

IU Simon Cancer Center researchers perfecting one-two punch for challenging adversary: glioblastoma

By Mary Hardin

Glioblastoma multiforme is a fickle foe. It has no hesitation about expanding its boundaries or modifying its structure to make itself resilient. It can host multiple cellular signatures within each tumor and is efficient at repairing therapeutic cellular damage.

These are some of the reasons glioblastoma multiforme (GBM) is such a deadly cancer. It may be a resilient opponent, but two IU Simon Cancer Center researchers are committed to developing new combination therapies for GBM, using the variable and fluctuating genetic signatures of the tumor to guide those therapies.

[Karen E. Pollok](#), Ph.D., and [Aaron Cohen-Gadol](#), M.D., M.Sc., are collaborating using malignant human tissue that can be grown in the brains of specialized immunodeficient mice to pinpoint the mechanisms involved that allows GBM to survive therapeutic attacks. Dr. Cohen-Gadol, a professor of neurological surgery at IU School of Medicine and Goodman Campbell Brain and Spine, specializes in the treatment of GBM. Dr. Pollok is a highly recognized associate professor of pediatrics at IU School of Medicine with a research interest in therapeutic strategies to modulate DNA repair in cancer. Drs. Cohen-Gadol and Pollok are co-directors of the [Signature Center Initiative for the Cure of Glioblastoma](#) at the IU Simon Cancer Center.

Using GBM tissue from neurosurgery, Dr. Pollok's team implants human glioblastoma tumors in mouse brains. Using the fresh tissue allows Dr. Pollok to more closely simulate how the tumor changes at a molecular level in human patients when treated with chemotherapy or radiation.

GBM is a complex enemy. It sends malignant finger-like invasive extensions into the brain, making complete surgical removal virtually impossible. GBM cells migrate along capillaries that provide a ready source of nutrition from the blood. This allows the cancer cells to spread and grow rapidly. Each tumor is a conundrum – different genetic signatures can be found in different sections within each tumor. Genetic signatures are what therapeutic agents target to kill cells, but if each tumor has multiple genetic signatures, targeting becomes more complex and only partially effective.

Karen Pollock, Ph.D.



Dr. Pollok

As if that doesn't complicate the process enough, Dr. Pollok said the GBM cells are particularly efficient at protecting themselves by activating a process called DNA damage response, which senses cellular damage and repairs it. DNA damage response is an effective tool at preventing cellular changes from foreign agents such as tobacco products or ultraviolet light; it also can block advantageous changes such as cell death from chemotherapeutic agents or radiation.

“You are really working with a genetically unstable situation,” Dr. Pollok said. “That’s where we are finding an approach that incorporates multiphase therapy useful.”

“The cancer cells respond to chemotherapy and then the DNA damage response increases,” she added. “There’s a window of time when we can use a drug to inhibit the DNA response. Our goal is to inhibit the pathways to decrease survival of the GBM cells and increase the effectiveness of the therapy while at the same time making sure that any toxicity to normal tissues is minimized.”

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Multiphase therapy employs standard chemotherapy (temozolomide) and additional targeted inhibitors to attack the GBM cells. Following each treatment, the tumor cells are tested to see how they have adapted, and then treated again with multiphase therapy before the DNA damage is corrected. This process is applied multiple times and, in mouse models, is proving effective.

“We have some exciting new results in lengthening survival rates,” Dr. Cohen-Gadol said. “We are hopeful about moving to the clinical trial phase in the future, perhaps as soon as five years. But for now we are still trying to prove their efficacy thoroughly in the mouse model, adjusting the dose to get the optimal effect.”



Drs. Pollok and Cohen-Gadol are optimistic their focus may ultimately result in a new approach to treating GBM. By understanding what changes occur on the molecular level and using multiphase therapy to target those changes, the researchers believe they will make the elusive GBM tumors an easier target.



Dr. Cohen-Gadol

Glioblastoma brain cancer cells under microscope

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Wright Scholarships awarded to 3 women with promising futures in cancer research

By Brian Hartz

The Indiana University Melvin and Bren Simon Cancer Center's 2017 William J. Wright Scholarship has been awarded to three promising future cancer researchers: IU School of Medicine students Ciersten Burks, Teresa Easwaran and Anna Filley.

The scholarship carries with it a \$6,000 financial reward but also the expectation that recipients will devote at least two months to a cancer-related project during their school year. Such projects can range from lab experiments to health outcomes research and cancer awareness programs.

This year's crop of Wright winners represent a wide variety of backgrounds, scholarly interests and motivations for pursuing a career in medicine, ranging from a former captain of the IU women's soccer team to a classically trained cellist and a Purdue graduate who originally aspired to become an engineer.

Burks, 26, is the soccer player. Or was. Hobbies and recreational interests tend to fall by the wayside when one is in medical school, she says.

"It's been a while, but I'm hoping to play again this summer," she says. "The last time I played was last summer, but I grew up playing the game. I started playing when I was 4 and played all the way through my senior year of college.

"Now I just play recreationally in the summers mainly or in the fall. I still love it. I mean, it brought me so much more than just playing the game including many of my close friendships."

Burks is on track to finish her medical degree in May 2018 and plans to make otolaryngology the focus of her career in medicine. Otolaryngology involves the treatment of disorders related to the head and neck, including specific structures such as the ear, nose and throat.

Otolaryngology, Burks says, "involves a great deal of variety, from head and neck cancer to laryngology and voice disorders to otology and everything in between. I enjoy it all. I had an uncle who was born deaf, so that has always been a subject of interest to me, especially being able to provide children with cochlear implants so that they can go on to live normal lives with as normal hearing as possible."

During the 2016-17 academic year, Burks was a research fellow in IUSM's otolaryngology department, working under the tutelage of Charles Yates, M.D., Marion Couch, M.D., Ph.D., and D. Wade Clapp, M.D. She conducted research on neurofibromatosis types 1 and 2, cancer predisposition syndromes of the nervous system that can lead to hearing loss, among other ailments.

"It has been exciting to pair my interest in otolaryngology directly with the research that I've been doing for this past year," she says. Burks adds that she plans to continue to study neurofibromatosis, both type 1 and type 2, during her fourth year at IUSM.

"It has been exciting to pair my interest in otolaryngology directly with the research that I've been doing for this past year." Ciersten Burks

Easwaran, meanwhile, is the music aficionado of the 2017 Wright Scholars group. She graduated from IU in 2012 with a degree in biology as well as a degree in cello performance from the Jacobs School of Music. Music seemed destined to be her future until her father was diagnosed with stage IV non-Hodgkin's lymphoma.

"His suffering not only brought me to medical school, but it has kept me motivated in medical school," she wrote in the personal statement that accompanied her application for the Wright Scholarship. "Because of my dad's personal battle, I decided then I must do something to serve others who are suffering – and I believe that research is critical in my pursuit."

Easwaran's passion for research is evident in the fact that she's done two stints (summer 2015 and then the entire 2016-17 academic year) studying developmental neuroscience; specifically, how a class of axon guidance molecules, the semaphorins, play critical roles in synaptic structure and organization in the lab of Alex Kolodkin, Ph.D., at Johns Hopkins University School of Medicine in Baltimore. To help facilitate those efforts, Easwaran twice received

fellowships from the Howard Hughes Medical Institute, a highly competitive award program.

“Cancer and development are very intertwined because a lot of cancer is like regression back to development but in some sort of malformed way,” she says, explaining her interest in developmental biology. “You can’t really understand physiology and cell biology unless you understand development.”

Like Burks, Easwaran, 27, says she wishes she had more time for her other interests, particularly cello, but she’s content to narrow her focus. “My mom will always say, ‘Oh, you should practice your cello for stress relief.’ I always tell her it’s actually stress-inducing because I know what I used to sound like, and now I don’t sound like that anymore.”

Easwaran manages to find time to help others, however, through her ongoing involvement as a volunteer with the Special Olympics and Down Syndrome Indiana. Her brother has Lennox-Gastaut Syndrome, a form of epilepsy characterized by treatment-resistant seizures and intellectual impairment, which spurred her interest in developmental biology research as well as her desire to dedicate time to organizations that aid people with developmental disorders.

Easwaran, who plans to pursue neurosurgery, says the Wright Scholarship will be a boon to her long-term goals because of the opportunities it presents to further her research. “Ultimately, I want to be a surgeon-scientist, so having more exposure to learning how to ask the right question and how to answer it, I think, is very helpful.”

The third 2017 Wright Scholarship recipient, Anna Filley, also took a rather unique, circuitous route to IUSM and oncology research. She grew up in West Lafayette, Ind., the daughter of parents who were both faculty members at Purdue University, and was a Boilermaker during her undergraduate years. Filley, 25, says Purdue was the most logical choice for her, not only because of her familial connections, but because of her strong interest in engineering and tackling complex problems and questions.

“I really liked engineering in general,” she says. “I really liked problem-solving, always have. It was a logical choice ... obviously their engineering program is fantastic, so I felt very confident when I picked that.”

However, Filley discovered during her time at Purdue that she wasn’t interested in pursuing a career in engineering. “I really didn’t want to do it,” she recalls. “Which was such a bummer to me because I really loved the theory behind it, and I loved what engineers do. I just didn’t want to be one.”

Fortunately, she chose to major in biomedical engineering, which led her to realize that “medicine, in general, is just one giant problem. Treating people is problem-solving – that’s really what you’re doing. Someone comes to you and says, ‘I have all of these symptoms,’ and you have to sift out what’s important, you have to ask the right questions, you have to run the right tests, you have to interpret them – and that’s fun.”

Filley, who expects to receive her medical degree in May 2018, says she has her sights set on a career in neurosurgery. During her time at IUSM, she has been doing research in the lab of her mentor Mahua Dey, M.D., that focuses on glioblastoma, a highly aggressive form of cancer that originates in the brain.

“I find glioblastoma research fascinating because people who’ve been diagnosed with it have such a poor prognosis,” she says. “That’s one of the things that really got me interested in this field ... that there’s seemingly little you can do to extend life for a long period.

“When I learned that, I just thought, ‘Wow, that’s terrifying.’ It’s really tragic. And that’s something that I really hope changes, that I get to help change in my lifetime. Hopefully, as with all of the forms of cancers, we will put ourselves out of the job – that’s the ultimate goal.”

Filley says she intends to make neuro-oncology research and treatment a big part of her career because of the importance of the brain and central nervous system to the overall health and functional abilities of the body.

“I’m biased, but I think it’s the most important organ in the body,” she explains. “It’s what makes people *people*; it’s what allows them to respond to their environment; it’s what gives you your thoughts, your feelings; it’s what gives your life purpose, I guess, what gives everybody’s life purpose. And so that’s why injuries to the nervous system are just so devastating. And so, if I’m a doctor, this seems like a good way to really make a big impact on someone’s life and to really give them their life back.

“Also, the more I learned about neurosurgery, the more I learned that there’s so much more left to be discovered, there’s

so much that we're starting to be able to do, but we could do a lot better. And that really intrigues me because I've always loved research, I've always loved problem-solving. I love the idea that you can discover something new, and it seems like a really perfect fit here."

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“Also, the more I learned about neurosurgery, the more I learned that there's so much more left to be discovered, there's so much that we're starting to be able to do, but we could do a lot better.

Anna Filley

Burks, Easwaran, and Filley are all perfect fits for the Wright Scholarship, and Filley's reaction to winning the award sums up what it means for all three of them:

“I was really surprised, thankful, and excited. I honestly love the research that I've been doing and I feel really lucky to have found it in general. This is kind of 'the icing on the cake,' and just one more reason to follow my dreams. I feel really lucky.”

William J. Wright Scholarship

The William J. Wright Scholarship is awarded to third-and fourth-year medical students, physicians in cancer-related post-doctoral training programs, and/or medical doctors who are employed by the IU School of Medicine pursuing cancer-related fellowship training, all of whom demonstrate the commitment and potential for conducting cancer research, and all of whom demonstrate outstanding character and well-defined professional goals.

The expectation for this award is that the student will devote at least two months of their school year to a project that will further the care of patients with cancer, including a formal basic, translational or clinical science research project, quality improvement project, health outcome research, or cancer awareness program.

Students with research grants that are already supporting their education are not eligible.

This award is supported by the IU Simon Cancer Center William J. Wright Scholarship Fund.

For more information, contact Elizabeth Parsons at eparsons@iupui.edu.



Ciersten Burks, Anna Filley and Teresa Easwaran are recipients of a Wright Scholarship.

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New breast surgical oncologist on board



Fisher

Carla Fisher, MD, associate professor of surgery at IU School of Medicine, is the new director of breast surgical oncology at IU Simon Cancer Center, IU Health West, IU Health North, and Sidney & Lois Eskenazi Hospital. Dr. Fisher most recently was an assistant professor of surgery at the Hospital of the University of Pennsylvania. She succeeds Linda Han, MD.

[Meet Dr. Fisher](#)>

Vaughn named research nurse administrator at CTO

LaTrice Vaughn, RN, recently was named research nurse administrator within the [Clinical Trials Office](#) at the IU Simon Cancer Center. In this role, she provides overall administrative support, management, direction and supervision for clinical research nurses, affiliate nurse manager, and clinical research patient specialists within the Clinical Trials Office. She was previously the interim research nurse administrator and affiliate research nurse manager.



Patrick Loehr, MD, director of the IU Simon Cancer Center, meets with Congressman Andre Carson (far right) to thank him for his help in securing National Institutes of Health funding. Rep. Carson toured the cancer center and met with representatives from the cancer center, IU, and IUPUI on Aug. 18.

JNCI: "Africa's Neglected Epidemic"

Eight oncologists work in Kenya, a country of 46 million people. In "[Africa's Neglected Epidemic](#)," the Journal of the National Cancer Institute looks at the challenges there. The work of the IU-led AMPATH oncology program is mentioned in the article.



Kendall Shepard (right), a student at Warren Central High School, gains hands-on cancer research experience with his mentor, Khalid Mohammad, MD, PhD, during the IU Simon Cancer Center's Summer Research Program. During the nine-week program, Shepard focused on bone metastases research.

Cancer center members in the news

- An updated American Society of Clinical Oncology clinical practice guideline clarifies the appropriate use of immunotherapy and provides new recommendations on the use of targeted therapy for patients with stage IV non-small cell lung cancer. The evidence-based recommendations focus on the use of immunotherapy in the first- and second-line settings, and targeted therapies for patients with changes in tumor EGFR, ALK and ROS1 genes. Not enough evidence existed to recommend for or against immunotherapy in the third-line setting. "Treatment for lung cancer has become increasingly more complex over the last several years," **Nasser Hanna**, MD, co-chair of the ASCO expert panel that developed the guideline, said in a release. "This guideline update provides oncologists the tools to choose therapies that are most likely to benefit their patients." Also, Dr. Hanna answered questions about a new treatment approved for non-small cell lung cancer in an [IU Simon Cancer Center Q&A feature](#).
- **Roberto Pili**, MD, and colleagues at the Wistar Institute recently announced results of a preclinical study demonstrating that entinostat, an oral, Class-I histone deacetylase inhibitor, enhances the antitumor effect of PD-1 (programmed death receptor-1) blockade through the inhibition of myeloid derived suppressor cells (MDSCs). The findings were published in [Clinical Cancer Research](#).
- **Lindsey Mayo**, PhD, and colleagues wrote "[Early stage metastasis require Mdm2 and not p53 gain of function](#)," which was published in the journal *Molecular Cancer Research* by the American Association for Cancer Research (AACR).
- In continuing coverage of the 10th anniversary of the Komen Tissue Bank at IU Simon Cancer Center, **Anna Maria Stoniolo**, MD, the bank's executive director, talked about past accomplishments and the future on "Inside Indiana Business." As part of the Vera

Bradley Foundation for Breast Cancer Research Laboratories, it is the world's only healthy breast tissue bank. [Watch](#)>

- **Feng-Ming Kong**, MD, PhD, **Jian-Yue Jin**, PhD, and **Susannah Ellsworth**, MD, will be participating in the American Society for Radiation Oncology's (ASTRO) 50th annual meeting in San Diego in late September. The meeting is the world's largest scientific meeting dedicated to radiation oncology.

- In "[Love in the Time of Cancer](#)" from the Journal of Clinical Oncology, **Lawrence Einhorn**, MD, wrote that he has often wondered what drives patients to battle seemingly insurmountable odds with hope and determination. "After all these years, I turn to love ..." he wrote.

- **Aaron Cohen-Gadol**, MD, MSc, answered questions about brain cancer and glioblastoma in light of the recent announcement from Sen. John McCain that he has glioblastoma. [Read Q&A](#).



Liu

- **Yan Liu**, PhD, has been awarded a scholar extension grant for \$115,000 from the St. Baldrick's Foundation. In 2014, Dr. Liu was awarded a \$330,000 St. Baldrick's Foundation Scholar Award for his work to improve treatment outcomes for children with acute lymphoblastic leukemia, or ALL, the leading cause of cancer death in children. Dr. Liu's team found that an enzyme called PRL2 is elevated in human ALL cells. Blocking PRL2 activity with a small molecule inhibitor kills these cancer cells. Dr. Liu's research aims to determine the effect of PRL2 inhibitors on human ALL cells in

hopes it can be a new target in the treatment of ALL.

New members

[Duykhanh Ceppa](#), MD

Department of Surgery

Associate member, [Cancer Prevention and Control](#)

[Xin Lu](#), PhD

University of Notre Dame

Associate member, [Tumor Microenvironment and Metastasis](#)

[Heather O'Leary](#), PhD

Department of Medicine

Associate member, [Hematopoiesis, Hematologic Malignancies, and Immunology](#)

[Ji Zhang](#), PhD

Department of Pediatrics

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