “The DDI focuses on solving important unmet needs in cancer and other diseases,” Wright says. “Our portfolio consists of novel mechanisms that address these unmet needs.”

Bence Boelcskevy, PhD, also a former pharmaceutical executive, oversees the day-to-day operations. The DDI currently manages 15 drug-development projects. Seven are novel anticancer agents that receive Pelotonia support. Here are five examples of those.

**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 identified several unique drug candidates that inhibit PRMT5 activity. As part of a structured preclinical development program, further testing is being performed to confirm that these molecules stop tumor growth. The DDI is also facilitating a parallel project with these inhibitors in multiple sclerosis, an example of the institute’s expansion beyond oncology.

**STAT3 INHIBITOR**
Tumor growth can be promoted or suppressed by signals that pass from one molecule to another in a cancer cell. STAT3 is an important molecule in some of these signaling pathways. OSUCCC – James researchers have synthesized a promising STAT3 inhibitor and are collaborating with Nationwide Children’s Hospital to define its effects in sarcoma. As part of a multi-pronged DDI research program they are also studying the effect of this inhibitor in melanoma, lung cancer, pancreatic cancer and oral cancer. Additionally, early evidence indicates that this molecule represses tumor growth in glioblastoma, a lethal form of brain cancer; in colon cancer, depending on tumor stage; and in ovarian and prostate cancer. Expansion of this program may be possible if these early results are confirmed.

**RAS INHIBITOR**
RAS is a family of genes that make proteins involved in cell signaling pathways that regulate cell growth and cell death. Members of the RAS family include the genes KRAS, HRAS and NRAS. There is strong evidence that links mutations in these genes to cancer, and agents that block mutated RAS genes or their proteins may inhibit cancer growth. OSUCCC – James researchers have developed antibody-mimetic agents that inhibit the protein encoded by mutated KRAS. The mutant protein is implicated in 30 percent of all cancers.

**EPSTEIN-BARR VIRUS VACCINE**
Epstein-Barr virus (EBV) is a common 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 autoimmune diseases. If EBV is present in donated blood stem cells or a donated solid organ, it can cause post-transplant lymphoproliferative disease (PTLD) in transplant recipients, resulting in organ and transplant failure, that is often fatal. Researchers at the OSUCCC – James are developing an EBV vaccine to prevent PTLD and help other EBV-related conditions.

**FENRETINIDE ORAL PATCH (a Pharma Industry partnership)**
About 300,000 Americans annually develop precancerous lesions in the mouth that can progress to oral cancer, and nearly 36,000 people in the United States develop oral cancer yearly. 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 an active ingredient called Fenretinide to treat them. The patch could provide an alternative to surgery and reduce the incidence of oral cancer. With help from the DDI, The Ohio State University, the University of Michigan and the pharmaceutical firm Venture Therapeutics have signed a co-development agreement and formed Sirona Therapeutics, a company to fully develop the Fenretinide oral patch. Development activities are in progress.
Instruments of Progress

A Mass Spectrometry Upgrade

The Orbitrap Fusion™ and Quantiva mass spectrometers are among the newest equipment purchased with support from Pelotonia funds. The funds were contributed by the OSUCCC – James to an Ohio State and state of Ohio investment in a major upgrade and expansion of OSU’s mass spectrometry and proteomics capabilities.

Mass-spectrometers are used in cancer research to better understand cancer-cell biology. The instruments are needed, for example, to identify the quantity and characteristics of proteins in tumor and normal tissues. The new mass spectrometers were purchased for the Proteomics Shared Resource (SR), which provides this critical technology and expertise for OSUCCC – James researchers and the cancer-research community across Ohio.

The Proteomics SR is part of the Campus Chemical Instrument Center that is managed by Ohio State’s Office of Research and the OSUCCC – James.

Proteomics SR Director Michael Freitas, PhD, an associate professor in the Department of Molecular Virology, Immunology and Medical Genetics at Ohio State and a member of the Molecular Biology and Cancer Genetics Program at the OSUCCC – James, says the sophisticated new mass spectrometers will enable researchers to identify compounds faster, more accurately and more thoroughly.

Vicki Wysocki, PhD, an Ohio Eminent Scholar in the Department of Chemistry and Biochemistry in Ohio State’s College of Arts and Sciences, and senior faculty adviser to the Proteomics SR, says the ongoing mass spectrometry upgrade/expansion has involved the purchase of several state-of-the-art instruments for measurements, and they include sample robots for high-throughput applications.

These new instruments are housed in the Campus Chemical Instrument Center, which was founded in 1981 as a unit of the OSU Office of Research to provide research facilities for the entire campus in three areas: NMR spectrometry, mass spectrometry and proteomics, and macromolecular X-ray crystallography.

“The Center is an interdisciplinary unit serving faculty from the colleges of Arts and Sciences; Education and Human Ecology; Engineering; Food, Agricultural and Environmental Sciences; Medicine; Optometry; Pharmacy; Veterinary Medicine; and Ohio State’s Comprehensive Cancer Center, to name a few,” Wysocki says.

She notes that the Center also is a hub for the Ohio Nuclear Magnetic Resonance and Ohio Mass Spectrometry MR consortiums, providing researchers in colleges and universities throughout Ohio with access to the Center’s facilities with on-campus user fees.

Michael Freitas, PhD

“The sophisticated new mass spectrometers will enable researchers to identify compounds faster, more accurately and more thoroughly.”
Pelotonia Participation Punctuates Survivor’s Recovery

Kathy Koontz, 52, of Dublin, has been to the bottom of the abyss and back.

She hit bottom with the jolt of a February 2013 diagnosis of primary amyloidosis (known as AL), an incurable condition in which plasma cells produce an abnormal protein that accumulates in organs, leading to a decline in function and, in many cases, organ failure. It is closely related to a blood cancer called multiple myeloma and is often treated with the same protocols.

She completed her comeback 18 months later when she rode the full 180-mile, two-day trek of Pelotonia 14—her treatment finished; her illness in remission, her spirits soaring.

To Koontz, crossing the finish line on the first day’s 100-mile ride side-by-side with her husband and her oncologist’s nurse practitioner marked the moment she stopped being a patient, having proven to everyone that she had overcome the effects of her disease and treatment.

“Riding the 180 miles in Pelotonia 14 was the most inspiring and overwhelming experience of my life,” she says. “Seeing all the people lining the streets and cheering us on, looking around at my fellow riders and thinking, ‘They’re out here to help me and others like me’—it filled me with gratitude and hope.”

Especially after all she’s been through, and despite the realization that her illness will likely recur.

Koontz says her diagnosis at Ohio State’s Wexner Medical Center came as a shock. “I was always healthy and strong, riding my bike 50 miles for fun, participating in workout classes in which I kept up with people 15 years younger than I,” she says.

Her online searches frighteningly revealed that average survival for 80 percent of patients with AL (amyloid light chain) amyloidosis was just four years. However, with advances in research and the approval of novel treatments, her chances now of being alive in five years are 66-80 percent.

The numbers led to troubling questions. “My daughter was a freshman in high school; would I see her graduate high school or college? My other daughter was married four months before; would I be around for any grandchildren? It was a really scary time,” Koontz recalls.

She considered going to other centers renowned for treating amyloidosis but chose Ohio State’s Comprehensive Cancer Center — James Cancer Hospital and Solove Research Institute because she “knew I could get the same level of care at The James. It’s such a fabulous combination of clinical competency with compassion and comfort. I had total trust in the team that was taking care of me.”

Just under two weeks after her diagnosis, she started one round of chemotherapy, and plans were made for her to have high-dose chemotherapy and an autologous stem cell transplant soon after she returned from a family ski trip to Colorado. She was weak, in pain and carrying 30 pounds of fluid in her abdomen after her initial treatment, but she skied with her family every day of the trip, fearing it might be her last vacation with them.

That spring she spent 24 days at The James for her stem cell transplant and nine days at Dodd Hall Rehabilitation Services at Ohio State so she could learn to walk short distances and climb a few stairs after gaining 60 pounds of fluid in the hospital.

When she returned home in May, Koontz, with the help of her husband, began the struggle of rebuilding her stamina and adjusting to life with amyloidosis. That summer, she was elated to learn that the stem cell transplant had been successful and she was in remission. Steadily, she returned to her exercise classes, started cycling again and set a goal of riding in Pelotonia.

“Pelotonia 14 was my first ride in that event,” she says. “I was a cyclist before I got sick and had done other long-distance rides. I had considered riding in Pelotonia before, but the fundraising commitment intimidated me.

“But once I got out of the hospital, I thought riding in Pelotonia would be an exclamation point on my recovery.”

Koontz credits her revitalized life to the grace of God and to the experts at The James.

“During my hospital stay, Dr. William Blum and my primary nurse, Bonnie Everett, were phenomenal,” she says. “My oncologist, Dr. Yvonne Efebera, and her nurse practitioner, Tammy Lamb, manage my care, and we are so close. I can’t think of two people I’d rather have by my side as we fight this disease long term.”

Because of the high likelihood of relapse, Koontz sees Efebera every three months to make sure her disease remains in remission. “If everything is normal at my next check-up, which will be two years post-transplant, my follow-ups will be every four months,” Koontz says.

Meanwhile, she is preparing to ride 180 miles in Pelotonia 15 with RideMmore, a Team Buckeye peloton (riding group).

“My life as a survivor is full and wonderful,” Koontz says. “I’m busy enjoying the health that The James helped restore.”

She admits that she sometimes becomes anxious over the high relapse rates for her disease. “But then I think about the thousands of people riding in Pelotonia and the hundreds of researchers at The James, and I don’t worry. I think, ‘We got this!’”

A sentiment shared by scores of cyclists.
Bringing the Best Research to Ohio State

The OSUCCC – James attracts some of the brightest minds in cancer research, and Pelotonia dollars help them resume their studies when they arrive. Among those recruited in 2014 are these three senior researchers.

ROMAN SKORACKI, MD, FRCSC, FACS, is a professor in the College of Medicine, Department of Plastic Surgery, where he directs the Oncology Section. Skoracki came to Ohio State from The University of Texas MD Anderson Cancer Center. His areas of clinical expertise include lymphedema surgery, reconstructive microsurgery of the head, neck and breast, sarcoma reconstruction and abdominal wall reconstruction—all focused on improving patient outcomes physically and psychologically. He also has a strong research interest and collaborates with scientists in various disciplines related to the care of patients with cancer.

JAMES ROCCO, MD, PhD, is a professor in the College of Medicine, Department of Otolaryngology – Head and Neck Surgery, where he directs the Division of Head and Neck Oncology. Rocco, who also is a member of the Translational Therapeutics Program at the OSUCCC – James, was recruited from the Massachusetts Eye and Ear Infirmary and Massachusetts General Hospital. As a researcher, he has translated basic science investigations on mechanisms of cell death after therapy into clinical practice by identifying novel biomarkers that predict survival in patients with head and neck cancer.

MICHELLE NAUGHTON, PhD, MPH, is a professor in the College of Medicine, Department of Internal Medicine, Division of Cancer Prevention and Control. Naughton, who also is a member of the Cancer Control Program at the OSUCCC – James, came to Ohio State from Wake Forest University School of Medicine. Her research focuses on the impact of cancer and its treatments on the health-related quality of life and daily functioning of patients and long-term survivors.
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 have three funding cycles/due dates 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 message to jeffrey.mason@osumc.edu.

REGISTER NOW FOR PELOTONIA 15

Online registration is open for Pelotonia 15, the seventh installment of the annual grassroots bicycle tour that raises millions of dollars for cancer research at the OSUCCC – James. Pelotonia 15 will be held Aug. 7-9 on routes between Columbus and Gambier, Ohio, the home to Kenyon College. Anyone wanting to participate as a rider, virtual rider or volunteer can register at www.pelotonia.org.

Riders may choose from routes of varying distances, with the longest extending from Columbus 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 money 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 Ohio State.

Questions? Visit http://pelotonia.org/about/contact.

INSIDE THE NEXT FRONTIERS

THE ORAL MICROBIOME

Researchers at the OSUCCC – James are studying interactions between the microbiome of the mouth and food-based phytochemicals. The project will establish the role of oral bacteria in the formation of bioactive compounds from black raspberries. Outcomes of these studies will help develop food-based strategies for disease prevention, point-of-care diagnostics and biological metrics for the successful treatment of oral cancers in high-risk populations.